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An edited version of this  
article was published in  
Bioprocess International,  
June 2005



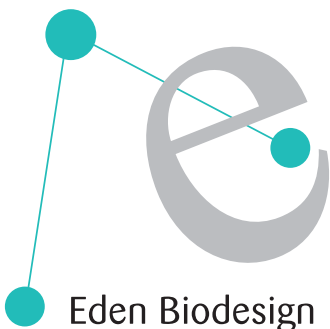
# Compliance by Design

**T**he introduction of EU Directive 2001/20/EC in May 2004 has not only provided regulation on the conducting of clinical trials but also lays down standards for the manufacture, import and labelling of investigational medicinal product (IMP) and ensures that quality assurance is an integral part of the manufacturing process. The directive also requires member states to set up inspection groups to monitor the use of good manufacturing practice (GMP) for IMPs and makes no distinction between academic institutions and commercial pharmaceutical operations.

Annex 13 of the The Rules Governing Medicinal Products in The European

Community, Volume IV which gives the 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



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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.”

Annex 13 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.”

This recognises the developing nature of the products but tries to minimise the impact of variation in quality arising from inconsistent performance of the facilities and equipment used for its manufacture.

The development of the National Biomanufacturing Centre (NBC) at Speke in Liverpool UK has recognised the requirements of the directive and from its beginning has attempted to “build in” compliance rather than try to “add on” at its completion.

Demonstrating compliance requires documented evidence that the facilities and equipment perform consistently as intended, that design has developed in a structured way and been evaluated during its progression. This meant that to begin we needed to develop a quality plan to govern how we would document and control the design. In the case of many projects the procedures for the plan can be transferred from existing documents in other parts of the organisation.

The NBC project has presented the opportunity to develop the quality plan from the ground up with individuals bringing their knowledge and experience to implement modern concepts of quality without the hang ups of “sacred cows” and long established procedure sometimes found in long established organisations.

The quality plan will grow as the project progresses into operation but from the start there will need to be definition of:

- The organisational structure and responsibilities for the project
- The standards and categories of documents that will be used
- The control of the documents generated
- Management of change
- Control of deviation and non conformance
- Validation and qualification
- Training

Achieving compliance by design will involve close working across a number of functional groups within an organisation. Most notable of these will be Manufacturing, Quality and Engineering. There will also need to a good working relationship with the design and purchasing groups whether these are part of the same organisation or contractors. Individuals within these groups will need to clearly understand their roles and have been given adequate time and resources to devote to the project and so they can work efficiently, be empowered to make decisions on behalf of their functional groups rather than to carry messages.

Demonstrating compliance requires documented evidence that the facilities

and equipment perform consistently as intended and this essentially means validation. An early step in achieving compliance is therefore to draft the Validation Master Plan (VMP). The structure for the VMP and constituent parts of validation are given in Annex 15 of The Rules Governing Medicinal Products in The European Community, Volume IV and practical guidance can be found in publications by the pharmaceutical industry organisations such as ISPE<sup>1</sup>. The VMP will encompass all validation activities and may give information in detail or refer to established procedures within the organisation.

To move from the project concept to a manufacturing facility with its support activities, the designer must understand what the user’s requirements are for the project, its facilities and equipment. In the context of meeting compliance the user should not be regarded as the operator or one functional group but the organisation in total. While Manufacturing will have requirements for equipment operating characteristics, Engineering will require information to correctly maintain it for consistency, Validation will require testing and documentation to support qualification, Quality Control may require specific access points to allow representative sampling. Understanding all the requirements at an early stage will have influence on the schedule of design and construction. It is likely that the designer will need to add considerable engineering/architectural detail to these specifications for bespoke systems to allow a constructor or supplier to evaluate the customer’s needs. This will result in a cycle of review between the client’s functional groups, designer and supplier/constructor. Finalisation of the design should culminate in its

qualification to ensure that none of the original user's requirements have been lost in the translation of the design and that the characteristics will be satisfactory for GMP. All the functional groups mentioned should contribute to this qualification and determine if the design is sound.

It is advantageous for the designer and suppliers to be present at the formal design qualification (DQ) review to justify their design. Where the system is purpose built there may need to be some accommodation of function and GMP compliance. The DQ is an early opportunity to determine whether both function and compliance are regarded as accommodated by all parties and identify any validation testing, routine monitoring or other procedural measures that need to be in place to ensure compliance is maintained. The DQ process will need to vary according to the system or facility evaluated for example the manufacturing facility should include an assessment that adequate segregation of different manufacturing activities and other activities exists and that there is adequate provisions for segregation of materials, personnel and waste.

Not every engineering system will need to be validated and determining which ones do not will allow better management of existing resources to evaluate those that do. There is clearly no advantage to validating the office air handling unit or the waste compactor to assure the integrity and consistency of the products manufactured. However, not every system's impact may be so clear cut. A documented review of all the engineering systems by the validation team against established criteria will help determine which systems it is appropriate to subject to the validation



process. Considerations should be given to including systems for validation that are in product contact, produce an ingredient or are monitoring or controlling device. The ISPE has proposed a process by which this assessment should take place<sup>1</sup>.

To understand what information is needed from the engineering systems to demonstrate compliance firm boundaries need to be established and an understanding is required as to the function of its component parts. Establishing system boundaries will be relatively straight forward for discrete systems supplied by one vendor that only require an electrical connection. Determining a discrete boundary may be more complex where the system is connected to water systems, other utilities or clean in place (CIP) systems. Identifying discrete boundaries between the systems will ensure that all critical components are evaluated as to their function and those that require calibration and maintenance are not omitted from the planned maintenance programmes. Once the boundaries for a system have been established all the components within the system can then

be evaluated for their impact on the quality of any resulting product. Components such as instruments, control valves and those in product contact can be identified and what operational testing or certification of construction or calibration will be required to ensure compliance. Such a system of identification of critical components within a system has been proposed by the ISPE<sup>1</sup>.

Suppliers of specialist 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 the validation programme. Once it has been established what qualification testing and documentation is required of the component parts of the system, the supplier's expertise should be used to determine how best the system can be demonstrated to operate correctly and consistently. Many of the manufacturers will be familiar with this process and have standard documentation packages that need little or no tailoring to your specific needs. These packages may not, however, be provided as standard and it is therefore important that any procurement documents should reflect the user's requirements in terms of what documentation and testing will be required to support compliance as should involvement in design qualification. The functional groups within the validation team should review the test protocols against sound scientific and engineering principles and using their knowledge of GMP to establish if meaningful challenges to the system and acceptable standards of documentation have been proposed.

This should also apply to any certification proposed.

Determining the scope of validation testing before the equipment arrives at site gives the opportunity to conduct some or all of it at the supplier's premises. It is likely that any problems encountered in the system meeting the predetermined acceptance criteria will be easier and quicker to rectify if still in the workshop than at the site.

The usefulness of Factory Acceptance Testing (FAT) as a contribution towards validation will need to be assessed by the validation team. Any testing will need to be conducted to the pre-agreed test protocols, witnessed by a validation team representative and consideration given to what any disassembly and shipment will have on the validity of the results. Consideration should also be given to the impact any other systems such as purified water supply may have when connected at the site and therefore whether the results will be meaningful.

The need to conduct an effective IQ and OQ as stated in Annex 15 of The Rules Governing Medicinal Products in The European Community, Volume IV can entail considerable time and resources. The traditional approach of engineering contractor handing over the system to the validation group for appropriate testing lengthens the project and in some cases doubles the activity as many of the tests/checks will have been conducted during installation and commissioning. Designing the validation programme so as to integrate the engineering contractor's tests and checks can have significant saving in time and cost. Just as the FAT can be seen as an opportunity to capture some of the IQ/OQ testing before receipt then Site Acceptance Testing is a chance to

ensure the systems meet qualification requirements while the suppliers representatives are there to advise on or rectify any problems encountered. Although the supplier may conduct similar tests/check during installation to those proposed at qualification what may differ is the standard of documentation and controls on the testing. The validation team need to give clear documented guidance on document content and controls on test execution if the data generated is to be of use. Careful integration of the installation and commission schedule with the qualification programme can result in significant reductions in the construction phase of the project.

All the measures stated in this process to ensure compliance will be meaningless if the design of the system has changed without the knowledge of the validation team. Decisions made on the adequacy of the design and the subsequent testing may be invalidated if there have been changes in components, material specification, system configuration, etc. All parties involved in the design, procurement, installation and validation of the systems need to be aware of implications of change on compliance of the resulting installed system. A documented system recording the change, the actions that are needed as a result of change and their completion should be implemented after DQ.

To ensure the manufacturing facility remains compliant monitoring programmes will need to be established on the quality of critical utilities such as purified water systems and cleanroom manufacturing environment. Performance Qualification (PQ) of the systems involved is an opportunity to evaluate the ability of these systems to perform consistently

by use of enhanced sampling plans and analysis of their product.

Guidance for acceptable specifications can be found in the pharmacopoeias and in The Rules Governing Medicinal Products in The European Community, Volume IV for the manufacturing environment. Review of trended data over time from these analyses will not only determine if the requirements of the PQ have been met but where the most challenging areas to compliance are. Using this data appropriate sampling points and analysis can be determined for an effective monitoring programme during routine manufacturing.

As the validation programme progresses into OQ and PQ it is likely the quality plan will need to be developed to accommodate new activities such as sampling, laboratory analysis and self inspection. New categories documents will be created such as batch records to allow placebo runs of routine manufacturing. SOPs will need to be expanded to support the need of PQ activity as will the training of personnel.

The task of meeting regulatory compliance can be designed to integrate into the project. An early definition of the quality requirements at the conceptual phase and an understanding by all parties involved will help prevent lost opportunities to gather essential data and prevent expensive rework. Efficient and detail planning of procurement and construction activities integrated with the validation requirements will help to reduce the projects total time span and make best use of test data and certification that is often gathered for commercial reasons alone.

Reference (1) ISPE Baseline Pharmaceutical Engineering Guide Volume 5 "Commissioning and Qualification".