Since the main goal of GMP requirements is to protect the patient who uses the product, it has been decided that the material used in clinical trials involving people must be manufactured according to GMP rules. However, there is some flexibility within certain areas depending on the phase of the trial.

The reason for this flexibility is to encourage the use of the rules relevant to the phase so that product quality and patient safety are not compromised. Different authorities have published informative guides on this flexible approach; these can be summarized easily in that we have fewer rules in Phase 1 but follow the complete GMP in Phase 3.

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**Examples of flexibility while manufacturing material for clinical trials :**

Some tests commonly carried out by the quality unit may be done by other departments

The documentation from manufacturing may be complied in ways other than the batch protocol required by GMP.

Limitations for yields are more tolerant and investigations of yield variations are not expected

Validation of processes is not as widely expected as in routine GMP manufacture

Changes have to be documented but not necessarily previously approved

Complete validations of analytical methods is not expected

*(from EU's GMP Part II, Chapter 19)*

The responsibilities and assignments of the quality department

Certain situations during the manufacturing of pharmaceutical products demand additional rules related to quality issues. A good example of this is handling of the labeling.

During clinical trials it is common to test the active product as well as a **placebo**, a pharmaceutical product without active ingredient. In order to obtain correct information

from the trial, neither the doctor nor the patient is to be informed on who receives an active product or a placebo.

*Active or placebo?*

Therefore, the labeling and packaging of these products demands rigid controls! This kind of situation hence demands other labeling and packaging routines than those used in commercial manufacturing environments.

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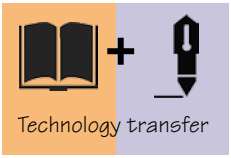
Another important factor for GMP work are all specifications that are formed and acquired during the development period. This comprises all product specifications, from the raw materials to the intermediate to the complete packed product. It also comprises the specifications for how this product is to be manufactured and what requirements are valid for the manufacturing environment and process. This is usually documented in some kind of 'development report' that is used as a basis for a great deal of quality work.




During the last years, several publications by the authorities have shown that we are getting closer to the concept of quality assurance used within other industries.

We can name as a comparison that ISO 9001 has a whole section that deals with product realization or development and that it is integrated to the quality system. The development of a product is regarded as a part of the entire quality system.

The authorities do not aim to change the basis of GMP rules and regulations, but it has been shown that there are benefits created by integrating development work, risk management issues and quality systems in a more integrated manner.

### Special requirements for sensitizing materials

Environmental monitoring

A specific area that is regulated by the GMP deals with situations related to the production of penicillin, for example or other materials that may cause allergic reactions or are toxic.

If we produce such substances we must do this in a completely separate area from other production. It is ideal to not mix this kind of manufacture with other products.

These requirements have been created since, as regards allergies, even small amounts can cause severe reactions. A pharmaceutical product aimed at relieving headaches that has been cross contaminated with penicillin is something that nobody wants to be exposed to.

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### Neat and clean

Cleaning of facilities

Material chosen for flooring, walls and ceilings should be easy to maintain clean. This means that smooth surfaces are preferred. Another important detail is that there should be enough storage space and working space. If a space or work area is crowded, the risk for messiness increases and thus the risk that we might make a mistake!

*Order and method are indispensable! All areas must be well cleaned and sometimes also sanitized.*

Imagine that you have a problem with your refrigerator's compressor. To reach it, a technician must step into your kitchen, pull out the refrigerator, identify the problem and make the repairs right in your kitchen. In the

pharmaceutical industry we often have a special plant room behind the "refrigerator" so that technicians can reach it without passing the "kitchen".

*Service and preventive maintenance are important to avoid production interruptions. We must reach machines and installations easily in order to service and maintain them.*

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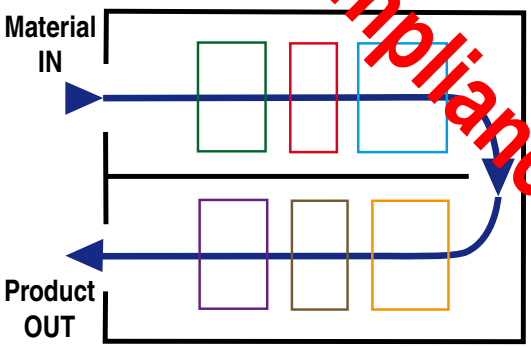
We are also expected to imagine beforehand how people and materials will move in the premises and thus adapt its design. This is one of the methods used to avoid mix-ups.




*When you build from scratch you can take into consideration the flow of materials and how people will move beforehand. In older and renovated buildings, routines must be adapted so that the risk of cross contamination or mix-up is avoided.*

Verification of the imprint

Inspection of labeling and packaging materials

Rejected labeling and packaging material

Inspection of the line, before, during and after manufacturing

Additional checks ensure that the correct labels and labeling material are available before the labeling begins. The unique information such as batch number and expiration date is added. This information is often called imprint and is carefully checked and documented.

During the labeling procedure additional checks such as random tests or scanning of each filled container are carried out.


Reconciliation of used material:

Released quantity (A) 5000

ed quantity (B) 4932

ejected quantity (C) 65

turned (D) 13

Total (B + ...) (E) 5000 5010 CALCULATING ERROR

2007-09-03

...ly if (E) is not eqal to (A)!

Calculated by : Date: 2007-09-03

Checked by : Date: 2007-09-03

*After labeling and packaging, reconciliations are done to compare the amount of material at hand, the quantity used and how much is left over. If there is too much or too little material left over additional controls are carried out since labeling material that is unaccounted for increases the risk of mix-ups.*

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## Sterile products

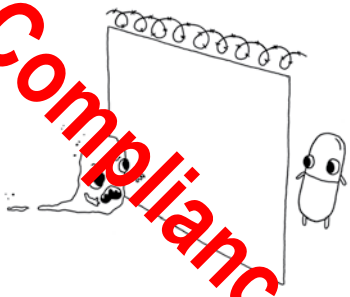
Requirements for the manufacture of sterile products

Some pharmaceutical products, for example intravenous drugs, must be sterile (sterility = lack of living microorganisms). For these products, sterilization is a separate step in the process usually carried out immediately after or during filling.

Commonly, the product is put in its container and then exposed to high pressure and heat in an autoclave (similar to a high pressure-cooker). After removing and cooling, a label or other mark is added and the container is packed in an additional pack.

Some products are sensitive to high temperatures and cannot be sterilised in this manner. These products are produced by an aseptic manufacturing technique. This demands very high hygiene standards, all equipment in contact with the product must be sterile, the personnel dressed in specific clean room clothing and the facilities and air handling systems must comply with high hygiene standards.

*It is not just the clothing that is important but also our actions while inside the clean room, i.e. we must move slowly and carefully and avoid conversation or other activities that might generate unwanted particles.*



*An important concept for manufacturing sterile products is to create an effective barrier between the product and everything that might threat its sterility.*

The high demands on sterile products are applicable to the entire chain of quality. The requirements for handling and storing raw materials are higher and the personnel must have special training to understand the connection between hygiene and quality of product.

The equipment must be made of materials that can be sterilized, the facilities must be divided into areas with clothing change requirements between each one and the environmental conditions must be measured and documented much more frequently than for non-sterile products.

When sterile products are manufactured by aseptic technique, data from the environment in the production area is added to the evaluation made before the product is released.

Assessment of environmental conditions

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