

Good Manufacturing Practice (GMP) regulations were introduced as a means to ensure that a given product is processed reliably, repeatedly, consistently, safely and to a high quality. In the pharmaceutical processing industry GMP is an essential part of the production process. Centrifuges are a major processing tool used in this industry. In the following article, Nigel Day discusses the implications that GMP has had on the design, manufacture and operation of industrial centrifuges, with a particular focus on horizontal peeler type machines.

GMP in pharmaceutical processing and its implications for centrifuges

Just prior to the start of the 2nd World War there was a serious poisoning incident in the USA. This prompted the introduction of the “Food, Drugs and Cosmetics Act 1938”, produced by the US Food and Drugs Administration (FDA). The intention of the new act was to ensure that food, drugs, cosmetics and biological products were safe for human contact. Hence the need to establish the Good Manufacturing Practice (GMP).

GMP regulations specific to the production of drugs and active pharmaceutical ingredients (API's) are covered by the FDA regulation 21CFR parts 210 & 211. Internationally, it has also been adopted and is currently covered by the European Union (EU) directive 356.

GMP regulations incorporate the keeping of records, individual's qualifications, cleanliness, sanitation, equipment verification, validation and procedural reviews.

While appearing at times rather rigid most GMP requirements are “open ended”, allowing individual manufacturers flexibility to decide for themselves how best to meet the necessary controls.

GMP is often referred to as cGMP, with the “c” indicating that the latest or “current” technologies and systems are required or being adopted. This simple prefix is important as it prevents errors or misunderstanding. For instance GMP requirements of one or two decades ago are almost certainly not acceptable by today's far higher standards.

Summary of GMP principles

The international Society of Pharmaceutical Engineers (ISPE) has succinctly summarized the underlying principles of GMP with a set of ten rules.

- Compile detailed written procedures
- Follow these procedures
- Document (record) the work
- Validate the systems and processes
- Design and build proper facilities and equipment
- Maintain the facilities and equipment
- Must be competent
- Maintain cleanliness
- Control of quality
- Audit regularly for compliance

Implications for industrial centrifuges

Having established the general principles surrounding GMP we now take a closer look at the implications they impart with specific thought to the horizontal basket filtration peeler type centrifuge.

Processing equipment such as an industrial centrifuge must be manufactured so it can successfully process a given product reliably, repeatedly, consistently, safely and to a high quality. All of which must be capable of validation.

GMP guidelines for an industrial centrifuge, especially those employed in the pharmaceutical processing industry, must ensure the following:

1. The equipment must not allow the product in question to become contaminated while being processed.
2. All contact surfaces must not allow products to become impregnated into its structure. They should also be of suitable specification, so as to prevent any chemical reaction. Lubrication products must be contained and prevented from coming into contact with the product.
3. Where ever possible the primary separation vessel should be fully enclosed for as long as possible, so as to prevent contamination of the product by the outside environment, as well as avoiding the product falling into contact with operators.
4. There needs to be provision to maintain product integrity



Image courtesy of Rouselet-Robatel UK

from batch to batch. This means the design needs to prevent the build up of product, microorganisms, pathogens, etc. To achieve this there needs to be acceptable provision to clean and/or sanitize the product contact areas. Residual product remaining on the filter media may also require removal periodically. Specific removal devices must, therefore, be incorporated.

5. The centrifuge must be operated, maintained, cleaned and inspected by adhering strictly to detailed written procedures. As indicated earlier GMP requirements are very much open to the individual's interpretation. Therefore it has fallen upon the centrifuge design engineers to generate far more specific guidelines and procedures for their own organization to follow.

A common starting point, adopted by several leading centrifuge manufacturers, is to divide the more detailed procedures into separate categories or zones. For instance there is the "product zone". This is where the product shall be processed. For a centrifuge this will need to cover the basket, feed and wash pipes, cake depth indicator mechanism, solids discharge mechanism (plough), the solid/liquid discharge arrangements and not forgetting the outer casing that encapsulates them all.

Contrary to the product zone there is also the "non-product zone". This takes into account components such as drive motors and transmission belts.

There is also a third zone, which can be easily neglected. Some manufacturers refer to this as the "splash zone". This zone is where product, following maintenance or inspection, comes into contact with such areas as the exterior of the centrifuge and equipment located on it.

Product zone

In order to prevent the accumulation of product, which could promote the development of bacteria or other microorganisms, the centrifuge engineer must pay particular attention to the following. This list is by no means exhaustive but does cover the most common aspects:

1. All surfaces need to be readily cleaned and not cause possible contamination or chemical reaction with the product being processed. The material of construction will have been decided upon prior to manufacture following consultation with the client. Any angles or tight corners must be rounded to create a smooth radius. If at all possible there should be no shelves, ledges or other projections that could hold up products within the processing area.
2. Product delivery and filtrate take-off arrangements must be free draining with no hang up areas. Solids discharge chutes or hoppers must have sufficient angle to be self-cleaning. Flowability properties of the final solid phase is frequently neglected.
3. Welded joints must be continuous [i.e. no stitch welding] and their fillets fully ground smooth to a minimum of approximately 3mm. Butt welds need to be ground and smoothed flush.
4. No permanent joints should be designed in such a manner that they minimize the level of product that can become held up or collected in recesses or crevices. Employment of threaded fasteners in the product zone must be avoided, unless it's practically impossible to do so.
5. Use of conventional bearings, lubricated with oils and grease,

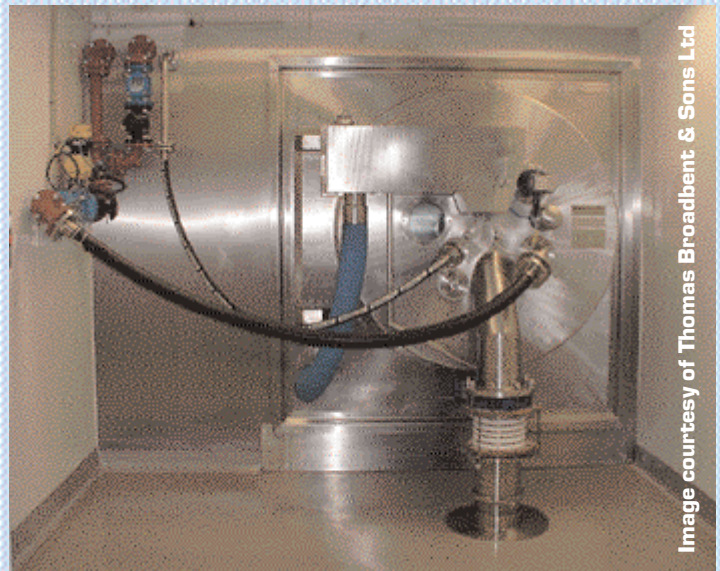


Image courtesy of Thomas Broadbent & Sons Ltd

cannot be located in the product zone. Dry bushings or product lubricated, such as PTFE, can be permitted, but must be fully considered before their incorporation.

6. Pipework and associated fittings should have been manufactured to a recognised standard such as BS4825 or DIN standard equivalent.

Given all the consideration above it is imperative that provisions are made to accommodate an automated cleansing system. Commonly referred to, as "cleaning in place" or "CIP", such a system will ensure the product zone is thoroughly cleaned. This drastically reduces the need to open the processing "vessel".

Certain products call for enhanced cleaning requirements. Here we may well find a "sanitize or steam in place" system (SIP) in addition to the CIP arrangement. The installation of either a CIP and/or SIP system requires them to be reliable, repeatable and most importantly, validatable.

Entry to the centrifuge at some stage will be necessary, if only to replace the filter media. However, the particular tasks required must have the simplest of procedures in order to minimize operator contact with the product zone, and the product zone with the environment.

Non-product zone

Requirement for the non-product zone are considerably less stringent. All exposed surfaces must be corrosion/erosion resistant or adequately treated with a protective coating.

Their overall construction must be such that it avoids retention of moisture or lubricants, while at the same time facilitating inspection, servicing and cleaning.

Splash zone

Areas of concern here are vary similar to those highlighted for the product zone. Having said that they are in general much less stringent. Material specification, surface finishes, corners, angles, and so on, can normally be of a reduced quality. Lubricated bearings are now acceptable, as long as their lubricants are compatible with the product to be processed.

Cleaning the centrifuge will be carried out manually so there is no requirement for complex cleaning systems, such as CIP or SIP.

Validation

A key aspect of GMP is the validation process. Validation is documentary evidence that provides a high level of assurance that a specific process will consistently produce a product that satisfies predetermined specification and quality.

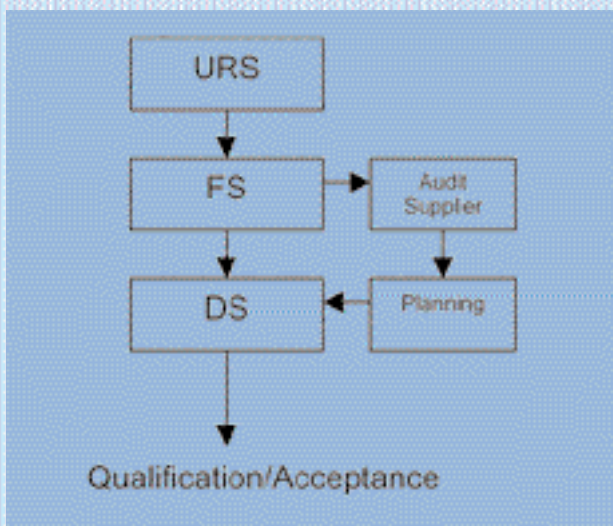
Validation procedures are rather detailed and difficult to fully explain in such a relatively short article as this. On the other hand how they interact with each other throughout the design, manufacture, installation and operation of the centrifuge is quite logical.

The figures below attempt to show how all stages of the validation process interact. The validation process can be conveniently broken down into three main categories:

- Specification
- Qualification
- Acceptance

(i) Specification

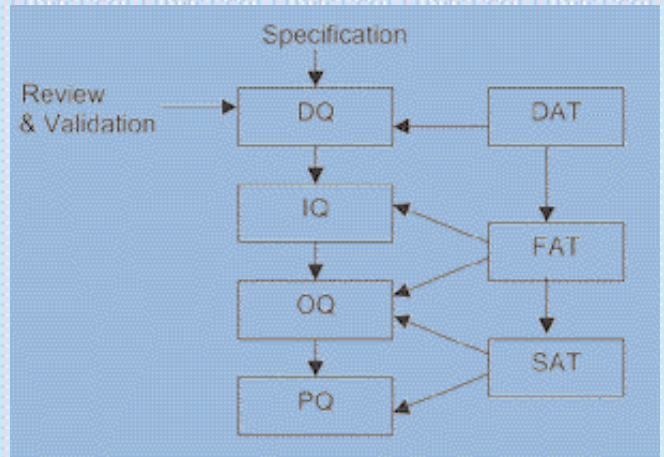
- **URS** (User Requirement Specification) - what the centrifuge is expected to do. Produced by the client.
- **FS** (Functional Specification) - what the functions of the centrifuge are and how they will comply with the URS.
- **DS** (Design Specification) - details how the FS and the URS requirements will be achieved. This normally includes mechanical, electrical and software specifications.
- **Audit Supplier** - the end user audits a supplier to ensure a quality management system is in operation that appreciates the importance of GMP.
- **Planning** - once a supplier is highlighted a comprehensive plan of action is produced. Essentially there will be an overall “project plan”, as well as a “quality plan” and a “validation plan”. Such planning will determine responsibilities, milestones and other time scales.



(ii) Qualification & acceptance

- **DQ** (Design Qualification) - verifies that the supplier has designed the centrifuge in accordance with an appropriate quality management system such as ISO9000.
- **IQ** (Installation Qualification) - verifies the centrifuge complies with current codes of practice and regulation and is in accordance with the requirements of the client.

- **OP** (Operational Qualification) - confirms the centrifuge operates fully as designed. It also confirms the requirements of the Functional Specification.
- **PQ** (Performance Qualification) - this confirms the centrifuge performs as intended. This also confirms that the URS has been successfully achieved.



Collectively the above provides documentary conformation that the centrifuge is fit for its purpose and capable of repeatedly producing the desired level of product quality.

At each stage of the qualification there is a series of “acceptance tests” to be undertaken before moving onto the next stage.

- **DAT** (Development Acceptance Tests) - client accepts the development and planning phases of the project.
- **FAT** (Factory Acceptance Tests) - prior to leaving the manufacturer’s premises the completed centrifuge is tested. The testing follows written procedures covering the function and operation of the centrifuge.
- **SAT** (Site Acceptance Tests) - once installed on the client’s premises the centrifuge undergoes another series of tests, again following detailed written procedures. It is at this point of the project that the centrifuge must demonstrate it is capable of processing the product in question, repeatedly and within the specified quality limits. Normally this test is judged following the processing of three consecutive batches.

Once all the above validation is completed a final document – the Validation Report – is required to successfully hand over the centrifuge to the care of the client.

Horizontal peeler type centrifuges

The horizontal peeler centrifuge has been around far longer than most people realize. Records show that machines that are almost 75 years old are still in operation. However, they are a long way removed from designs and specifications of today's pharmaceutical industry.

Originally they were specifically designed to fully process a product at a single speed, thus challenging the performance of the more conventional vertical batch basket centrifuge configuration, which had a considerable amount of “dead” time as it accelerated and decelerated between differing processing speeds.

While this is still the case to some extent, many more benefits can now be realized with the horizontal axis designs, especially when closely following GMP requirements.

From the images kindly provided by leading manufacturers to accompany this article, it can be seen how the following of cGMP

requirements has resulted in the configuration/design of the centrifuge becoming almost identical.

One common feature adopted by most of the manufacturers is to incorporate a “through the wall design”. Essentially this is where the centrifuge layout is divided into two, forming a “clean end” and a “dirty end”. This is achieved by a large plate that goes around the centre of the centrifuge. The centrifuge is then pushed through an opening in the wall up to the plate and sealed in place via a flexible membrane.

Compliance with GMP requirements in the pharmaceutical processing industry, especially when considering centrifuges, has resulted in virtually all new installations being of the horizontal axis type. The days of the vertical axis batch filtration centrifuges in today’s GMP orientated pharmaceutical processing sector are sadly numbered. On the other hand for those offering horizontal axis units, and continually developing their designs, the future appears very promising. ●

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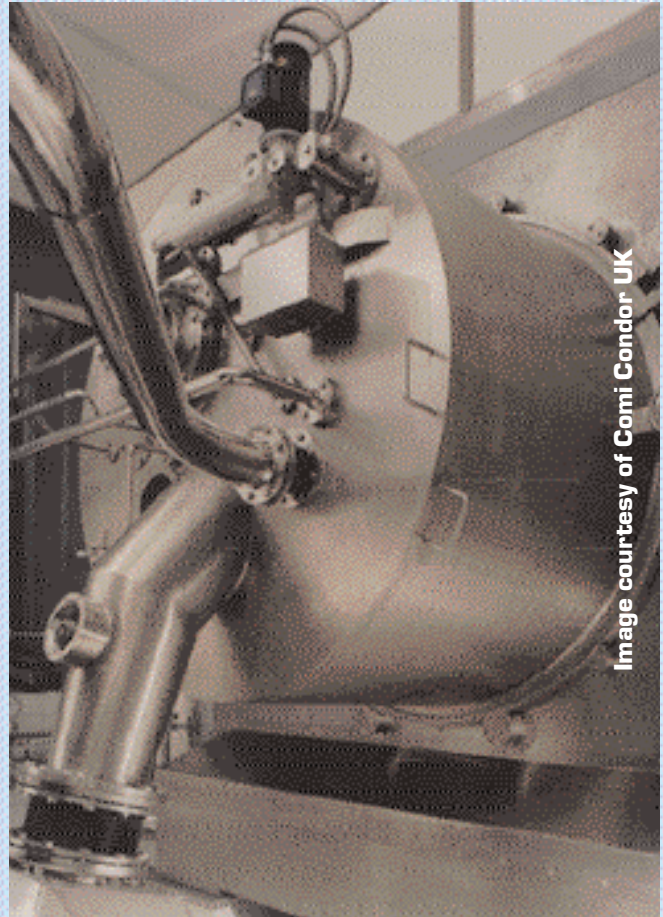


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