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

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 first part of the article is focused on a general view analysing in depth information to be retrieved to allow continuing with later conceptual design steps. The 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.

Introduction

A new plant project may originate from an idea involving innovation and starting from zero, activated to cover a particular need or to solve a problem that has been identified in an existing facility requiring a revamp.

In all cases, it is important to identify the central goal of the project and the ideas to be incorporated into it, so that its development, complying with the relevant regulations allows the right economic and technological evaluation of the project's viability.

This step should be carried out before investing financial resources and before starting any construction operation, deciding to go ahead if the project is feasible.

The design of new facilities can be compared to the planning of a tailor-made suit, with the complication that in the future it will continue being tailor-made, fulfilling and supporting the growth and evolution of the company itself. Design shall consider future expansions from day one, which requires an effort from sponsors who should define these future needs that are usually quite uncertain.

Several elements need to be analysed in detail to ensure that the design is appropriate and meets the expectations.

Collecting the right information is the first goal, starting with the plot and products' details:

- Available plot to develop the plant or existing facility to be revamped to make everything fit in the available space.
- Type of product.
- API (active pharmaceutical ingredient).
- Forecast expected (production).

From the technological point of view, it is essential that the design considers:

- Processes to manufacture the selected products in the new facilities and their critical steps.
- Technology that will be used.
- Batch sizes.
- Number of people involved and their department (production personnel, quality unit, maintenance, and other functions), to size gowning areas and rooms.

Other points that must be confirmed to make the appropriate design are:

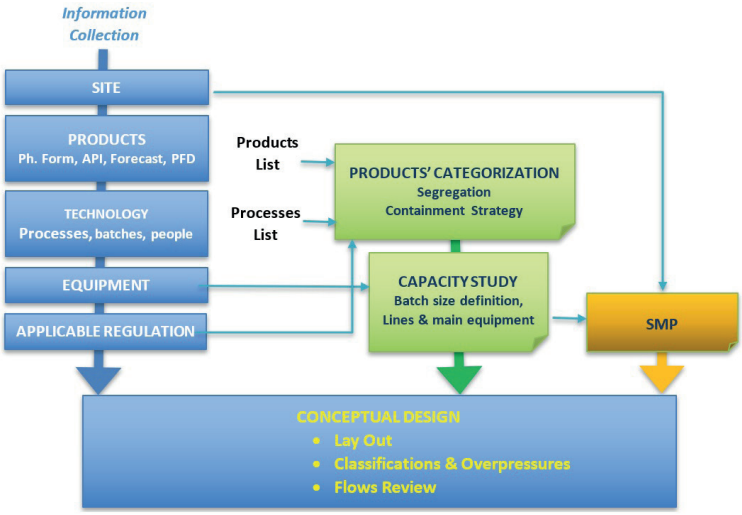
- Preferred machine suppliers or existing machines that will be used in the new facility, so that the design is adapted to this equipment.
- Market where the production is going to be sold, to consider the corresponding GMP.
- Safety aspects must be highlighted from the earliest stages of the project.

Once the information is available, it is possible to start with the characterization of products, which will lead to the definition of the different areas needed, linked to the type of product (some products must be segregated from others while some others have certain containment needs) and type of pharmaceutical form.

When the areas are set, a capacity study will be developed to define the number of lines that should be foreseen to reach the forecasted production (if this information is not available upfront).

It is then the right time to start drawing, with the available plot and knowledge of the different steps required for every product manufacturing process: areas' distribution, their sequence, dimensions, communication, classification, type of finishes, critical systems and services needed for the operation, moving then to the next steps where everything is increasingly defined.

The figure below shows the phases to develop a conceptual design:



Conceptual Design Steps

Information Collection

Gathering the appropriate information can be considered itself as the first step of a conceptual design. This is not a single time task, as contact with project sponsors should be frequent throughout the project.

To help analyse the information, it can be split into site information, product related information, technological needs, and regulatory requirements.

Site information

- **Green field projects**

In some cases, the design is developed to define the needed surface to build the plant, but usually there is an existing plot where the design will fit. Unless it is impossible to include in the available surface everything that has been identified (in these cases, sponsors will reduce what was initially foreseen to make it fit), this site will be where the project will be built. Therefore, a drawing of the area is needed, with information about the area flatness (sometimes the slope of the area affects the design), surrounding roads, foreseen entrance, limitations in height and use of the available surface according to local regulations, ancillary buildings to be considered in the area, and in general everything influencing the design.

Modular growth, use of spaces and even the aesthetic aspects of the architecture and style of the future installation must be considered at an early stage of design.

- **Brown field projects**

When talking about revamping an existing area or facility, the drawings and details shall be obtained and reviewed with the sponsor to understand existing problems to be addressed, total surface to be used (it is possible that a certain expansion is allowed or, on the contrary, that not all the available space may be used) and the constraints that will affect the design.

If in either case, green field or brown field projects, the project is executed in phases, it shall also be considered in the design to simplify future works. The same applies to an expansion in an adjacent area: Even if it is not going to be immediately designed, it will be included in the current design to avoid eventual complications for a future expansion.

Design philosophy may be led by the available space or by the preference to manage materials. If a horizontal flat design fits, it is usually cheaper and simpler to do it that way. But often the price of the land is expensive, so it is commonly a preference to have a second level with offices, laboratories, or activities not needing heavy equipment.

If the available space is not enough, a vertical design with several levels shall be considered.

Heavy equipment can then be placed at ground level. Nevertheless, this is not always possible so then the best flows must be foreseen, independently from the weight of the involved equipment.

In many cases, the size of certain components recommends making the activity in several levels. For example, when talking about large reactors, common in API production or LVP (large volume parenteral), the reactor may be placed between distinct levels, loading from an upper level, where compounding is placed, and unloading from the bottom level, where next steps, commonly filling machines, are placed.

In other scenarios, gravity may be used to transfer materials from one step to the next. It is quite common for solid forms to have containers or bins in an upper level and loading from there the tabletting or capsule filling hoppers by gravity.

Additionally, a kind of hybrid design can also be adopted, where production factories are on a single level depending on the pharmaceutical form, having warehouses at the bottom of the building.

In the case of a brown field project, knowing the availability of utilities (capacity, how far from the final revamped area, restrictions) and other buildings (warehouse, QC...) will be helpful to avoid considering them twice (or even in some cases, to complement something missing in the existing facility).

The same happens with the equipment coming from the existing factory to be used in the new one, as it shall be defined, as part of the information collection. Clarification is also necessary if the strategy is starting with the existing equipment or, on the contrary, starting with the new one, moving the existing one to the area once everything new is already working.

Product related information

- **Pharmaceutical forms to be handled**

Each pharmaceutical form has properties and specifications that influence the unitary operations of their processes and the regulation to be applied. A facility to produce oral liquid forms is different from a facility to produce finally sterilized products and different from a facility to produce aseptic products.

- **Product list**

Information relating to the products, their specifications and active ingredient's (API) content is essential for the development of a proper design that considers containment systems, protection systems and mechanisms to prevent contamination. It is not the same designing a dedicated facility or a multipurpose facility.

For those involved in the design, it is essential to know whether the product is a high potent product or a product with restrictions such as oncologic, biological, beta-lactam or hormonal, or is it a product that is sensitive to light, temperature, or moisture.

Depending on the type of product, segregation is necessary, leading to areas differentiated and with complete separation of people and materials.

Hygroscopic products, sensitive to light or temperature in certain ranges should be known to consider the adequate conditions for them in their process design.

As part of this list, the primary and secondary packaging to be used should be identified. The different steps to be considered depending on these components, the necessary space to store them and the correct flows for these materials, will be considered in the design.

- **Production forecast**

The volume of production and product's batch size will determine the frequency of manufacture of each product allowing different alternatives in the handling of raw materials, packaging materials and products.

As production strategy for certain products, several considerations are to be evaluated: Dedicated lines, producing by campaign, or others, calculating the space needed for materials in each case; in-line manufacturing versus keeping white stock; technology linked to every type of production with pros and cons shall also be evaluated with sponsors.

The company's growth projection needs to available to size the new installations in terms of

installed capacity to design a facility suitable for many years. It may be possible a development in several phases will start at different intervals, but correctly designed from the beginning.

That is the reason marketing and sales departments should be involved in the process, to provide the necessary information regarding these future requirements in terms of specific areas for products with different pharmaceutical forms or processes and products with different specifications.

- **Process flow diagrams**

Some processes are quite standard, but in some cases, there may be specific steps that need to be included in the design. Process flow diagrams are a fundamental tool for the development of process analysis and understanding any specific aspect to be considered. They allow to schematize, in an orderly way the unit operations of the entire process, indicate the activities, the controls, the decision alternatives and much more information that can be related to the type, size and location of the area or room where it was carried out.

All these aspects leading to a final decision must be correctly documented. If this point is omitted or not well covered, a future review, where team members of the initial conceptual design are not involved, may lead to the conclusion that a design is developed incorrectly when the reality may be that it was thought for a different purpose. For example, if a certain sterile product is to be produced by final sterilization but the product finally selected is produced by aseptic processing, what any outside observer may see is that the room classifications, steps, and equipment initially foreseen are completely wrong. That is why having a clear starting point and documenting all decisions is so important.

Technological needs

There are several different technological options to produce the same pharmaceutical form and it is not always something that is known by the sponsor. This definition, linked to the type of pharmaceutical form and products' needs, must be discussed based on the experience of both sponsor and design developer. If the sponsor has a clear definition of the steps to develop a certain product, equipment, utilities required and rooms sizes for this, it will be beneficial. If not, information shall be collected, working together, and agreeing on the best choice among all options.

The design should consider the process that will be done, its sequence and how it interacts with other elements, its specifications, needed care, variables that may affect it and the dimensions. These elements are part of the technological needs.

- **Equipment**

It is also a key element for a clever design, defining sizes, room classification, necessary utilities, number of people needed and flows to feed such equipment. A good plant design may become flawed if identified equipment is not the appropriate one for the foreseen process. An efficient oral liquid filling machine may be a disaster if you are trying to use it to aseptically produce a sterile eye-drop.

Several elements need to be considered when talking about equipment in a conceptual design, such as segregation between the parts to be allocated in the clean and technical area, brand name & model definition and the technology used.

- If it is possible to leave a big part of a machine out of the classified area, even better, as it is less the volume of air movement and easier for any maintenance operation. Not so long ago, it was quite common to have a complete coater in the classified area, while now, the coater is usually located out of the classified area, with the loading port inside the area, as it is the only part where product is exposed to the environment. The same approach is increasingly used in reactors and other type of equipment.

- Many times, when developing the design, there is not a special equipment brand name preference. The design should consider any existing machine so that at least it is a feasible design where equipment will fit. Once the brand name or model is known, the design is usually adapted for better fitting as it is never the same size as the one used for the design. This slight modification of the spaces may be difficult in tight areas if the selected machines are much larger than the ones used in the design. It may even be necessary to start the design from the beginning again.

- When the sponsor has the correct brand name and model, the design becomes easier as the space can be calculated accurately to make it fit and there are less uncertainties. This usually occurs when the brand name is one of the few providing solutions for the process or when the sponsor has already got experience (and it is good) with a certain brand name, as it may be convenient continuing with the same brand name: training of staff is easier, the same after-sales service, spare parts, type of technology, ...

- When the same process can use different technologies, for instance a granulation that may be done using traditional methods or by using a fluid bed drier, the product dossier must be checked as its modification always implies a huge amount of work. Only when efficiency is noticeably different between one method and the other, or the dossier has already been modified, is a change in the technology considered.

A standard deliverable from a conceptual design is a list of main machines considered and whenever possible, their brand name and model.

In this list, if part of the equipment is going to be installed in a second phase, it should be noted. In the design, the method to install it later will be taken into consideration, foreseeing the way to bring equipment to its final position and how to minimize disruption to the rest of the factory while working in the following phase.

In the same way, if part of the equipment is coming from an existing area such as a revamp, it should be known and the strategy may vary depending on the sponsor needs: If it is a new area where part of the equipment is new and part is the existing one, it is very common to start placing the new lines and once everything is running, moving the existing ones. If the area is the same, usually the existing equipment is the one installed first.

Another point to consider when talking about equipment, even though it is not strictly linked to the conceptual design, is the long delivery time that some of the machines may have. It may be a clever idea to develop URS (User Requirement Specifications) for long delivery time equipment to take a decision on them as soon as possible to avoid delays later in the project.

Regarding utilities, the main part of the work linked to them will be covered in the basic engineering, a first approach on consumptions and points of use may be helpful.

- **Personnel needs**

A proper design of people (staff & visitors) and material (all type) flows will simplify operations, gaining efficiency and preventing quality problems.

The number of people involved and their type (production personnel, quality unit, maintenance, and other functions), must be identified to size gowning areas and rooms. This number will depend on the production lines to be installed, the batch sizes and frequency, the changes between various products or formulations, the degree of automation and control required for the equipment and systems installed and the shifts.

If not known, a calculation of the number of people working in each area, categorized by gender and type of function will be completed. In the design, the operation performed inside, and people access should be considered: If a machine operates from a classified and unclassified area, two people may be needed as it is not efficient for two people to be going in and out of the classified areas.

Access for Quality Control people and the maintenance team will be evaluated to make it as simple as possible.
Visitor access should be examined, allowing, as much as possible for them to view the operations to in the classified area from outside that area so not to interfere with the manufacturing process.

The same aspect applies to auditors or inspectors: The easier the observation from outside the area, the less need of getting into that area to evaluate it.

Regulatory requirements

The pharmaceutical industry is one of the most regulated markets, therefore the appropriate regulations must be taken into consideration. Information that need to be collated is:

- **Markets where products will be sold**

Depending on the market where the products manufactured in the new facility intend to be sold, the applicable regulation will vary. Even if the products may initially be exclusively for the local market, if there is a future expansion plan where products will be exported, an international standard will need to be discussed so that the plant design does not become a barrier for a future business. And, of course, the local GMP will be adhered to.

In some cases, certain GMP may require a specific design or technology to be used and it shall be evaluated in the design.

It is advisable making the design compliant with the highest standard that may be needed to comply with if going to a certain market so that the facility is ready. The difference in investment should not be much and what can be done, until the moment the product goes to that market, is that the day-to-day operation complies to the lower regulation and not with the higher one.

To give an example, if certain GMP requires performing an operation in D grade, but this will be a future market, and the current market GMP does not require it, what can be done is designing the area as Grade D but working as CNC (controlled not classified) until the moment it is decided to go to that market.

- **Standards to consider**

Of course, GMP compliance is completely necessary. If it is known that a certain standard is being reviewed, the design needs to consider the new standard that will come into force when the facility is finished, not the existing one that may be superseded.
The same approach shall be applicable to certain products changing category: If it is known that according to a regulation being reviewed that these products shall be considered in a higher level of compliance, this higher level should be applied to the design.

In many multinationals, some other standards that may need to be met are corporate standards, often even stricter than GMP.

Regulation for Health and regulations related to Labour and Social Welfare, Ecology and Environmental Protection should also be considered to focus the design to its fulfilment. The list of regulations and standards that must be complied with must be drawn up.

Safety standards must be included from the very beginning, too, to avoid later reworks to implement measures not considered in the beginning and shall be proportional to the complexity and operation of the plant. Distance to emergency exits shall be reviewed, if not, it may mean having to redesign an area to include a corridor or an exit closer than initially thought.

And another regulation to consider is the local one regarding the building: Distance to the adjacent plot, maximum height to be built, percentage of the surface that can be built. All these aspects will limit the design meaning a redesign if not considered from the beginning.

Bibliography

- "Pharmaceutical Facilities Design, what to consider for a GMP compliant result and last industry trends" – 2nd Annual MENA Pharmaceutical Manufacturing Congress – Jeddah, Saudi Arabia, November 2016, Rafael Beaus

- "Diseño de Plantas Farmacéuticas" – Academy entry lecture – November 2016, Felipe de Jesús Cuevas Pérez

- "Concepción y diseño de una planta" – UFV Pharmaceutical Engineering Master – October 2021, Jordi Sumoy

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