Introduction of the European Union Directive 2001/20/EC in May 2004 (1) not only provided regulation on the conduct of clinical trials but also lay down standards for the manufacture, import, and labeling of investigational medicinal products (IMPs). The directive is intended to ensure that quality assurance is an integral part of every manufacturing process that falls under its auspices. The directive also requires EU member states to set up inspection groups that monitor the use of good manufacturing practices (GMPs) for IMPs, and it makes no distinction between academic institutions and commercial pharmaceutical operations.

Annex 13 of the European Commission rules governing medical products, which details specific requirements for the manufacture of IMPs, states that

The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk — and that the results of clinical trials are unaffected by inadequate safety, quality, or efficacy arising from unsatisfactory manufacture. Equally it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials — and that changes during the development of an investigational medicinal product are adequately documented and justified. (2)

It further states that, “production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production, but premises and equipment are expected to be validated.” That recognizes the developing nature of such products but attempts to minimize the effects of variation in quality that arise from inconsistent performance of facilities and equipment used for their manufacture.

A Case Study: In developing the National Biomanufacturing Centre (NBC) at Speke in Liverpool, UK, we have recognized the requirements of that directive and from the beginning attempted to “build in” compliance — rather than trying to “add it on” at a project’s completion. Demonstrating compliance requires documented evidence that facilities and equipment perform consistently as intended and that design has developed in a structured manner and been evaluated as the project progressed. So to begin, we needed to develop a quality plan that governed how we would document and control our design.

In many projects, the procedures for such a plan can be transferred from existing documents in other parts of the organization. But the NBC project presented an opportunity to develop a quality plan “from the ground up,” with the individuals involved bringing their knowledge and experience to implement modern concepts of quality without the obstacles of “sacred cows” and long-established procedures that can sometimes get in the way of such efforts in established organizations.

Planning Ahead: A quality plan grows as a project progresses into operation, but from the start the following must be addressed and defined:

• organizational structure and responsibilities for the project
• standards and categories of documents that will be used
• control of the documents generated
• management of change
• control of deviation and nonconformance
• validation and qualification
• training.
Achieving compliance by design involves working closely across functional groups within an organization. Most notable of those will be manufacturing, quality, and engineering. A good working relationship with the design and purchasing groups is also needed, whether they are contractors or in-house. Individuals within each group must clearly understand their roles and must be given adequate time and resources to devote to the project. To work efficiently, they must be empowered to make decisions on behalf of their functional groups rather than simply to carry messages back and forth.

Demonstrating compliance requires documented evidence that facilities and equipment perform consistently as intended — in other words, validation. An early step in achieving compliance is therefore to draft a validation master plan (VMP). Suggested structure of a VMP is given in the EC rules on medicinal products, along with the constituent parts of validation (3). Practical guidance can be found in publications by pharmaceutical industry organizations such as ISPE (4). A VMP encompasses all validation activities and may provide detailed information or refer to other established procedures and documents within the organization.

**Validation and Qualification**

To progress from a project concept to a manufacturing facility with full support activities, a designer must understand what the users’ requirements will be for the facilities and equipment. In the context of compliance, the “users” should not be regarded as merely the operators or particular functional groups, but the organization as a whole. For example, the manufacturing group will have certain requirements for equipment operating characteristics, the engineering group will require certain information to correctly maintain it for consistency, the validation group will require testing and documentation to support its qualification efforts, and quality control may require specific access points to allow representative sampling. Understanding all those requirements — and more — at an early stage will influence the schedule of design and construction.

**Design Qualification (DQ):** Very likely, the designer(s) will need to add considerable engineering and architectural detail to specifications for dedicated systems to allow constructors and suppliers to evaluate customer needs. That will necessitate a cycle of review involving the client’s functional groups, the designer, and each supplier or constructor.

Finalizing the design should culminate in a qualification step to ensure that none of the original user requirements were lost in translation and that the design’s characteristics will be GMP compliant. All the functional groups mentioned should contribute to that qualification effort in determining whether a design is sound.

Designers and suppliers should be present to justify their work at formal DQ reviews. With purpose-built systems, some accommodation of function and GMP compliance may be necessary. **DQ presents an early opportunity to determine whether all parties see both function and compliance as accommodated and to identify validation testing, routine monitoring, and other procedural measures needed for ensuring that compliance is maintained.**

For example, a manufacturing facility **DQ should include an assessment for adequate segregation of different activities (manufacturing and otherwise) and adequate provisions for segregation of materials, personnel, and waste.**

**Engineering Systems:** Not every engineering system needs to be validated. Early identification of those that do not allows better management of existing resources to evaluate those that do. Clearly validating an office air handling unit or waste compactor does not contribute to assuring the integrity and consistency of products manufactured. But not every system’s impact (or lack thereof) is so obvious. A documented review of all engineering systems by the validation team against established criteria helps determine which systems are appropriate to undergo validation. Consideration should be given to include systems for validation that are in product contact, that produce an ingredient, or that monitor or control a device. The ISPE has proposed a process by which such an assessment should take place (4).

**Vendor Assistance:** Suppliers of specialty equipment for the pharmaceutical industry are likely to be familiar with the requirements of validation and GMP. Their knowledge, expertise, and familiarity with their own equipment should not be overlooked in designing a validation program. Once the requirements for qualification testing and documentation of a system and its component parts have been determined, the supplier’s expertise should be used in determining how that system can best be demonstrated to operate correctly and consistently.

Many manufacturers will be familiar with this process and offer standard documentation packages that need little or no tailoring to each customer’s specific needs. Such packages may not, however, be provided as standard. It is thus important that any procurement documents reflect user requirements.
for documentation and testing in support of compliance. Functional groups represented on the validation team should review test protocols against sound scientific and engineering principles, using their GMP knowledge to establish whether acceptable standards of documentation and meaningful challenges to each system have been proposed. That should also apply to any proposed certification.

**Installation and Operational Qualification (IQ and OQ):** Determining the scope of validation testing before equipment arrives on site provides the chance to conduct some or all of that testing on the supplier’s premises. Most likely, any problems encountered (in meeting predetermined acceptance criteria) will be easier and quicker to rectify if a system is still in the workshop. Validation teams should assess the usefulness of factory acceptance testing (FAT) as a contribution toward validation. All testing should be conducted according to the agreed-upon test protocols and witnessed by a validation team representative, taking into account what effects disassembly and shipment will have on the validity of the results. Consideration should also be given to the effects of other systems (such as purified water supply) when connected at the site.

Conducting effective IQ and OQ (1) can entail considerable time and resources. A traditional approach — an engineering contractor handing a system over to a validation group for appropriate testing — adds time to a project, in some cases doubling the activity because many of the same tests and checks are conducted by the contractor during installation and commissioning. Designing your validation program to integrate those tests and checks can create significant savings. Just as FAT can be seen as an opportunity to capture some IQ/OQ testing before receipt, site acceptance testing (SAT) provides an opportunity to ensure that systems meet qualification requirements while supplier representatives are there to advise or rectify any problems encountered.

Although vendors may conduct similar tests and checks during installation to those proposed at qualification, what may differ is the standard of documentation and controls on that testing. A validation team needs to provide clearly documented guidance on document content and controls of test execution if the data generated are to be of use. Careful integration of an installation and commission schedule with a qualification programme can significant reduce the time/cost of a project’s construction phase.

**Management of Change:** All the measures stated here for ensuring compliance will be meaningless if a system design changes without the knowledge of the validation team. Decisions made on the adequacy of a design (and subsequent testing) may be invalidated by changes in components, materials specifications, system configuration, and so on. All parties involved in design, procurement, installation, and validation of systems must be aware of changes and how they affect compliance. Documented records of all changes, including the necessary actions that resulted with details of their completion, should be implemented after DQ.

**Performance Qualification (PQ):** Establishing monitoring programs will ensure that a manufacturing facility remains compliant in the quality of its cleanrooms and critical utilities such as purified water systems. PQ of the systems involved offers an opportunity to evaluate their ability to perform consistently using enhanced sampling plans and product analyses. Guidance for acceptable specifications can be found in the pharmacopoeias and in the EU medicinal products rules for manufacturing environments (4). Review of trended data over time will not only show where the PQ requirements have been met, but also identify the areas most challenging to compliance. Using such data, appropriate sampling points and analyses can be determined for effective monitoring programs during routine manufacturing.

As your validation program progresses into OQ and PQ, it is likely that your quality plan will need to be developed to accommodate new activities such as inspection, sampling, and laboratory analysis. New categories of documents will be created (e.g., batch records to allow placebo runs of routine manufacturing). SOPs will need expanding to support the needs of PQ activity — as will the related training of personnel.

**Compliant from the Start**

Regulatory compliance can be part of a new facility design and construction project. Early definition of quality requirements during the conceptual phase — and an understanding by all parties involved — will help prevent lost opportunities for gathering essential data and preventing excessive rework. Efficient and detailed planning of procurement and construction activities integrated with validation requirements will help reduce the total time of a project and help your organization make the best use of test data and certifications often gathered for commercial reasons alone.

**REFERENCES**


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