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Bringing in the New

Installing a new granulation suite is littered with technological and legislative obstacles and often has to be undertaken in existing production facilities. This article looks at how SB overcame the problems associated with this task. This is particularly difficult when there is a tight project deadline. Hence a specific window of opportunity in the planned production programme for a shutdown of the manufacturing area based on the desired stock build of products to cover the sales volumes to satisfy the markets during the installation of the system. The shutdown was limited to the time required to move every item of equipment into the area.

A survey of literature on modern pharmaceutical processing will advise that it is essential to prepare a User Requirements Specification to ensure that the design of the equipment/ system is procured and installed according to the needs of the end user. The design and fabrication of a production system with optimal process flow is then based on this document. The system can then, finally, be installed into a building.

Unfortunately, it is rarely possible to locate the system in a new building and it is usually necessary to utilise existing buildings to increase the production capacity - while still meeting stringent regulatory requirements - within a previously used production area. Needless to say, the project has to be cost-effective with as little impact on existing and continuing production processes as possible. This article describes how such a scenario was achieved at SmithKline Beecham in Crawley.

Background
SKB has manufactured solid dosage forms on its Crawley site since 1980. Within Granulation Suite 1, the original equipment was nearly 20 years old and no longer fulfilled the GMP demands or health & safety requirements. The weakest points of the existing installation were:

- poor separation of production and technical areas
- open product handling
- no automated batch recording
- minimal equipment qualification and process validation.

After an internal audit in 1996 it was decided that Crawley would remain a production facility within the worldwide SKB organisation, but existing equipment would need to be replaced.

SKB decided to carry out a design study with Aeromatic-Fielder as the company was already contracted to carry out onsite calibration and maintenance and its ability to provide a 'turnkey' supply for a whole new suite. The main requirements for the new production facility were that it must:

- allow contained product handling
- have a full separation of production and technical area
- be equipped only with qualified machines to allow a full process validation
- allow automated batch recording.

As well as these requirements the whole project had to be carried out within an existing manufacturing building without interference to continuing production. As a result of the design phase a flowsheet, installation strategy and a detailed layout was created with proposals for machine specifications and necessary ancillaries. This was presented in December 1997.

Planning

The plans were given the go-ahead in January 1998 and included the design and building of the equipment as well as

- a full factory acceptance trial duplicating the final layout (all interconnections pre-assembled to reduce installation time)
- decommissioning and Removal of the existing equipment
- planning of the necessary services and ancillaries
- co-ordination of the building works with SB
- co-ordination of services tie ins with SB projects
- control of the area as a site within a site for Health and Safety CDM Regulations.

The project was to be totally completed by 13th of November of the same year (Fig 1).

fig 1.

Process
The equipment was designed to perform a vacuum loading of the raw material into the mixer/granulator, prepare a dry mix there, add binder liquid and form granulates. These granulates are then discharged and transferred via an integrated wet mill into a fluid bed. There the product is dried, discharged afterwards via an integrated dry mill and transferred via vacuum conveying into an IBC for adding a lubricant, final blending and transport to the tablet press. The installation is equipped for water-based products only. As well as the process described above it is also possible to use the fluid bed as a spray granulator.

Layout
A fundamental requirement was the ability to use the existing production building; therefore the installation was realised in a one level concept. The maximum height was 4,50 meters. The complete equipment was executed in a 'through-the-wall' design. This means that material and personnel can access the process room out of the production area while all technical installations can be accessed from the technical area.

Leading of raw materials
The raw material is delivered in drums from the dispensing room. It is then loaded into the Mixer/ Granulator by the use of a kill-vacuum so that the bowl is evacuated to a certain vacuum level before the vacuum line is closed. The product infeed line is then opened and the raw material is sucked in. This is repeated until the complete batch is in. The whole action is automatically controlled by the PLC. To load a batch of 300 kg takes typically less than 10 minutes. Advantage of the use of kill vacuum for loading is that the risk for a filter blinding is minimised.

Granulator
The Mixer/Granulator is an Aeromatic-Fielder PMA 800. This is a bottom drive machine with a chopper on the side. In this installation the granulator is equipped with vacuum loading, sight glass and a spray lance for the introduction of the granulation liquid. A fixed location peristaltic pump from a solution container wheeled into the production room delivers this liquid.

Transfer of wet granules screening
After the granulation the wet granules are discharged via an integrated wet mill (Comill U20) directly into the fluid bed. Due to a special conveying airflow creating a vortex effect, this is possible without blocking the mill or the transfer line. Because of the optimised airflow the granules are immediately fluidised after entering the fluid bed and do not start to build up on the wall opposite the inlet valve, which is equipped with a DC motor variable speed drive to allow accurate control of the discharge rate.

Fluid bed drying
The fluid bed can also be used as a dryer. Upgrading to a spray granulator is simply a matter of introducing a spray arm. The process filter system is executed as a double shaker with cloth filters. The bottom of the hinged product container does not contain the traditional mounted sandwich of hole plate and mesh but a Niro overlap

non-sifting gillplate. The advantage of the gillplate is that it can be cleaned without disassembling. Additionally it creates - alongside the tangential air infeed in the lower plenum - a homogeneous air distribution, which results in an even temperature distribution and a reduction of lump formation. It is also possible to realise a side discharge without any moving parts in contact with the product because of the tangential air inlet (Fig 2).


fig 2.

Discharge/screening

After drying the granules are discharged via a mobile dry mill and then by vacuum transfer dumped into an IBC where the lubricant is added.

Cleaning

The complete installation is equipped for washing-in-place (wip). This means that in the technical area a Water Preparation Unit is installed where all fluids (cold water, hot water, DI-water, surfactant solution) are prepared, brought to the correct temperature, pressure and concentration and then delivered to the nozzles and spray heads inside the installation. All this is controlled and monitored by the PLC from a production recipe.

Cleaning liquid is introduced into the granulator through the same openings used for the air purge at the seals of main impeller and chopper. Operating the impeller and chopper assists the cleaning.

The fluid bed is equipped with fabric filters, which can be made wet before removal to bind dust. After removal of the filters, the fluid bed can be cleaned completely by the nozzles installed in the tower and in the lower plenum in a top down process. The complete equipment can be dried afterwards by the use of the process air of the fluid bed.

Current status

Full installation, operation and process qualification has been performed on the integrated granulation equipment. Following full process validation of an anti-viral formulation, the granulation suite is in full time operation. It is intended that a further two products will be validated for manufacture within this equipment shortly.

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