

This article describes a new configuration for the layout of an OSD facility that closely integrates all of the facility contents plus optional R&D and administration areas. It presents a number of operating and GMP advantages, as well as potential capital and operational cost savings.

A Hub Layout Concept for Oral Solid Dosage (OSD) Facilities

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Introduction

Oral Solid Dosage (OSD) facilities producing tablets and capsules use well-defined unit operations, regardless of differences in production volumes or usage of such facilities for single or multi-product manufacture. The contents of such a facility typically include warehousing with re-

ceipt and dispatch areas, clean process rooms (which are conveniently called 'white' areas) containing process equipment, clean support process areas for items such as washing, movements, and staging, QA/QC laboratory, and black normal factory finish technical space for process ancillary equipment and ventilation, and basic utility supply equipment if it is a stand alone facility. To gain competitive advantage, companies aim to minimize capital and operating costs for such facilities, which primarily means reducing the size of such a facility, as well as improving the operational and internal logistics of the facility without compromising current good manufacturing and engineering practices.

Process and Facility Outputs and Size

Dispensing with sieving, blending, granulation, compression to form tablets, capsuling, tablet coating, blister packing or bottle filling, cartoning, and packaging are some of the discrete batch unit operations in an OSD facility plant. The numbers, capacity, cycle times of the equipment, and daily operating time will determine the output of the facility. Different companies may require different facilities whose outputs can range from 100 million to two to three billion tablets a year. Increasing equipment capacity by factors of 5-10 does not greatly affect facility size (area), though its capacity may increase by a factor of 5-10. Increasing plant utilization from a one day shift for five days per week operation to a 24 hour, seven days

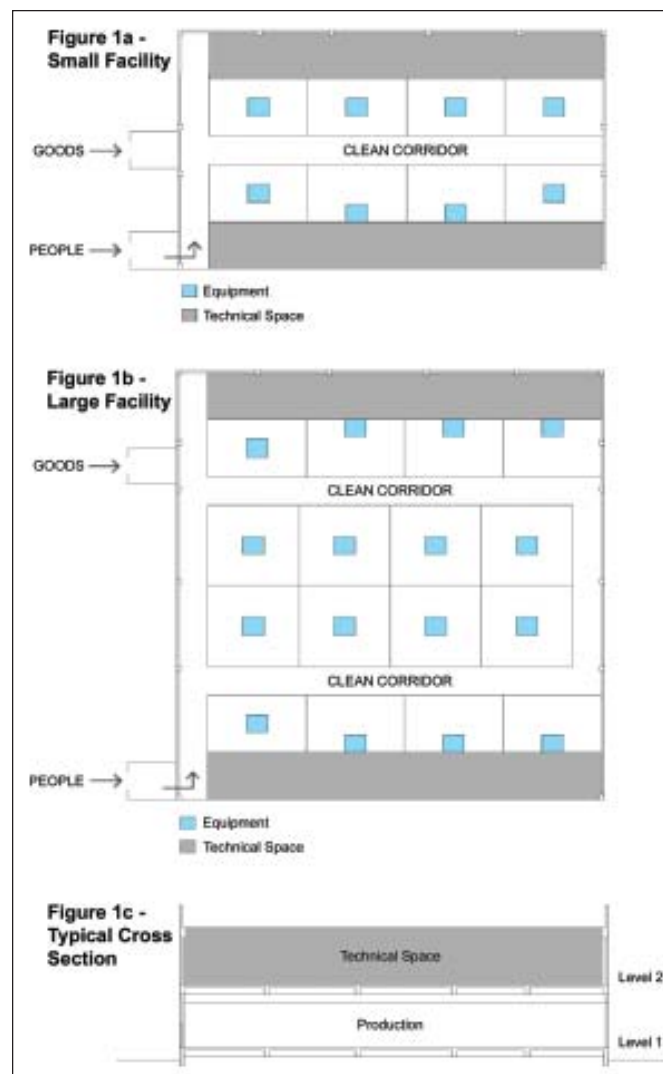


Figure 1 (a, b, and c). Typical production suite arrangements.

operation will increase outputs by a further three to four times without any significant increase in production area sizing. However, increasing equipment numbers and types to achieve more capability and flexibility will greatly affect facility size, and efficiencies in space utilization. Nevertheless, since the facilities are expensive, any unnecessary increase in OSD plant size will have a significant cost impact.

Materials Handling

A key requirement of an OSD plant is solids materials movement between each batch unit operation. Movements of solids between unit operations can be achieved by gravity flow from 'directly' coupled equipment (advantageous in large output single product stream plants) or more frequently by collecting the batch in an Intermediate Bulk Container (IBC) and moving this to the next stage by emptying the contents of the IBC by gravity to the equipment.

One or two level plants are common for smaller plants with smaller batch sizes (e.g., typically up 500L), while the three level plant is often used for larger batch sizes (e.g., above 1000L).

Process Arrangement - The Cleanroom Suite

For OSD plants, ISO Class 6 (equivalent to Class 100,000) particulate environments are typically used for process equipment rooms and adjoining areas where 'open' product or items which could be in contact with the product (including people) are present. Consequently, the process area is typically composed of a 'clean' room suite with 'clean' corridors and 'clean' process rooms for production equipment. Technical areas are needed for ancillary supporting equipment to the production equipment, e.g., blowers, heaters, vacuum systems, being located either 'behind' the wall of the production equipment at the same level and/or in a technical space above the production suite. Technical areas adjacent to production rooms allow 'through the wall' installation of some

process equipment, e.g., coaters. Such desirable facility features also can facilitate the process equipment installation.

In addition to the production rooms, the cleanroom suite also will require space for materials staging, wash rooms, store rooms, and sometimes a small operator batch log room and an in-process control laboratory.

Figure 1a shows a typical arrangement of a plant with a single corridor and adjacent process rooms, allowing a technical space on either side of them. In Figure 1b, a larger multi-corridor cleanroom suite facility is schematically indicated, and in Figure 1c, a cross section is provided of a single, level plant with a technical level above it.

Operator access to the cleanroom suite will be via a change room and materials enter or leave via one or more airlocks.

Filling and Packaging

While a number of OSD plants may just make the capsules or tablets in bulk to be shipped to other filling and packaging facilities around the world, most OSD plants incorporate these operations within them. For multi product plants, it is usual for the filling equipment to be in a cleanroom with the 'line' then extending into the lower GMP category packaging and cartoning room. Thus, the filling rooms are typically accessed off the process cleanroom suite with the associated packaging area next to them accessed directly or indirectly from the warehouse.

Mechanical Ventilation

OSD plants require large ventilation systems where 15 or so air changes per hour are required for the cleanrooms, and low humidity may be needed for specific product requirements. The ventilation systems typically consist of Air Handling Units (AHUs) and their associated control dampers and ducting systems, plus chemical dehumidifiers if required. There may be six plus such systems in a facility supplying clean areas, support areas, warehouse, laboratory, and support offices depending on the product(s) and plant type.

AHUs and their ducts are primarily located and distributed in technical areas, which are located near the clean areas. The conventional approach is to provide a top floor of the facility dedicated to AHU system as indicated in Figure 1c. This area also may include water chillers and other services if the plant is remote from central facility services. Quite often the process and support functions (i.e., the overall facility) floor area requirement is greater than the space required by the AHU systems, and this can result in underutilization of the floor created at this level.

Good Manufacturing Practice (GMP)

GMP guidelines cover all aspects of manufacturing including validating process methods and analytical control, equipment usage, facility layout, environments, storage, documentation, labelling, and the required training of personnel employed. Regardless of the arrangement of the facility, a number of key principles should be applied, including:

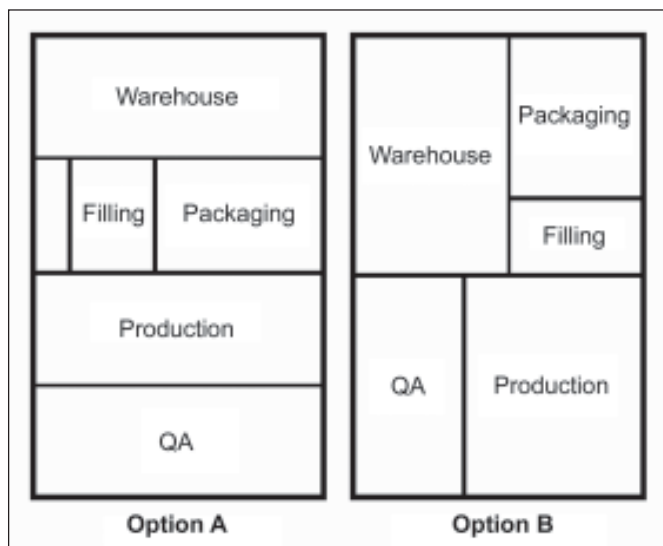


Figure 2. Typical conventional facility layout arrangements.

- avoiding mix ups
- provide suitable environments
- take measures to avoid contamination
- provide suitable materials flow around the facility
- provide adequate space for operations taking place
- design to allow for cleaning
- adequate labeling (at point of operation)

Some layouts are better than others, to meet these GMP guidelines, but in practice the following are preferred:

- segregate raw materials and final products
- segregate different production suites involving different classes of products
- closed operations where possible
- segregate physical barriers or other proven means 'open' operations with different products
- ensure an orderly flow direction
- provide distinct staging areas if required between process steps
- provide cleanable production suites and equipment
- provide suitable environments for controlled areas where products and their active material are stored and processed

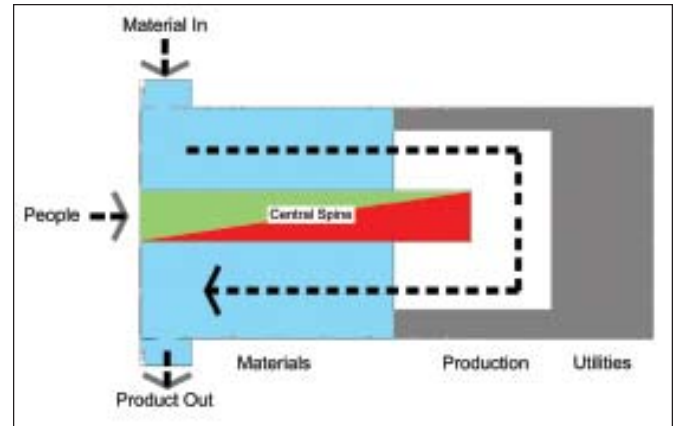


Figure 3. U SPAH concept.

Typical Overall Layout for a 'Conventional' Design Facility

As stated previously, there is no one single arrangement adopted by facility designers to meet the following issues affecting the layout:

- relative location of warehouse to the production and packaging suites
- cleanroom suite arrangement
- usage of different levels and IBC movements

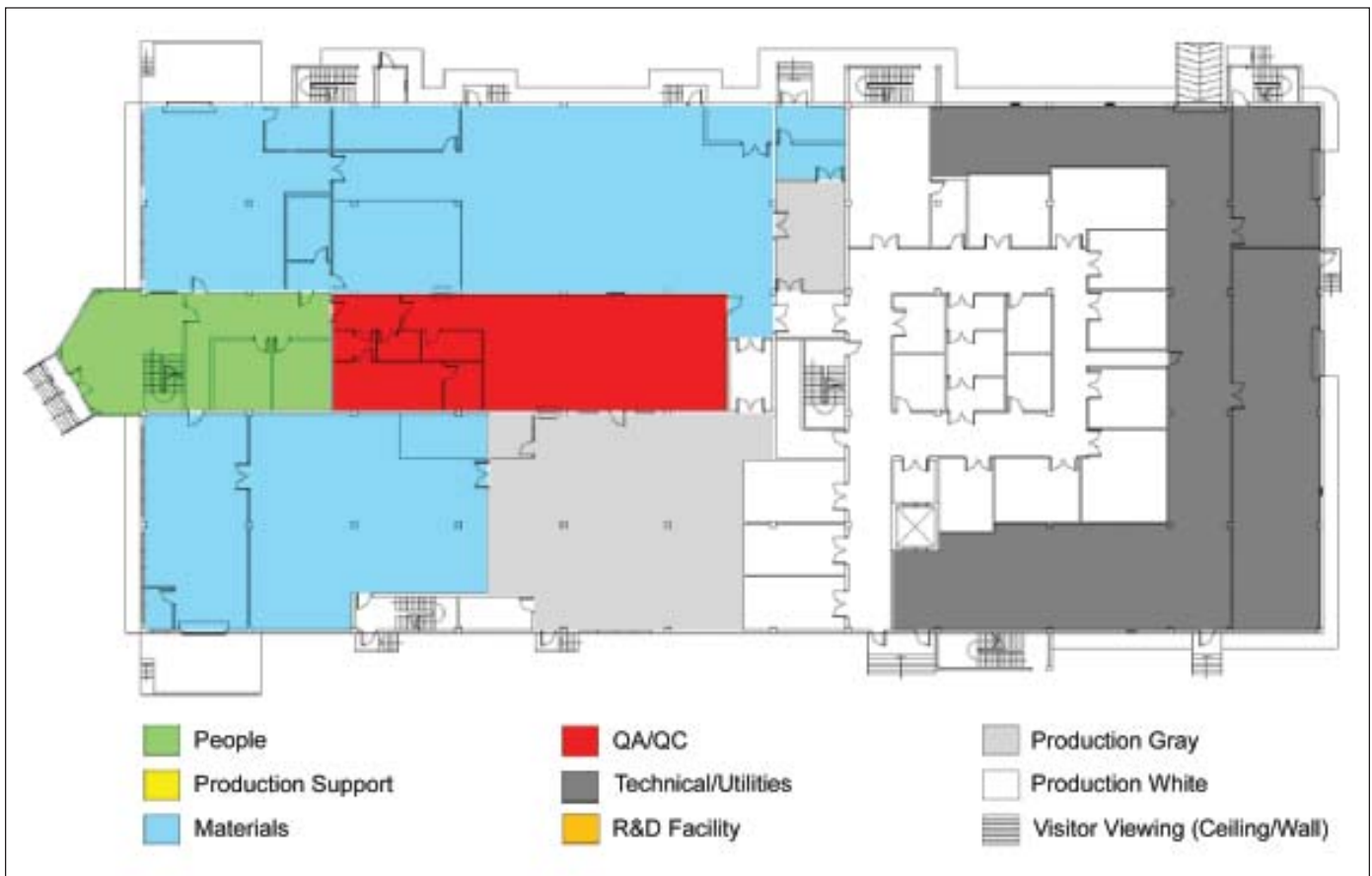


Figure 4. Ground Floor (Level 1) U SPAH facility layout.

Parameter	Approximate Facilities Comparison(1)					
	U SPAH 1	U SPAH 2	Project A	Project B	Project C	Project D
'White' production	20	21	28	17	15	14
Production staging (w + g)	7	7	12	5	5	4
Production support (w + g)	19	14	14	15	15	11
Technical black areas	29	31	39	45	51	47
Warehousing/Dispatch	25	27	7	18	14	24
Total facility area – approx m2	3200	7000	18000	10000	7400	8000
Approx Output (billions tabs/yr)	0.2 – 0.6	2	3.5+	2.5+	0.1 – 0.3	1
Notes: (1) Numbers are percentage of total facility area required by this part of facility w 'white' area, i.e., clean area in facility used for production support, e.g., washing areas, staging g 'grey' area, i.e., areas of facility used for production operations/support, but lower level of cleanliness						

Table A. U SPAH vs. conventional facility features.

- adjacency of technical areas to production rooms
- QC laboratory location
- separate raw materials and finished product routes
- minimization of expensive 'clean' areas
- avoidance of 'white' areas adjacent to external walls
- dispensary location

Other layout considerations, which could be taken into account in facility design, but are often lacking, include visitor viewing access, central supervisor area, and external visibility of process room operation.

Two generic schematic arrangements for OSD plants are shown in Figure 2 indicating potential locations of the key components. In these schemes, the technical area is generally on the upper floor of the facility.

The Proposed Hub Facility Arrangement

Overall Concept

A proposed hub arrangement for an OSD plant has been developed,¹ which is believed to offer advantages over conventional layouts. It can be applied for plants with outputs of 0.2 to two billion tablets a year or more, in principle, where a one or two process level approach is adopted. Its first application is considered for a 'standalone,' greenfield two process levels plant manufacturing a number of similar class products on a campaign basis. The scope and requirement for the facility includes warehousing, manufacturing, support areas, technical space, and utilities generation, and company administration offices. In addition, its scope includes a GMP pilot plant for process R&D plus small-scale manufacture for trial material.

In developing this layout arrangement, a number of key attributes and features were sought, namely:

- adopt an overall unidirectional materials flow through the plant starting with raw materials in and final product out with two (relatively) small warehouses
- maximize adjacency of materials storage with production suites

- adopt a central 'spine' in the building in both the support areas and process area around which materials flowed and the process functional rooms are located
- maximize technical space adjacency to production rooms
- provide an IBC handling and discharge level above the process and filling rooms
- integrate the R&D suite into the facility in an optimal way
- close adjacency of the QC/QA laboratory to all operations
- avoidance of a separate upper floor technical area above all of the facility footprint
- minimize under-utilized technical plant space and clean corridors
- provide a visitor viewing gallery through the plant which maximizes visibility of the process areas without entering them
- analysis of final product only with no inter-stage QA hold points, thus minimizing staging area requirements
- optimize facility space need for minimal cost

In order to achieve these aims, the facility concept was developed by adopting an overall U flow of materials and process operations around a central spine at the two building levels, and designated as the U Satellite Process Assurance Hub (U SPAH) layout - *Figure 3*. There are three geographical zones along the building within the overall 'U' flow pattern where materials handling and production operations are 'wrapped' around the central spine which provides access for people, the QC laboratory at Level 1 (ground), and people circulation at Level 2. The spine forms the hub in the production suite.

The proposed hub layout is shown in more detail in Figures 4 and 5 for each of its two levels for the production

scope of the facility which includes dispensing and IBC filling, two granulation rooms, three tablet rooms, two coater rooms, one capsule room and three filling lines plus support areas.

Material Handling and Support Services

This consists of warehousing and QC at Level 1 with offices, support areas, and technical space at Level 2. Two separate warehouses are provided for raw materials and final products respectively, with raw materials entering at one side and going into the production area and final packaged product coming out the other side of the 'U' into the final product warehouse and dispatch area. The larger raw materials warehouse extends to roof height, while the smaller final product warehouse is limited to Level 1.

The QC/QA laboratory is located in the central spine at Level 1 between these two areas to give it adjacency to sampling, production, and packaging.

Level 2 provides the main space for office staff and people circulation to the production suite by incorporating in the 'spine' corridor a clean change (gowning) area for production and R&D staff.

R&D Pilot Plant

Although the GMP 'mini' production suite pilot plant is embedded in the facility, it is located in a discrete separate zone within the building. Given that this part of the facility

is separate, but adjacent with the production facility, it is believed that such arrangement has decreased cost and increased efficiency and control in technology transfer, and such implications may lead to corporate competitive advantages.

Adjacent to the cleanroom R&D suite is the stability chamber room and R&D staff offices with visibility into the suites and a technical space on the outside wall to facilitate installation of supporting items to the processing equipment in the suite.

Production Area

The key concept developed is to 'wrap' the process rooms around the central hub in the 'spine,' and 'wrap' the technical space at Level 1 around the clean process rooms. Hence, raw materials directly enter the production area via the adjacent pre-dispensary/dispensary on one side of the building with filling and packaging on the other side of the building such that final product then directly enters the final product warehouse.

This concept provides at Level 1, the minimum clean corridor and a compact production room arrangement. Process support rooms have been allocated to the 'central hub' including a wash area, small process control lab room, supervisor office, and storeroom.

The operational concept is that IBCs are filled in the dispensary and then taken via the lift in the production area

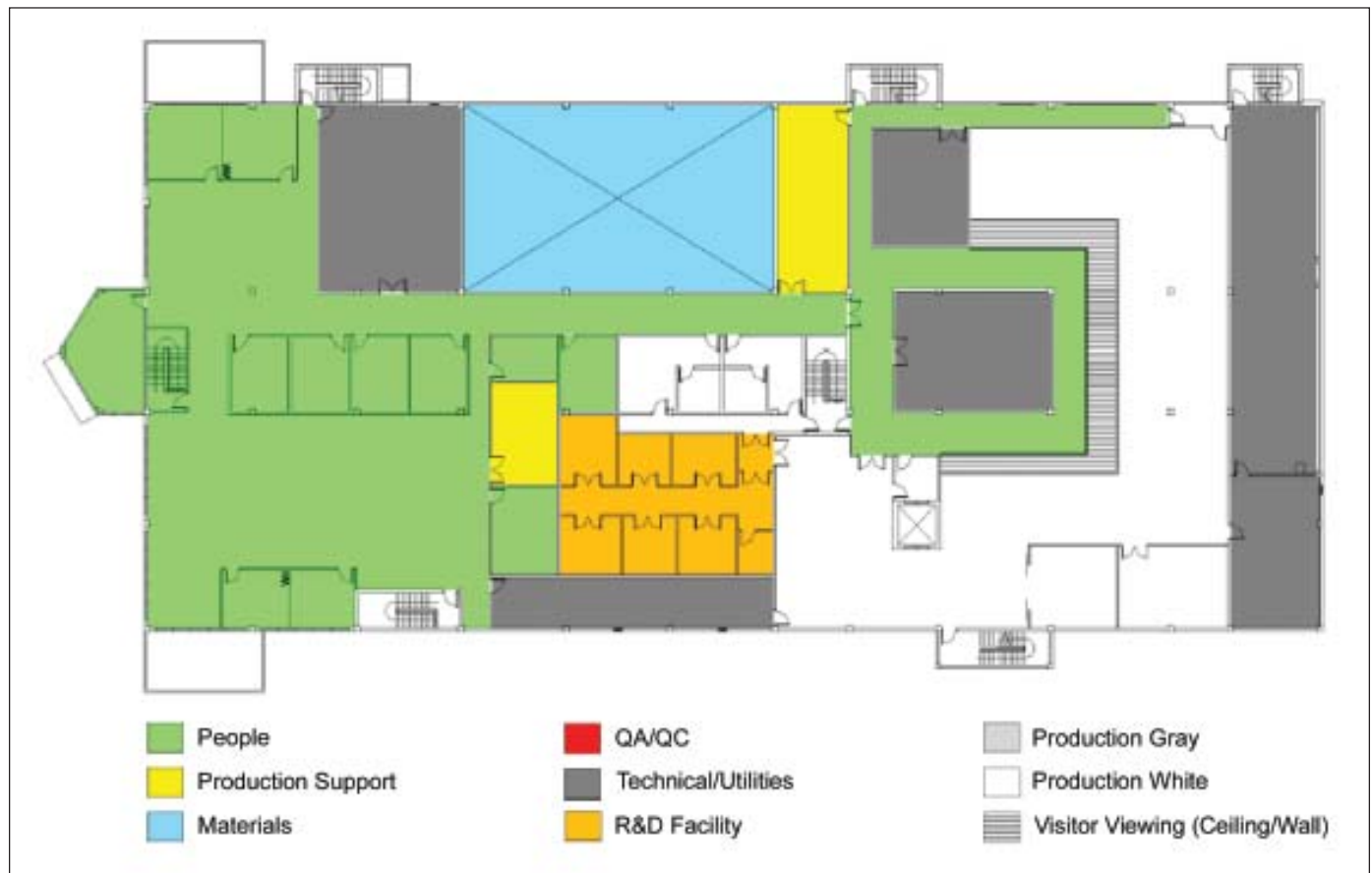


Figure 5. Upper floor (Level 2) U SPAH facility layout.

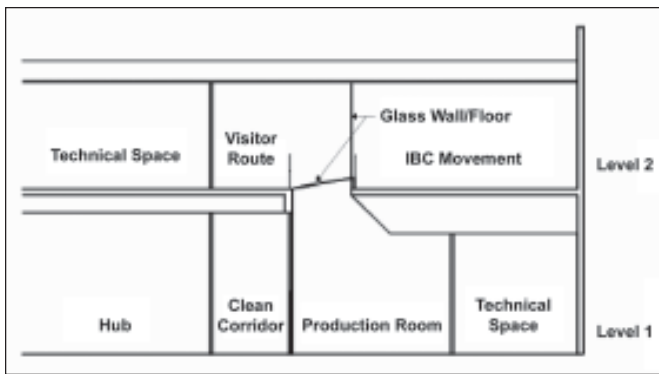


Figure 6. Visitor viewing gallery concept.

for blending at Level 2 and charging to the various equipment items below. Different IBCs are then filled with process material after each unit operation in the various process rooms at Level 1. Finally, tablet IBCs are filled with tablets and then fed from Level 2 to the filling machines below. The usage of the second floor IBC discharge minimizes the plant footprint, which was a key requirement.

Within this 'U' concept, the number and size of all rooms can be adjusted to suit the amount and size of the equipment. The surrounding technical space has in it support equipment for the production equipment such as coater air handling units, together with pipework, cabling, and ducts. The filling rooms are accessed off the clean corridor extension from the hub area.

Level 2 consists of the IBC handling/discharge station area around the 'black' central hub. The IBC handling area consists of lift access, closed IBC discharge stations to the floor below, IBC blender room and IBC washroom.

Since all operations are nominally closed, and since the products are nominated to be of the same activity class, then it is not considered necessary to segregate each IBC discharge station in its own room, but a partial height barrier and different time discharge procedures could be used.

Central Hub

We believe the central hub area offers a number of advantages. At Level 1, it provides a central location for common functions. At Level 2, it provides a central area adjacent to and above the cleanrooms in which to locate their AHU plant in a space efficient way, and it allows circulation around the clean area for personnel in factory 'black' clothing. In this central hub arrangement, a viewing gallery as indicated in the partial building cross section can be provided in the facility - *Figure 6*. In this arrangement, visitors and company staff can have un-precedented direct visual access into most of the production rooms below and across into the IBC handling area via transparent material ceiling/walls. A control and information room also can be located at Level 2.

This is an advantageous arrangement to companies who deem accessible visitor viewing into production operations a good feature to support company image and sales.

Utility Plant

The green field site facility necessitates the need for basic utility generation equipment and this equipment has been located at Levels 1 and 2 at the end of the building strategically adjacent to the technical space for cost minimization. These include chillers, air compressors, hot water system, process water, purified water, and electrical MCC room.

Believed Advantages of U SPAH Layout Efficient Space Utilization and Cost Savings

A key aim of the project was to develop a compliant lowest cost 'lean' plant design incorporating all of the components many manufacturers could need in their facility and operation. Cost reductions can be considered both in lower overall facility floor area for the same production output, and the lower area of the high cost clean areas for production.

A preliminary comparison of this facility against other designs has been carried out using a number of criteria. In order to attempt to provide a numerical comparison with other production facilities, we have normalized the new

SPAH vs. Conventional Facility Features		
SPAH Feature	Benefit	Conventional
Control hub overlooking production suites	For monitoring production processes for safety, compliance, quality	Usually not available
Tech corridor wrap around production suites along perimeter of plant	Non-intrusive maintenance of thru-the-wall process equipment	Usually not wrapped around
Viewing gallery	Non-intrusive visitor viewing	Usually not available
Uni-directional U-shaped layout of production suites according to process flow	More efficient and ergonomic operations	Usually not in a compact U-shaped flow
QC labs in close proximity to production suites	Speeds up QA time	Usually not in close proximity
Separate raw materials and finished goods loading areas	Eliminate mix-ups	Usually shared areas
One cost effective security Hub (concentration) at the entrance monitoring both material and people flow	Better and cost effective monitoring of people and material flow	Material and people flow entrances and exit are not in close proximity to facilitate one security hub
R&D pilot lab well embedded and integrated with the production facility in single building	Facilitate cost, compliance and performance of technology transfer from process lab to production	R&D pilot lab unavailable or not well embedded and integrated with the production building

Table B. Comparative area requirements - U SPAH vs. conventional facilities.

facility by taking out area allocated to administration and R&D area since these are specific to this facility. Comparative values are given in Table A, where we have included two SPAH sizes, one for 150-600MM tablets a year for the production scope given and another estimated for two billion tablets a year containing two dispensaries, two blenders, two granulators, four compression stages, two coaters, one capsuler, and four filling lines.

It can be seen that the area ratio profile generally follows the same shape for all plants. However, it can be seen that the SPAH layout differs to the benchmark and the other plants in that it appears to have a distinctly lower black technical space percentage.

As stated earlier, due to the variations in equipment numbers and plant weekly operation times, normalizing facility area to output is difficult to judge, but from the Table A data, at least a 20% reduction in area appears achievable overall, which could provide significant savings when fully serviced facilities typically cost \$3000-5000/m² to construct.

We believe the lower white circulation area can be attributed to the 'loop' white corridor in the process area and the lower black technical area percentage can be attributed to the absence of a space inefficient upper floor technical area for the ACMV plant since this has been located centrally in the 'hub.' These two items result in reductions in facility floor area and consequently provide capital and operating costs savings compared to conventional designs.

GMP and Technology Transfer Considerations

While all qualified OSD plants in production meet GMP requirements, the degree of attainment of GMP objectives above "basic" levels can vary from plant to plant. It is proposed that the new layout concept has the following intrinsic GMP advantages over conventional plant designs:

- segregated raw material and final product warehouses
- clear and separate raw materials and final product flow paths through the plant
- good access control of process personnel to production areas
- availability of the technical space behind every production room, allowing easy use of 'through the wall' technology to minimize congestion in the rooms
- convenient location for a centralized information room to facilitate the implementation of the FDA initiative
- through the wall technology is available for each production room, allowing less congested process rooms easier to clean for multi product facilities

Another wider GMP consideration is the benefit of the integration of the R&D pilot/development plant with the production plant. Even though segregation of such activities is common, integrating these two operations on one site for

many companies will allow much easier technology transfer from a regulatory and speed/cost of transfer perspective.

Operational Considerations

We propose there are operational considerations and potential benefits with the SPAH concepts as indicated in Table B. The production suite 'U' shape around the hub has a number of advantages. The transparent wall and ceiling at Level 2 allows production management outside the cleanroom areas to observe operations and provides visitor access to see the cleanroom operations with no disturbances to operations in them and the costs incurred by this. This ease and scope of direct visual access to the unit operations can facilitate supervisors or managers to identify and monitor the stage and situation of the unit operations. Such visual accessibility benefits can easily be taken advantage of for the entire life cycle of the plant operation, including equipment hook-up, qualification, validation, assurance of good practice of cleaning and manufacturing operations etc.

Also the corridor around the process rooms allows easy materials movement between each room, and with the relative near location of the IBC lift to all the suites, it allows easy logistical access to the charge points and operations at Level 2.

The central hub area at Level 1 provides a convenient strategic location for cleaning operations as well as supervisor office and in process IPC lab.

Each production room has a rear wall to the technical space, and can be easily isolated from ongoing production operations for equipment change or new equipment installation and hook up via the technical space.

Project Implementation - Standard Design

Many different dosage form facility designs have been developed to date in terms of content and layout configuration, both horizontally and vertically. Each 'new' design costs money and time to develop which can significantly affect project implementation. We believe that this compact arrangement could offer a lower cost standard design solution for many companies either as a small and strategic new product launch facility or as a production facility with the consequent capital and project cost and time savings when utilized.

Conclusion

Many different designs and sizes of OSD facilities are utilized by most pharmaceutical companies to manufacture dosage forms. In this article, we have proposed a compact layout design concept. We have made a preliminary comparison of the area and facility space usage with a number of other layout facilities. Through this comparison, it is believed that the hub design offers a smaller and lower cost facility in addition to some key GMP and operational advantages that the SPAH presents. Such advantages and feature benefits – with or without R&D operational support – could initiate the SPAH concept to become an adopted design standard for companies embarking on future production facilities or for a new drug launch facility.

References

1. USPTO Patents Publication Figure 20030230031.

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Dr. Michael P. Brocklebank has been involved in the pharmaceutical industry for more than 30 years both working initially with a major manufacturer and then for most of this time with engineering design and construction companies. Over this period, he has developed a wide knowledge of the developing trends and design principle of a number of plant types for API, biological science, and dosage process.

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