Management of GMP Projects and New Factory Buildings

A summary of the GMP DIALOGUE at the GMP-BERATER Tage 2018

8 min reading time

by Sabine Paris, PhD

At the GMP BERATER Days in October 2018, the GMP Dialogue on "Management of GMP Projects and New Factory Buildings" took place. Questions about the topic were asked by the participants and answered by the experts Dr Helmut Bender, Boehringer Ingelheim, and GMP inspector Dr Daniel Müller and in a lively discussion.

The planning and management of new production sites is becoming more complex. In addition to high flexibility and scalability, cost estimates must be adhered to - with the best possible quality. How do you keep this under control? Where are the pitfalls? How do you organize projects today?

At what point in time should the competent supervisory authority be involved in the planning of new buildings as well as in the conversion or alteration of production rooms?

New buildings of pharmaceutical production sites can only be used for routine operations after official GMP inspection and issue of the manufacturing authorization. As a rule, in Germany, the authority must decide on an application for a manufacturing authorization within three months. However, this period will be extended accordingly by missing or subsequent documents. It makes sense and is necessary to involve the authorities at an early stage in planning and execution. In any case, a concrete concept should already have been worked out before the initial contact with the authority. GMP inspectors should not act in an advisory capacity.

In the case of major projects, it may make sense for the authority to carry out the inspection in two stages: First of all, the inspection of the buildings and equipment takes place as soon as they are qualified. A little later, after the first validation batches (or PQ batches) have been produced, the second inspection can take place with a focus on the transferred processes and products. The respective competent authority decides on the concrete procedure.

The Spanish authorities were involved in the construction of a new production facility for Boehringer Ingelheim Spain near Barcelona two months before the foundation stone was laid. In this case, the deadline could be so short because the basic material and personnel flow is virtually identical to that of an existing production site in Ingelheim that has already been accepted by the authorities.

In the case of conversions or changes to the existing structure, the involvement of the authorities and also the obligation to carry out a GMP inspection depend on the type and scope of the project. If, for example, a cleaning room was converted into an equipment store, then this is not a change that the authority would need to know before implementation or would even entail a change in the manufacturing authorization. Also an extension by a second packaging line, which is identical with an already existing one (provided that products and activities do not change!), often does not require a new, extended manufacturing authorization and thus also no GMP inspection. However, changes of this magnitude should be notified to the authority before completion.

Open and prompt communication with the authorities is important. The authority should be informed in good time of any planned conversion measures. It must also be clear which data the authority may wish to see, e.g. prior description, planned procedure for room qualification.

In the case of special product groups, e.g. ATMPs, vaccines, genetically engineered drugs and active substances, the German supervisory authority issues the manufacturing authorisation "in consultation" with the competent higher federal authority (BOB) that is responsible for issuing the marketing authorization. As a rule, a BOB expert also takes part in the GMP inspection. Particularly in these cases, it may make sense for the competent GMP authority to carry out an initial partial inspection alone, without the BOB, in order to first examine the basic GMP aspects (e.g. room and plant qualification). In a second inspection, together with the BOB, the processes can be concentrated on. In the meantime, initial validation batches could also be produced (possibly on hold, as the manufacturing authorization has not yet been issued), the results of which would then be available for this second inspection and would be of particular interest to the BOB experts.

How can other authorities be involved, e.g. fire protection authorities, authorities responsible for infection control, genetic engineering laws or immission control?

The GMP authorities are not responsible for monitoring other aspects such as fire or immission protection. This may lead to conflicting requirements. For example, the GMP inspector demands that washbasins should not be in the clean area, and the infection control authority demands exactly the opposite. At the regional council Tübingen (Germany), representatives of all departments (among others) involved in the construction of a new pharmaceutical factory meet regularly. In this way, jointly coordinated solutions can be found.

Every eight weeks, the Spanish fire safety authorities visit the construction site of the new Boehringer Ingelheim factory and thus participate directly in the further development of the topic. In addition, the internal requirements for fire protection are very high and in some cases even stricter than the legal requirements.

New building in Spain: How could the teams in Germany and Spain be brought together? How does the cooperation take place in concrete terms (project model, technology)?

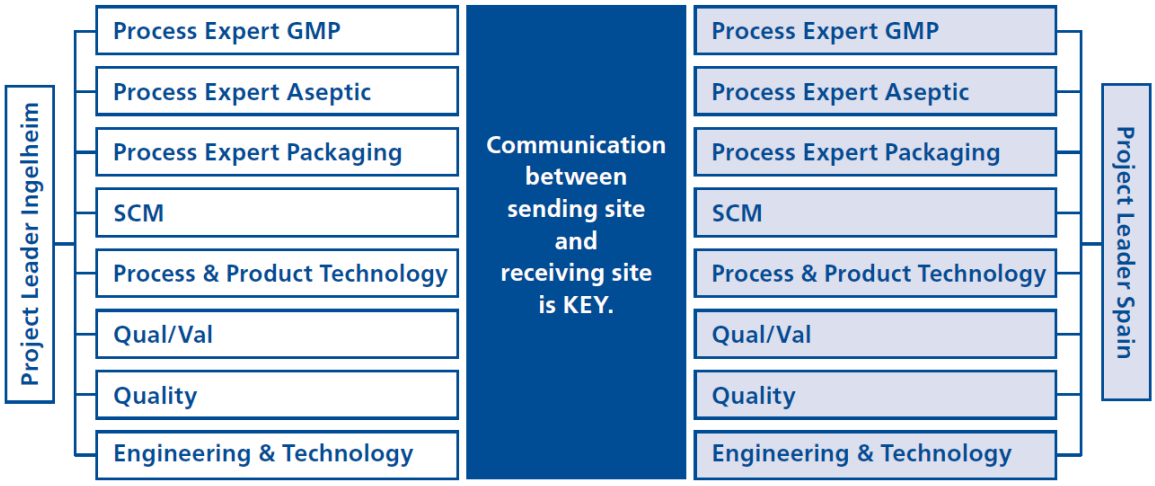
Boehringer Ingelheim has created a mirrored team structure. In Spain, the team was set up exactly like the existing team in Ingelheim.

The employees responsible for the individual topics work together directly. For example, two engineers from Spain and two from Ingelheim met every two weeks with the suppliers of the technology and sat down with the local engineers. In each case, the delivery status was monitored together.

The validation master plan was also drawn up jointly by the two qualification teams in Spain. The validation strategy for the filling and packaging line has been defined. Important questions that flowed in were: What experiences have you had in Ingelheim? What can we learn from this? What can/should we do differently?

As part of the planning process, the Spanish packaging team identified a process improvement that will now be implemented not only in Spain but also in Ingelheim. The project work is very concrete and target-oriented.

The transfer team meets every four weeks via Skype or video conference.



How did the four-week delay in the FAT come about in Spain?

The four-week delay at the factory acceptance test (FAT) was ultimately due to the changed prioritisation of the project by the equipment constructor. Commitments made by the supplier were not kept, as other projects were given priority. The situation did not improve until a personal relationship had been established with the managing director. In the end, the delay could be compensated for by subsequently carrying out parts of the FAT in Spain. The supplier sent three employees to Spain to do this.

Other participants also confirmed that it is important to build personal relationships with your suppliers - also at the employee level - in order for collaboration to work and delivery to schedule.

Small and medium-sized pharmaceutical companies often work more efficiently with smaller suppliers, who are more flexible and would also be willing to make special products that are not of interest to the large suppliers.

How, when and with what system do you train your employees in Spain?

Employee training starts immediately after recruitment. Approximately 140 employees have already been hired for the new production facility. There is a training manager for training management. A computer-aided training system (LOS) is used to assign training courses to employees.

New Spanish employees are also currently working in Ingelheim to gain practical experience and get in touch with their future technology in advance.

Documentation of business processes: What makes sense? What does the agency want to see?

A structured and comprehensible documentation of business processes is meaningful and indispensable for the company itself. However, there are no concrete GMP regulations. As a rule, the supervisory authority does not look at the complete documentation, but is interested in detailed processes and the actual results, e.g.: Are the employees working on a transferred product trained? However, the regulatory framework does not specify how early training should be started.

As part of a GMP inspection, the authority shall also review the validation of computerised systems, in particular the handling of data and the granting of rights. It looks at how the processes are mapped and the IT structure behind them.

Would the authority like to have its own access to company data?

The authority may inspect all documents held by the firms. As a rule, however, it does not want its own access to electronic documents. The manufacturing documentation may be completely electronic. Certain documents or even screenshots of the batch documentation may be printed out for the authority.

It does not make sense to take data (e.g. extensive batch data, results of in-process controls) with you on a data carrier and to evaluate them in the authority, because the data is usually not readable at all without the corresponding software systems. Companies are also currently discussing whether and how important data/results can/should be extracted in standardized formats.

GMP inspectors usually take a closer look at the systems on site. An official inspection can only ever be a random sample. Here it is particularly important to see how good the know-how of the employees is and whether they work in compliance with GMP.

Conclusion:

- It makes sense and is necessary to involve the supervisory authorities at an early stage in planning and implementation. In any case, a concrete concept should already have been worked out before the initial contact with the authority.
- The involvement of other responsible authorities (e.g. for fire protection) is important and sensible.
- A mirrored team structure has proven to be ideal for a new construction project for a product to be transferred.
- A good, personal relationship with the suppliers is an important building block for a successful project.
- A structured and comprehensible documentation of business processes is meaningful and indispensable for the company itself.
- As a rule, the supervisory authority does not consider the complete documentation, but is interested in detailed processes, actual results and GMP-compliant behaviour of employees. Direct official access to electronic data is generally not required.

Author:

Sabine Paris, PhD
Editorial Department
Maas & Peither AG – GMP Publishing
E-Mail: sabine.paris@gmp-publishing.com

