Conceptual Design, a key challenge in production efficiency (Part II)

The impact of the conceptual design phase on the feasibility of a tailor-made fit pharmaceutical plant

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WHITE PAPER

ABSTRACT

Conceptual design has frequently been regarded as an unnecessary step when talking of a facility design, but, on the contrary, it should be seen as a key step to have a compliant facility suitable for the operations to be conducted.

A good conceptual design may lead to a well thought and managed facility...or not, but an unsatisfactory conceptual design will for sure lead to a defective facility, non-compliant or very inefficient. Therefore, it is extremely important to dedicate the time to execute this process, and produce the correct design for the operations and products for each facility.

Divided into two chapters, this article explores the relevance of this stage in the development of a new pharmaceutical plant, their impact in the future production performance and the keys in the design phase defining the feasibility of a tailor-made fit pharmaceutical plant. This second part of the article addresses the key points of the management of subsequent phases following the information collection, such as the product categorization, capacity study, Site Master Plan (SMP), layout development, classifications & over pressures and flows review.

Product categorization

Once the information is gathered, product categorization is the first step: It will be the way of defining the number of areas, or even buildings, needed.

The list of products to be manufactured, with their API and pharmaceutical form, shall be carefully reviewed to make the categorization.

- **Segregation**

  The classified area should be limited to the minimum and to its lowest level of classification. If, from the beginning, it is possible to have areas not needed to be classified, out of the GMP areas, it will mean a saving, not only in the initial investment, but also in the daily operation. For example, in some facilities, offices for technical meetings are inside the classified area which means more expensive HVAC systems to cover that area plus being changed every time anyone wants to enter to those offices for a meeting.

  Also, certain areas may be dedicated for a product or for certain type of products. For instance, an area may be prepared for products requiring ATEX (explosion proof) finishings, while the rest of the facility may not be ATEX, which is also a good saving.

  The same approach may be used for products with a specific relative humidity request, which can be all of them produced together in a general area with an airlock to guarantee the right relative humidity level, while the rest of the facility does not have such requirement.
  And of course, when talking about segregation, it is important to mention that according to GMP, certain products are not compatible with others, which means that a differentiated production workshop needs to be reviewed for such products.

  Under this category, the products that are usually listed are sensitizing products that can induce some people to have an allergenic shock only with a presence at a level of traces. For those products, working in campaigns or talking about cleaning validation is not a good idea as showing absence of cross-contamination is nearly impossible. Assuring a complete absence of crossflows of both people and materials, between these products and other products, is necessary. The most known sensitizing products are beta-lactam antibiotics such as penicillin derivatives. Segregation is imperative between different beta-lactam families (penicillin derivatives (penams), cephalosporins and cephamycins (cephems), monobactams, carbapenems and carbacephems) that present different sensitizing reactions requiring different production workshops.

  Other products that are segregated are the ones that mean handling living microorganisms such as vaccines or monoclonal antibodies, even in some cases, differentiation between upstream process (where the living microorganisms are handled) and downstream process (where

purification takes place until the end), has been accepted by authorities and some processes of fill and finish (downstream) are being done in areas with the corresponding isolation but where also high potent products are manufactured.

Another category used to segregate products is linked to the potency of the API and this should be defined in the containment strategy.

Also, radiopharmaceuticals are usually produced in isolated facilities.

All the other products will fall into the category of generic products and can be manufactured in the same facility. Their differentiation is defined according to other characteristics: relative humidity or light product sensitivity, ATEX requirements, pharmaceutical forms, sterility.... This differentiation is necessary to produce every product in its lowest required category: Of course, a tablet can be produced in a Grade A with Grade B environment (the one needed for aseptic production), but this is complicating the operation making it much more expensive (and the investment, too) when there is no need. The same occurs if a product not needing an ATEX facility is produced in it, as the investment is higher without providing any added value to the product.

- **Containment strategy**

Linked to the product characteristics, when talking about highly active API, the degree of containment shall be defined. This means that the information collected will include the product OEL (Occupational Exposure Limit) and dustiness potential, totally depending on the API, quantity managed and task or transfer duration, depending on the operation. With this data, the strategy will lead to a certain technology for each product and operation. Oncology products and hormones usually fall under this type of products, which have one of the three characteristics: Therapeutic dose below 10 mg or OEL below 10 µg/m3 or API is mutagenic. Segregation between different type of high potent products is not always needed, even though there is a trend to split them as with oncology products and hormones.

Once the information of where every product on the list is being produced, the next step is to find out how many lines or what sizes are needed.

Capacity Study

If the number of lines or equipment size needed is not known, the approximate figures should be calculated. If the sponsor already knows the sizes and number of lines, this study can be disregarded.

It needs to be completed for every differentiated workshop according to the results of product categorization.

With the knowledge of the manufacturing processes and their steps, the products are grouped. For example, if both capsules and tablets are going to be produced by wet granulation and later blistered, they can be grouped in these steps even it is clear that the part of tabletting and capsule filling are independent processes and shall be considered as such.

For every step, a feasible equipment will be selected. The size, capacity, or speed of every piece of equipment will be defined according to the batch sizes to be managed. An initial review of the units or amounts to be handled in every step will show if the project needs high-capacity equipment or low-capacity, allowing the selection of equipment with a stated preliminary capacity.

When batch size is not defined, the following step of the study is establishing a reasonable batch size for every product, so that a balance is achieved between efficiency (the larger the batch, the cheaper), product needs (it doesn't make sense having a batch lasting for longer than its expiry date, which may happen if the forecast for a product is small and the batch size is very large) and available equipment (batch size should be adapted to the available equipment as much as possible, giving higher flexibility to the facility).

Experience is always useful, and it is known that for high potent products, usually batches are small while for LVP batches they are large, but it will be checked case by case.

Once the batch size has been identified, an appropriate machine can be selected for every operation.

This exercise will be carried out for every product, trying to harmonize as much as possible the selected batch sizes to avoid having many different ones that cannot be handled by the same equipment. If there are large and small batches to be produced, two (or even more than two) sizes of machines will be selected.

Once the equipment capacity/size has been harmonized, the following step is calculating how many pieces of equipment are needed.

Working hours for each one must be calculated, considering shifts, weekends, and downtimes (holidays and maintenance). In the process, cleaning and line set up shall be considered as well. With all these factors, a certain output will be achieved by each machine. This output should be compared with several years' forecast of all the products that are going to use this machine. The result will show if a single machine is enough, if more than one is needed and in which year they will be required and will also reveal the machines remaining capacity.

This calculation of how many machines is needed at every operation and of which size or capacity will define the number of machines, lines, and rooms.

With this information, based on experience, a certain dimension is assigned to every room where the machine is placed, including ancillary areas. These dimensions are extended in a certain percentage to consider corridors and pass boxes leading then to the rough size of the facility.

As part of the capacity study, it is common for warehouse dimensions to be evaluated. This calculation is based on the number of product units needed to keep a certain safety stock, considering a ratio for raw materials, primary and secondary packaging materials, and intermediates, transforming these figures into pallets.

If certain raw materials or finished products require special temperature conditions, these chambers or warehouse areas shall be dimensioned accordingly.

It may seem that a capacity study is easy to complete, but it needs quite an important expertise on pharmaceutical processes to know the steps for every product manufacturing and experience on the distinct types of machines available for these processes to make the right selection.

The importance of the capacity study is to confirm that the new facility will be capable of producing the required forecast.

As the forecast is recorded by years, it will also show what the needs are for every year, allowing for the development of the facility in steps including only the areas or equipment needed for every year thus optimizing the investment.

Site Master Plan (SMP)

Allocating everything in its adequate place right from the beginning is particularly important to prevent reworkings or limiting future expansions. It is very convenient to develop a site master plan, especially in the case of a multisite project, where all buildings, the ones involved in the project and the future ones, are positioned.

It will require evaluating the position of different buildings (centralized utility building, centralized QC lab, centralized warehouse...) to make them logical and the future flows easier.
The definition of such buildings and all the areas to be contained (offices, laundry, canteen with or without kitchen, praying area, toilettes, training room...) must be conducted from the beginning. Also, if any building requires a specific shape, either due to the plot shape, to take the maximum profit of it, or due to architectural requirements, the sooner this is known the better as it will be easier to place everything in its correct position.

The most logical flow for goods and personnel to get into the factory will be defined before starting with any layout development. Once the best option, according to the area roads and entries is selected, the design may start.

Lay out development

Once the approximate surface of the building, its position in the plot and orientation is known, the design of the layout can begin: It is convenient to have activities of the same classification performed in the same area to save gowning areas, even compromising efficiency for this reason is not advisable.

It is also an innovative idea to have a perimetral corridor that will allow visitors to see everything from outside and facilitate the flows. If due to the available space this is not possible, other options may be assessed: Making a corridor in the upper level that allows people to view the activities on the production floor, positioning cameras in the areas where interesting activities happen ...

Reception/Expedition

As the incoming materials flow has already been decided, it may be convenient to begin with this area.

The reception bay may be quite different if it provides access to a warehouse or if it is just the reception for the building having a centralized warehouse where the main reception has already been completed.

If it is a general reception, here are several points to consider:

- Direct connection between the general warehouse and the outside should be avoided to prevent entry of insects, birds or other animals or dirt.

- The design should allow that the truck gets to the bay to be unloaded, preventing any entry of dirtiness in case of rainy or windy conditions. There are many types of loading bays, some of them coupling the building to the vehicle, with or without dock shelter, with the goal to increase the hygienic condition of the operation.

- It is convenient having an area to place all incoming pallets for the first visual inspection and identification.

- From this area the containers to be sampled may be also taken apart and brought to the sampling area, being convenient to place it close to the reception area.

- An office to do all the paperwork shall also be in that area, if possible, with access from inside for the internal people and outside the building for the driver, to make it simpler. An adjacent toilet in the outside area, may be also a good idea.

- Other areas that should be close to the reception are:

    - Rejection area in case something is rejected when being received it can stay here away from the general warehouse.
    - QC area, or at least easy access to reception from the lab, as some people from QC are going to be constantly evaluating the receiving goods

If it is a reception in a building, but the initial reception has already been done in a centralized warehouse, most of the areas suggested before are not needed.

Expedition may be close to the reception or on the other side of the building, depending on the flow of materials.

If it is close to the reception, the materials flow in and out should not be crossing to avoid mix-ups.

In the expedition area, there should be an area where pallets prepared to be sent are left to be reviewed and labelled. These pallets will wait there until the truck arrives, moving then them inside the truck.

Dispensing rooms

The number of dispensing rooms should be calculated depending on the number of batches (and components of each batch) to be produced. According to the weight and activity/type of raw material, there should be an isolator (very active or sterile raw materials), or specific cabinets. Dispensing rooms are placed in at least a grade D area, and it is quite common to have them in C areas as well.

There are two philosophies, each one with pros and cons: Having them in the warehouse or having them in production.

- Warehouse dispensing rooms: In this case the movement of raw materials is shorter. The containers with the raw materials to be dispensed are brought to the dispensing area where they get in through and entry airlock. Once dispensed and collected in a bin or bag, the remaining raw material is left in an exit airlock, and then brought back to the general warehouse. Once the whole batch is dispensed, it is placed in a closed container or cage and brought back to the warehouse and then through the corridor to the production area where it gets in through an airlock.

- Production dispensing rooms: Raw material containers are moved from the warehouse to production, where they get in through an entry airlock. Once dispensed, the remaining raw material gets into an exit airlock where it is collected and brought back to the warehouse. The dispensed batch is already in the classified area and can be directly moved to the compounding area without the need to get out of the classified area as in the warehouse dispensing rooms.

Filling rooms

Usually filling lines are the longest and less flexible elements and that is why it is convenient to try and allocate them in the provided building grill to

see if it may be better placing them horizontally or vertically, depending on the available space and the number of lines to allocate. This will condition the whole design and that is why it should be the next step to consider once the materials and people entry have been decided.

When the filling line is connected to a washing/loading machine from one side (in the case of sterile production with a sterilization tunnel, too) and to a packaging machine from the other side, it becomes even longer and more difficult to place. If the line is aseptic, the use of isolators or RABS will make their placement even more complicated. And it is even more difficult when several lines want to be placed in parallel, as the lines are crossing different classification areas, splitting the whole surface into small independent facilities: The line does not allow crossing from one side to the other, which requires the designers to think about independent gowning rooms and ancillary areas for the different lines.

Gowning rooms

Once the incoming people direction is decided, a general gowning room is needed. This is the point where street clothes are left and it is usual differentiating it for male and female, as it may have some showers as well as toilets. In some cases, this gowning room may be common for all personnel, but sometimes it is more convenient to have warehouse staff using a different one closer to the warehouse. The same may happen with QC lab personnel who may have a specific gowning room.

In general, the process should be researched to minimize changes and people moving long distances. This is the main point to consider when deciding if a single general gowning room or differentiated ones will be used.

The same approach should be used when designing every different classification gowning room: If it is possible to have a single one (differentiating male and female if needed) for the whole area, perfect. If distances are too long, or if it complicates the design of the area, it may be better having different gowning rooms.

For grade B areas, the way in and out should be differentiated and it is also convenient for grade C areas. If it is possible to have different ways in and out in D grade areas, it may be better, but it is not entirely necessary.

It may be extremely useful for these designs to use double-door lockers, where garments worn in the way in are left to be recovered from the other side on the way out. They are not needed if the gowning procedure consists of putting on an over gown, discarded when getting out.

The last part of the gowning rooms should have the same degree as the area acceding. As the starting part it will need to be the same degree of the area getting into them, this means that at least two steps are needed, and if the access is from more than 2 degrees (D to B, for instance) at least three steps. In some cases, if there is not enough space, the two steps are done in the same room having a division between the two areas (usually a bank splitting the room into two); the whole room is designed to comply with the higher degree, but the lower grade area is declared as such.

Another aspect to consider is the inclusion of showers (air or mist ones) when it may be required due to the nature of the product handled to prevent cross contamination.

Other rooms

The remaining rooms are not less important, but their position is conditioned by the available space after having placed the already mentioned areas.

In general, the design shall try to minimize the number of movements to make them more efficient, bringing rooms as close as possible to the next operation.

Compounding rooms are preferably placed very close to collecting rooms, in case of aseptic operations, or to filling rooms. And it should be kept in mind that close could mean in vertical, having the loading port of a filling machine or a tabletting machine in the upper level.

Corridors shall be minimized, too. They are useless space, with the only function of connecting areas.

All needed rooms shall be considered, and their size be the adequate one for the operations to be done inside. If the room is too small, it will be impossible to perform the foreseen operations, while if it is too large, it means a waste of space and air treatment. Nevertheless, in case of doubt it is always better that the rooms are a little larger than a little smaller, as the basic and detailed design will reduce the room's final effective size by including returns and furniture. Some room for

intermediate product allocation and for allocating batches between different steps, may be needed and it shall be considered.

Technical areas

Technical areas should allow the placement of the foreseen equipment but, at the same time, they should allow easily performing the maintenance operations. So, apart from space to freely move, the right height shall be considered to avoid uncomfortable operations.

In many cases a certain air treatment may be needed: Either extraction to cool down the area or heating in cold countries where these areas are exposed to low temperatures.

Future expansion space shall be considered in these areas, too.

Classifications & over pressures

When the design is developed, the different rooms' classification is taken into consideration, but it should be confirmed once everything fits together. To make it easier, it is convenient to colour differently every area in drawings to confirm all these classifications comply with regulation's requirements. The separate way in and out for materials and people in every classification area shall be thoroughly checked to avoid omissions.

Once confirmed that the areas' classifications are correct and nothing has been forgotten, it is the time to define overpressures.

Based on the annex one of EU GMP, it is common having 15-10 Pa overpressure between different grade rooms (10 Pa according to the reviewed Annex 1 draft) and 10-5 Pa between rooms of the same grade.

Overpressures are the barrier to avoid contamination when a wall is not possible, or a door is there. Therefore, air shall be going from the place wanting to keep the contamination out to the adjacent area.

But the decision about which area shall be protected is not always that obvious. The first aspect to be protected is personnel and environment safety. When talking about a highly active product, the overpressure avoids any residue getting out of the area where it is manufactured. The same approach is used to contain OSD (oral solid dose) products, which are kept in their manufacturing rooms by having overpressure in the corridor or over pressurized airlocks.

In some cases, like in biologically active products, negative pressure may be used (real or relative) to have a sink effect, assuring no air leaves that area.

In liquid products and even more in aseptic production, overpressure cascade is used to protect the area where product is exposed, having more pressure in such areas, and decreasing it across the different steps until reaching the outside of the classified area.

Flows review

In the development of the design, the flow is implicit, it is refined throughout, thinking, and evaluating about the different flows for people and materials. Despite that, it shall be carefully reviewed to prevent forgetting any relevant detail: all type of materials, samples, settle plates.....

The design team will ask the sponsor to explain any potential options that may occur: Components that take part in an aseptic operation which are already sterilized, sampling operations that should be done as part of a certain process, intermediates that should be on hold until a certain analysis allows the releasing of them....

Very often, when reviewing the different flows, forgotten aspects, or the possibility to improve some of them, is highlighted.

Waste flow shall also be reviewed in detail as waste is going to be produced in every step and the way to get rid of it needs to be addressed.

Final steps

When the conceptual design is finally agreed by all parts, it should be frozen, as it is common to continue thinking about possible improvements or having ideas that appeared to solve some of the issues raised in the conceptual design development. It could be a never-ending process unless it is formally stopped.

As the last step, before deciding that it is over, when there is a doubt about a movement of material or a certain piece of equipment that should be moved and whether it will fit, a mock-up (with light cheap material) may be built to do a final live verification. It is not common, but it is

the final confirmation that it will work.

Today most conceptual designs are developed in 3D BIM (Revit or similar) and this model shows quite well the effect of any movement without the need of building anything.

The only remaining step to finalize the conceptual design is preparing the report where all the points considered, and discussions held in meetings are included. It will help solving any further doubt that may arise in future, as it is very normal that when teams change it is not that evident why something was designed in a certain way.

The standard deliverables from a conceptual design are:

- Project basis
- Building location plan /plot plan
- Lay-out
- Classifications and differential pressures
- Materials/waste flow
- Personnel flow
- List of equipment/utilities
- Equipment layout
- AHU distribution area
- Conceptual design report

And many times, depending on the available information and type of product, also:

- Site Master Plan
- Capacity study
- Containment strategy
- Budget ± 30%

Next steps

The conceptual design is the starting point where ideas become something real, but still many aspects are not decided yet. These decisions that are going to be taken during the project are related to the type of technology used to cover certain needs, the finishings or quality of certain materials, equipment brand name and model according to specific URS and calculations to provide the needed utilities. They will gradually be developed through the following steps: basic and detailed engineering.

These steps constitute the total design package containing all the elements to be able to construct the new buildings and install all their infrastructure. This phase requires coordination, understanding the requirements and involvement of specialists in the different disciplines.

The engineering involvement is very high as calculations are needed and many drawings are developed: For utilities, piping and instrumentation diagrams are prepared with the necessary diameters knowing where utilities will be produced and the final location of the production equipment and the required points of use; for equipment, detailed diagrams and drawings are developed knowing the needs, automation features and process to be done; for HVAC, final filter positions and returns, ducts, instrumentation and the necessary characteristics so that the desired air quality is guaranteed during the operations.

This development is executed by disciplines, and it ends up with the BOQ (bill of quantities) where the amount of every single element and its specifications is detailed.

The usual deliverables from a basic and detailed engineering (part of the documents delivered in the basic, while others are issued in the detailed engineering), without getting into an exhaustive list, are:

- Budget
- Equipment layout and identification
- Utilities points of use
- Technical description
- Bill of quantities
- Layout
- Classifications and differential pressures
- Personnel & material flow
- Equipment list, layout, and defined characteristics
- Fire protection zoning & detection system
- Civil architecture calculations and drawings (with the set of documents intact to obtain all the project permits)
- Architecture:
  - Clean room wall panel
  - Clean room ceiling panel
  - Clean room covings
  - Clean room window
  - Clean room door
  - Clean room luminaries
  - Ceiling height
  - Ceiling elements distribution
  - Wall panel distribution
  - Clean room wall panel assembling details
  - Return air risers distribution
  - Ceiling qualities
  - Ceiling panel distribution
  - Clean room ceiling panel assembling details
  - Coving profiles details

    - Floor quality
    - Door and window specification
- HVAC:
    - Heat loads calculation
    - Air handling units' calculation
    - AHU distribution area
    - HVAC diagrams
    - Double line duct routing
    - Ductwork sections
    - Details for construction (supports, ductwork, dampers, etc)
    - HVAC - technical specifications
- Utilities:
    - P&I diagrams. Black utilities
    - Black utilities piping layout
    - Waters P&I diagram
    - Waters piping routing
    - Other utilities P&I diagram
    - Other utilities routing
- Electricity:
    - Electricity calculations
    - Main electricity components - technical specifications
    - Electrical architecture
    - Electrical tray layout
    - Door interlocks
    - Electrical boards one-line diagram
- Control:
    - System architecture
    - I&O drawings
    - Equipment automation

In certain cases, while developing basic and detailed engineering, fine tuning and review of the conceptual design is needed, as different machines model or ideas are developed in the basic/detailed design which will require adaptation to what was developed. It is normally a minor adjustment that will not affect the work too much that has already been completed.

Conclusion

The explanation about Conceptual Design can be summarized in the following points:

- Conceptual design is key for any project as the initial step that will guide the whole development.

- Conceptual design is focused on defining the layout of the plant and the approach of the logic of design covering the structure and the operation of the facilities for the foreseen processes to manufacture the forecasted products and amounts.

- Knowing and understanding the requirements, plans of the company and certain preferences such as architectural aesthetic type and design guidelines can be set out in a document which describes the general structure of the different sections of the facilities, their basic characteristics, interrelationships of areas, equipment, operating logic, alternatives capacity increase and areas of expansion.

- The resulting design shall be simple and efficient but must be 'frozen' before moving to the following development steps.

- Future needs must be considered but without forgetting that the facility will be operational from the moment it is finished: Whenever possible different steps or phases will help moving ahead, maximizing the return of investment.

The success of a plant design is materializing the ideas and theoretical design into a factory build that works in an efficient and compliant way for years, as conceived.

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