

**ABB Life Sciences**

**General Validation  
Capability and Experience**

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## 1. INTRODUCTION TO ABB LIFE SCIENCES

ABB Life Sciences was first formed in 1989 to meet the needs identified during the early FDA inspections of Automated Manufacturing in Europe. From this beginning we have grown our own breadth and depth of expertise to become a leading supplier of Validation Services to the U.K., European and increasingly the U.S. and Far Eastern life sciences industry.

ABB Life Sciences was initially part of ICI Eutech. Eutech was formed by ICI as their engineering company in response to the demands placed by ICI's chemical and pharmaceutical operations. When ICI divested the pharmaceutical division to form Zeneca (later to become AstraZeneca), a number of practitioners with pharmaceutical experience stayed with Eutech to provide services to the wider Life Sciences industry.

In 2001 Eutech was bought by ABB to supply an in-depth chemical and pharmaceutical engineering capability. ABB is a very large world-wide engineering company that provides a wide range of automation, power transmission and distribution products and services. Today ABB Eutech has two main offices in the U.K. in Cheshire and at Teesside, with satellite offices throughout the U.K., Europe and the world. ABB Eutech employ in the order of 500 professionals and the portfolio of services include:-

- ❑ Asset management
- ❑ Manufacturing supply chain
- ❑ Organisation and competence development
- ❑ Performance measurement and benchmarking
- ❑ Plant support
- ❑ Process engineering
- ❑ Project consultancy and execution
- ❑ Regulatory compliance
- ❑ Safety and environment

ABB Life Sciences employ in the order of 50 skilled consultants ranging from principal consultants to validation engineers. We work with both manufacturers and suppliers to the life sciences industry in the U.K., Europe and overseas. This document tells more about our skills, capabilities and experience in delivering validation services to the regulated industries.

There are three key characteristics that identify ABB Eutech and ABB Life Sciences:-

- ❑ Our business is built on people, and the quality, experience and development of our staff is paramount to the operation. ABB Eutech has been awarded 'Investor in People' accreditation. On average we spend 10% of available man-hours on professional training and development to keep our people fully

aware of the latest regulatory issues and to promote the development of best practices. This is significantly higher than the industry average. We are active speakers at validation related seminars both in the U.K. and in mainland Europe. ABB Eutech is a founding member of the GAMP Suppliers Forum, and we continue to take an active role in the development of GAMP by leading Special Interest Groups (SIG).

- Quality of delivery is central to the business. ABB Eutech has been certified to ISO 9001 since 1993, and the current certificate is issued by Lloyd's Register Quality Assurance and covers ISO 9001:2000 till November 2004. This certificate covers a wide range of our activities including validation consultancy services.
- Coming from a background as owner / operator of chemical and pharmaceutical plants, safety is always a key consideration to everything we do. ABB Eutech holds the RoSPA gold award, and have carried out in excess of 8 million man-hours work since the last reportable incident (RIDDOR). Our safety performance is consistently better than the industry average.

We hope that this document will prove to be informative. More detailed information is available from the contact person stated on the front page. We look forward to hearing from you and being of service.

## **2. ABB CAPABILITY IN THE LIFE SCIENCES - OVERVIEW**

As your customers demand lower prices, increased responsiveness and higher quality products, Life Sciences supply organisations are forced to continuously improve operations to sustain competitive advantage.

ABB have particular experience of working with clients at a strategic level to understand the business drivers with a view to developing an operations improvement strategy that will deliver this competitive advantage.

### ***Improve Operational Performance***

By providing an integrated service to measure and help you improve performance within R&D, manufacturing or supply chain in terms of flexibility, quality, dependability, capacity and cost.

### ***Assure Compliance***

By cost effectively helping to comply with appropriate regulations and codes including EU and US cGxPs, Electronic Records and Signatures, Validation, Auditing, Health, Safety and the Environment. We have a good dialogue with the regulators (MCA and FDA) as well as industry bodies like GAMP, ISPE, etc.

### ***Deliver Investment Productivity***

By providing expert support and management in project definition, specification and implementation to ensure delivery of project benefits on time and within budget.

### ***ABB is a Leading Supplier of Consultancy and Execution Services to the Global Life Sciences Industry***

We are experienced with Computer Systems such as Computerised Laboratory Equipment, Laboratory Information Management Systems (LIMS), Process Control Systems, ERP, MRP II, MES and Business Information Systems. We have experienced Consultants, Validation Co-ordinators and Validation Engineers working on client sites in the U.K., mainland Europe and in the U.S. and the Far East. The services that ABB offers range from Consultancy in Validation, Good Automated Manufacturing Practice (GAMP), 21 CFR Part 11 ERES rules, Auditing, cGxP reviews, etc. through Project Management to the production and execution of validation documents, protocols and reports.

### ***ABB has Wide Experience in Conducting Audits for Clients in Life Sciences Industry***

These audits include Internal Audits, Computer System Supplier Audits, Life Sciences Equipment Supplier Audits and Business Systems Supplier Audits. ABB auditors are trained according to the Lloyds Register Quality Assurance accreditation or TickIT schemes or equivalent organisations, and are experienced validation practitioners with an in-depth understanding of Quality Standards, GAMP and European and US regulatory requirements.

### ***Maintaining a Current Awareness of the Regulations***

ABB Consultants are frequent presenters at national and international meetings on the subject of Computer Systems Validation and regulatory compliance. A number of consultants are experts on 21 CFR Part 11 interpretation and assessment programmes and have presented on this topic. ABB Consultants also support companies engaged in supplying computerised equipment to the Life Sciences industry and have chaired the GAMP Supplier Forum since its inception.

### ***ABB can Draw on Extensive Experience in the Life Sciences Sector***

We have Consultants that “can do” and this differentiates us from other consulting organisations by offering a broad base of technical and functional expertise gathered in the real world. This attitude and ability allows us to help *deliver the identified improvements* rather than just tell you where to find them.

We usually work very closely with client teams drawn from all levels of the organisation, bringing discipline, pace and working style as well as structured methodology and tools, thus there may be a requirement to involve other parts of your company. ABB Consultants will work flexibly with your organisation, adopting the most cost effective project/work structure to suit your particular requirements. This means that you can most efficiently dovetail our capabilities to your needs.

By combining ABB's hands-on operations experience with our understanding of the issues and technologies in the Life Sciences sector, we can offer *practical solutions* to the challenges facing your business.

As a totally separate group within the ABB organisation, ABB Life Sciences will at all times maintain its independence and the level of objectivity required to deliver a quality job in line with regulatory expectations. Although ABB is a premier supplier of process control, data processing and laboratory equipment and systems, we are not tied to the promotion or use of such ABB systems. The Life Sciences group is solely interested in solving our clients' regulatory and validation issues as cost efficiently as possible. Being part of the larger ABB organisation does bring other advantages, however, such as in-house detailed knowledge of the above systems and a vast knowledge base in all engineering aspects.

### 3. COMPUTER SYSTEMS VALIDATION APPROACH

Over the past decade, ABB has developed an approach to Computer System Validation, which is incorporated into the overall specification and design of a facility and is based on the industrially accepted V-model standard (see fig 1).

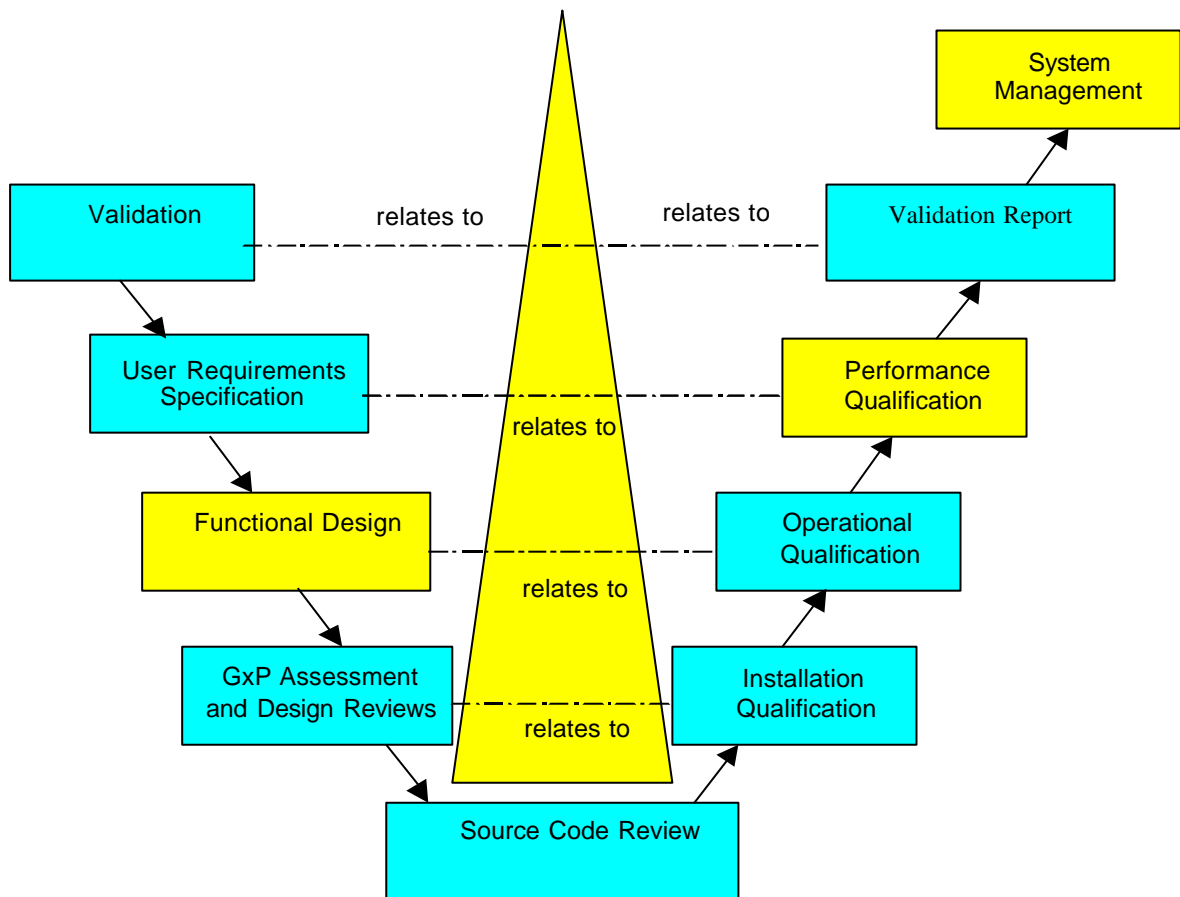


Fig 1

This model has been fully recognised by the FDA and European regulatory authorities as being a suitable approach to achieve the appropriate level of computer system validation for a new facility. This integrated approach ensures that validation principles and requirements (e.g. documentation, reviews, testing, etc.) are included in project documents such as vendor scope of supply, specifications, project plans, etc. In this manner validation is “built into” the project from initial planning phase through to handover of the facility and commencement of cGxP operations.

With our knowledge of the pharmaceutical processes, commonly used equipment and systems, an in-depth understanding of how to interpret and deal with regulatory demands, and ability to communicate and manage at all levels at the client's organisation, ABB can deliver:

- ❑ Reduced timescales through integration of automation and validation activities
- ❑ Lower risk of Computer Systems failing to meet business / regulatory requirements through applying criticality factors and using a risk based approach to validation
- ❑ A better facility by pulling through the benefits of implementing robust and workable validation / engineering systems that will lead to a better understood, functioning and easier to maintain facility
- ❑ Building awareness of the benefits available from implementing electronic solutions in lieu of paper based operations

The overlapping responsibility of both the system supplier and the validation supplier is demonstrated in figure 2 below. This also highlights the Regulatory, System and Procedural requirements needed to successfully validate the Computer System in its operational environment. This diagram can only serve as a general guidance, the exact split of responsibilities will differ from client to client and between different systems.

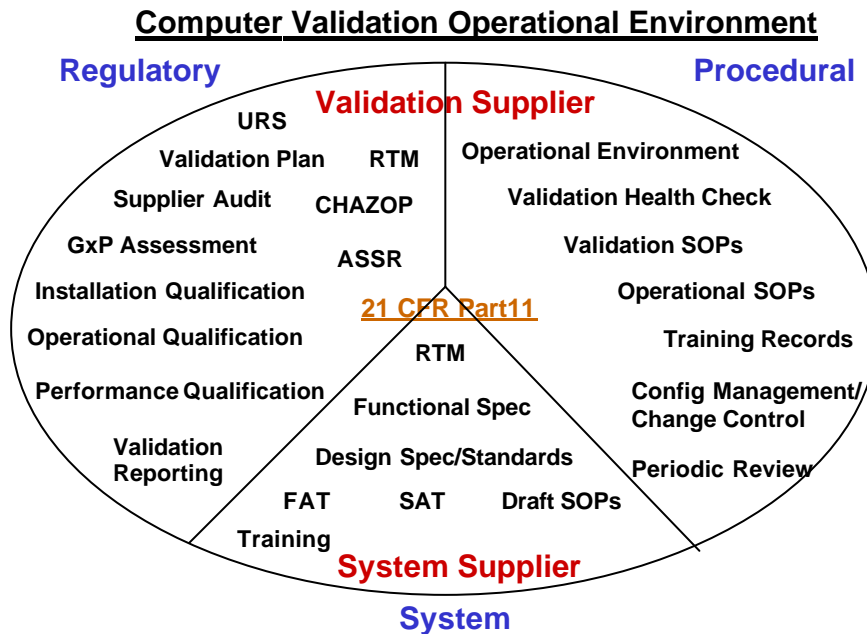


Fig 2

## **Key Lifecycle Phases**

Below the key life cycle phases are briefly described. These descriptions can only be generic in nature, and the exact activities and the order they are carried out in may differ from system to system and are dependent on the client's circumstances.

### ***User Requirements Specification (URS)***

This formal document defines the user's requirements for the Computer System. The URS should be written in 'plain' language, and it is advisable for all key stake holders to 'buy-in' to the URS, as it forms the basis of development or supply of the Computer System. The URS is viewed as a key document by the regulatory bodies.

### ***Validation Plan (VP)***

This is a key document which outlines the validation strategy for the overall project. In particular the following is usually covered by the plan:-

- ❑ Validation scope, assets, physical and logical boundaries
- ❑ Interfaces to other assets
- ❑ Key lifecycle phases; content and strategy (e.g. strategy for qualification / testing)
- ❑ Applicable standards, procedures, guidelines, and work processes
- ❑ Validation team personnel
- ❑ Roles and responsibilities
- ❑ Deliverables to be produced
- ❑ Engineering systems, such as document management, equipment history files, calibration / maintenance, change control / configuration management, etc.
- ❑ Validation project management

### ***Supplier Audit***

Supplier Audits are a powerful and cost effective tool in pre-qualifying suppliers and identifying potential issues and non-compliances. Depending on system criticality, audits can be conducted as postal, telephone or site visits. The findings of the audits will be used to build any required additional validation requirements into the validation plan or protocols.

### ***Functional Specifications/Design Specifications***

The Functional Design Specification (FDS) is usually prepared by the supplier, and is a key deliverable, since it incorporates the supplier's system solution to the user's requirements. Experience has told, that a validation review of the FDS to determine that it is suitable, comprehensive, accurate and testable is warranted.

Other design specifications and design standards are often less critical and a reduced validation review can be justified.

### ***GxP Assessments***

This formal process defines and documents the potential impact by the Computer System on the product quality or product related data. The results of the GxP assessments are used to determine the appropriate level of validation of the various system hardware and software components. Full validation would be limited to GxP critical items, with other items being either qualified or subjected to Good Engineering Practice.

Providing that a sound rationale for this approach has been documented, this process is fully compatible with regulatory expectations and has been demonstrated to deliver the following benefits:-

- ❑ Focus of scarce resources on critical process functionality
- ❑ Reduced project risk as critical items are highlighted at an early stage of the project
- ❑ Reduced timescales for completion of validation activities

### ***Design Reviews***

At this stage the design is usually reviewed to provide evidence of compliance to cGxP, and also the user's requirements specified in the User Requirements Specification. Often a Requirements Traceability Matrix (RTM) is produced to map across URS requirements through to the FDS, FAT, SAT, IQ, OQ and PQ lifecycle phase as appropriate.

For critical bespoke or highly configurable systems it is recommended that a series of reviews are held as the design is refined and developed. The design reviews can be documented either by means of minutes of these meetings or through formal approval of Design Review protocols.

In addition the following design review activities may be executed:-

- ❑ Computer Hazard & Operability Study (HAZOP) to verify the integrity and security of the Computer System in its operational environment.

- ❑ Dependent on the system GAMP categorisation, use, complexity and criticality, it may be opportune to execute a Source Code Review (SCR) or Application Software Structural Review (ASSR). This is a cost effective tool that will review critical elements of the application code to confirm adherence to standards, source code maintainability and address critical aspect of the code.
- ❑ Assessment of the Computer System against 21 CFR Part 11, Electronic Records / Electronic Signatures (ERES), including system and procedural requirements beyond the control of the system supplier.

### ***System Build and Coding***

This is a supplier activity that should be subjected to normal project management activities and supervision.

### ***Test System***

For bespoke and highly configurable systems, the Factory Acceptance Test (FAT) is a key milestone. From our experience, effort spent at the FAT is more than repaid during site qualification. Validation may ensure that FAT records are comprehensive and suitable for avoiding unnecessary repeat testing on site. In some cases Site Acceptance Tests (SAT) may be appropriate, but these can often be executed as a sub-set of the FAT.

### ***Installation Qualification (IQ)***

During this phase the formal IQ protocols will be executed to provide evidence that the installation is in accordance with the agreed design and specifications. Normally we would plan to use the supplier's acceptance test procedures/plans as the basis for the IQ, supplemented as appropriate to incorporate the operational environment and supporting procedural requirements. In a well managed project, the IQ is largely reduced to documentation review that the system is ready for Operation Qualification.

### ***Operation Qualification (OQ)***

During this phase the formal OQ protocols will be executed to demonstrate that the system provides the required functionality. Where appropriate, we would plan to use the supplier's acceptance test procedures / plans as the basis for the OQ, supplemented as appropriate to incorporate the operational environment and supporting procedural requirements. Where a fully documented FAT has been carried out, the scope of the OQ is reduced to cover the site related tests.

### ***Performance Qualification (PQ)***

During this phase sustained performance of the system over a prolonged period will be demonstrated. This is normally executed by the client and jointly reviewed and reported. ABB can help you define and set up the on-going PQ regime and its review. For many Computer Systems PQ is not appropriate, but system performance is instead monitored through the site production, maintenance and calibration systems.

### ***Validation Report (VR)***

This formal deliverable contains a brief summary of the validation activities carried out as specified in the original Validation Plan. Any outstanding issues will be clearly identified and responsibilities and timescales given for addressing them. The VR will detail any constraints in use of the Computer System.

### ***Validation 'Health Check'***

Pharmaceutical facilities are commonly validated to EU and / or FDA standards. As Current Good Manufacturing Practice (cGMP) continually evolves, however, and people, processes and systems change, ABB recommend a periodic 'health check' of the existing validated environment to identify any deficiencies that will need to be addressed in order to maintain the validated state. In addition there is a regulatory requirement that documented validation reviews are conducted annually. What constituted good practice in the area of computer validation just ten years ago, is today viewed as being insufficient. It is not uncommon to find during these reviews that computer systems have been up-dated without this being fully reflected in the supporting documentation.

### ***Summary***

ABB have recent and relevant experience of providing independent validation services for new and existing pharmaceutical facilities. This experience includes validation of clean utilities, bespoke and off the shelf process and laboratory equipment, and the computer systems used for control, facility management, analytical functions and materials management. In addition, ABB's track record in the management of multi-functional site based projects where multiple stakeholders are involved, gives us the experience necessary to co-ordinate and control the compliance activities for larger multi functional projects as well as smaller ones.

It is essential to fulfil the needs of the regulator without allowing the validation process to become too bureaucratic and overbearing. If this is allowed to happen the validation element may begin to dictate the pace of the project, and there is a significant risk that there will be an escalation of costs and late project completion.

It is this fine balance between regulatory compliance and timely completion of the project to budget, which forms the basis of the very strong case for the appointment of an

experienced, independent validation team, which fundamentally understands the needs of the regulator through rational interpretation of the directives.

## 4. LABORATORY SYSTEMS VALIDATION APPROACH

### LIMS Implementation Support

#### *Laboratory / Business Process Mapping*

This initially involves analysing the process flows in the existing sampling, analysis and data treatment and use environment. During this process the process flows are re-defined and improved to strip out any non-value adding elements and make maximum use of the prospective LIMS capabilities. This enables the project to maximise return on investment delivering optimal efficiency improvements through time savings, streamlined processes and convenient management of, and access to, data.

#### *Validation Planning*

Many companies still fail to consider validation at the early stages of a project. Regulatory inspectors expect to see prospective validation plans in place at the start of the project. Vendor selection and indeed the User Requirements Specification (URS) documents form an important part of the overall validation process, and dates on your validation lifecycle documentation need to be in keeping with the logical sequence of project events. Consideration of validation issues at the onset of a project will pay dividend as the project progresses, with suppliers and end users in advance having a common understanding of service and documentation requirements.

As the project progresses, ABB can offer validation services that range from an advisory capacity to a total managed service. Examples of provided individual services are:-

- ❑ Review of Validation Plans and Reports with GxP assessment
- ❑ Review of Test Planning and Execution documentation
- ❑ Review of all LIMS related documentation
- ❑ Assessment against 21 CFR Part 11
- ❑ Checking of data capture and managing migration of historic data
- ❑ Preparation of Operation Qualification and Project Controls documentation
- ❑ Preparation of GxP Requirements Traceability Matrices to ensure that tests adequately cover GxP and user requirements
- ❑ Preparation and execution of OQ Test Scripts

Other services may be provided on request.

### ***User Requirement Specification (URS) Development***

The URS is a critical document in a LIMS project. It enables you to compare products from a range of suppliers and evaluate coverage of the standard product functionality against your key business requirements, and it can form a part of the contract of supply. It is advantageous if the need for bespoke coding can be minimised as far as is possible, as this has a significant impact on implementation and validation time-scales and costs. The URS will also help to ensure that the product is designed and implemented to comply with the relevant regulations (including 21 CFR Part 11) and to facilitate validation. If a critical user requirement has not been specified up-front, the cost impact to incorporate this at a later stage may be severe.

There is a need for a second level URS documents. These documents cover such items as I.T. infrastructure specification and installation, instrument interfacing requirements, associated instrument software upgrade requirements, links to other enterprise management systems, etc.

### ***Vendor Evaluation and Selection***

The vendor selection process for a LIMS system needs to be formally documented and would normally form a part of your inspectable validation documentation for the system. Included in the vendor selection process, and also in the formulation of the validation and test plan, there will be a vendor audit. ABB carry out vendor audits in line with the recommendations of Good Automated Manufacturing Practice guide v.4 (GAMP 4). The audit checks that the product has been developed following a recognised quality orientated software development and testing lifecycle. In addition it confirms that the product developers are suitably qualified and trained to carry out this role (21 CFR 11 requirement), and that the product will be supported adequately by the vendor in the medium to long term (including any ESCROW agreements).

### ***Package Evaluation and Tendering***

The vendor's response to your URS (or functional specification for the proposed system) needs to specifically address every numbered entry in your URS in a clear and unambiguous way. Our knowledge and experience of the key system vendors in the market place, coupled with our independence, enables us to help you to review the technical and commercial responses from your shortlist vendors, and help choose a vendor and system which best suits your needs.

We have experience, which will help you to set up an effective payment plan between yourself and the vendor, with well defined delivery milestones. This will ensure that at each stage you are happy with the product and its associated support and services before payment is made.

### ***Project Planning and Management***

It is not uncommon for the LIMS vendor to offer this service as a part of their associated consultancy services. ABB believes, however, that the project manager role is more effective if this responsibility is held by an independent professional. The project manager must operate with the best interests of the client as a main driver. All parties involved in the project must have clear roles and responsibilities and understand their remit, and be accountable for their contribution to the project.

Proposed project management methodologies to be used in the course of the LIMS implementation project include:-

- Planning and Resourcing
- Estimating
- Project Control and Reporting
- Change Management
- Project Risk Management
- Document Control
- Document Numbering Procedure
- Checking and Approval
- Revision Control
- Issue and Distribution
- Filing
- Archiving and Distribution of Final Documentation
- Project Auditing

### **Analysis and Measurement Systems Validation**

Recent reports of regulatory non-compliance have cited laboratory systems as being the main area of deficiency. Increasing numbers of regulatory inspectors are being trained in the application of regulatory requirements to computerised systems. Your laboratory systems are a prime target for regulatory scrutiny.

ABB's approach enables us to help you to demonstrate documented evidence of:-

- Structured vendor selection
- Full validation life cycle documentation
- Validation procedures
- Instrument/equipment use procedures

- Periodic review
- Change control

ABB will develop a partnership with you to turn your regulatory challenges into compliance successes. Whether you are looking to validate a new laboratory system or are reviewing existing validation ABB can add value. We have expertise in validation of many laboratory systems (see Appendix 1), and have a history of successful validation projects with a broad pharmaceutical client base (see Appendix 3). Whether you require assistance with one part of a project, e.g. vendor audit, or the entire life cycle, ABB can supply the required expertise. With our history of laboratory systems validation, ABB can offer independent and constructive advice to enable your validation activities to be successfully executed.

## 5. EQUIPMENT, FACILITIES AND PROCESS VALIDATION

### Validation Approach

The purpose of the validation and qualification programme will be to establish documented evidence that provides a high degree of assurance that the equipment and facilities operate in compliance with the manufacturers' specifications and the user's requirements.

Our validation approach will be consistent with the ISPE / FDA Baseline Guides and GAMP. Similarly, qualification will comply with the intent of the cGMP defined by the Rules Governing Medicinal Products in the European Community, Volume IV, Good Manufacturing Practice for Medicinal Products, also the United States Code of Federal Regulations, Title 21, Parts 11, 210 and 211 (for finished pharmaceuticals, other parts of volume 21 apply for medical devices, medical gases, etc.). The main validation phases are described below, and the typical activities are outlined. These are for general information only, and the actual activities will vary from client to client and be project specific.

### **Validation Master Plan (VMP)**

The Validation Master Plan (VMP) or sometimes just Validation Plan (VP) follows largely the same format as that described in section 2 above, with the following additions:-

- Description of facility, services, equipment and services
- Flows of product, people, material and waste

### **System Impact Assessments**

Impact assessment is a process used to determine GMP criticality, and to identify which systems and system components should be validated, and which systems should be commissioned only in accordance with Good Engineering Practice (GEP).

Systems are divided into direct, indirect or non-impact systems, which are defined as follows:-

#### Direct Impact System:-

- This is a system that is expected to have a direct impact on product quality or data, via product contact or direct influence on quality or data.

**Indirect Impact System:-**

- ❑ This is a system that is not expected to have a direct impact on product quality or data, but typically supports a Direct Impact System.

**Non-impact System:-**

- ❑ This is a system that will not have any impact, either directly or indirectly, on product quality or data.

System Impact Assessments will be carried out on all systems as part of the cGMP Review in accordance with the Pharmaceutical Engineering Guides for New Facilities, Volume 5: Guide on Commissioning and Qualification First Edition, March 2001. Normally only direct impact systems will be validated, and all other systems to be commissioned only in accordance with GEP. In some cases indirect impact systems will also be validated.

The System Impact Assessment process is divided into two main activities. The first identifies the system boundaries and evaluates the impact of the system on the product quality. The second evaluates the criticality of the components within each direct impact system with respect to their role in assuring product quality.

For direct impact systems, or those indirect impact systems with critical components, qualification documentation will follow a generic lifecycle approach and consist of the following:-

- ❑ Design Qualification (DQ) reviews
- ❑ Installation Qualification (IQ) protocols and reports
- ❑ Operation Qualification (OQ) protocols and reports

For non-impact systems, verification will be limited to the usual tests and documentation associated with current good engineering practice (GEP).

***Design Qualification (DQ)***

Design Qualification will be conducted through cGMP design reviews for equipment and services. These checks will confirm that the design will meet:-

- ❑ User Requirement Specifications (URS)
- ❑ cGMP Requirements
- ❑ All documentation requirements

These reviews will be minuted to provide documented evidence that cGMP compliance has been addressed at the design stage.

### ***Installation Qualification (IQ)***

The installation will be reviewed to verify that each system has been installed as specified, and that the installation and documentation meets cGMP and regulatory requirements.

Our experience has been that time invested with equipment suppliers at an early stage of the project is invaluable. ABB therefore recommends an early validation review of vendor document requirements for qualified systems.

ABB has considerable experience of FATs / SATs and commissioning. We would expect to ensure that vendors' FATs / SATs are structured, comprehensive and accurate, and to witness at least part of the execution to ensure accurate management of test records. The objective is to ensure that activities are adequately documented as they occur, to enable the FAT / SAT to form the basis of IQ and OQ, and to avoid any need for duplication.

### ***Operation Qualification (OQ)***

The Operation Qualification (OQ) protocol will challenge the operations and documentation provided to ensure that it meets the issued specification, cGMP and regulatory requirements. Individual protocols will follow the test plan and include method statements, acceptance criteria, and data collection forms. Each protocol will have provision for review and approval by the client, both before execution of the testing and finally of the completed record.

Operation SOPs may need to be prepared and used during OQ testing. It is a regulatory requirements that SOPs are tested, including those for system administration, back-up and disaster recovery.

For each system or piece of equipment a series of test functions and acceptance criteria will be defined to verify correct operation. The basis for the acceptance criteria, e.g. manufacturer's specification or in-house specification, will be detailed. Alarm testing, where appropriate, will be conducted as part of the OQ requirements. All data will be collected using calibrated reference equipment, which is traceable to NAMAS or other approved standards.

### ***Performance Qualification (PQ)***

Performance Qualification (PQ) is normally carried out by the end user, since the PQ activities will be closely linked to the (final) product. ABB can assist with the drafting of the protocols, execution / monitoring and report writing, e.g. we have experience in setting up sampling plans for utility systems.

One often overlooked aspect of PQ is to identify all the systematic factors that can adversely affect performance. It is not until these have been eliminated, that the three

PQ runs will constitute a valid statistical sample. Where this is not possible, more than three PQ batches may have to be performed.

Performance Qualification is not normally performed for computer systems, but may include system performance monitoring during a defined period, say 3 months. In most cases, however, PQ for process equipment will also adequately verify the performance of the computer system.

### ***Commissioning***

Commissioning, although not a direct validation activity, needs to be controlled, documented and performed to GEP. Where this is the case, IQ is greatly simplified.

A key aspect of commissioning is the setting up of Equipment History files. These will contain all engineering related information related to a particular system, and forms the basis for system qualification and change control. ABB has experience in the setting up and management of these files.

### ***Validation Summary Report***

The Validation Summary Report is written for each system, and contains a brief summary of the carried out validation activities, the validation status and any limitations in use. The report should highlight any deviations from the strategy as defined by the Validation Plan. This report will form the basis for any subsequent work and the annual validation review.

## 6. ELECTRONIC RECORDS AND SIGNATURES

### Regulations

The use of Electronic Records (ER) and Electronic Signatures (ES) in a regulated environment is largely guided by three pieces of legislation:-

- ❑ 91/356/EEC is an E.U. directive that defines GMP as it applies to medicinal products. The accompanying Guide for medicinal products Annex 11 defines GMP as it applies to computer systems, and defines good practice for ER.
- ❑ 1999/93/EC is an E.U. directive that has been incorporated as law by the European member states. The directive enables the use of ES, but is not restricted to the regulated industries.
- ❑ 21 CFR Part 11 deals with both ER and ES and applies to all regulated data under the U.S. volume 21. The law, which has been in existence since 1997, is applicable to legacy systems as well as those systems only containing ER.

ABB has been working closely with the E.U. Annex 11 regulation for over 10 years and have incorporated the practices, together with those of GAMP v4, in our validation strategy for computer systems. So far the EU 1999/93/EU directive has had very limited impact on the Life Sciences industry, but we are monitoring the developments. We have actively worked with 21 CFR Part 11 since early 2000, and our capabilities are described in the next sections.

### 21 CFR Part 11 Strategy

ABB has taken a leading role in the development and execution of strategies and solutions for dealing with 21 CFR Part 11. This legislation has come to have an immense impact on life sciences companies, and it is imperative that strategies are developed and action plans are in place and executed to minimise the risk for adverse inspection findings. ABB has therefore developed a comprehensive strategy for dealing with this situation. The key elements of this strategy, which is named 'ABB Accelerated ERES Programme', are as follows:-

### *Awareness Training*

The first step is often to conduct awareness training of the client's management, validation personnel and system owners / users, to be able to leverage the maximum participation and ownership from these key people. In a one day interactive seminar, the background to the rule, its implications and strategies for dealing with it are covered

extensively. Where necessary, an introduction to computer system validation and GAMP is provided either as a separate training day or included in the Part 11 training.

### ***Initial Assessment***

Assessments of existing systems are carried out using a simplified questionnaire and conducted through a structured interview with the system owner. In this interview the criticality of the system, its use and replacement cost, the main deficiencies and likely remediations are all captured and checked with the owner.

For prospective new systems a more detailed questionnaire is used. For ease of completion, this is structured in three parts relating to the different types of questions, i.e. system, ER and ES related.

### ***Planning***

Based on the initial assessment a fairly detailed plan can be generated. This will enable the prioritisation of systems based on their criticality and feasibility of corrective actions. This is a key element of the ABB strategy, since by careful prioritisation the risk of non-compliance can be disproportionately reduced compared with the required effort. The planning also enables the scheduling of resources, and allocation of budgets that include the remediation effort not just the assessments.

### ***Developing Solutions***

In this phase the initial findings are verified with regard to implementing compliant or near compliant solutions. The work is captured by writing minutes from the various review meetings. Corrective actions that do not have a significant cost and resource implication are implemented straight away, e.g. the up-dating of SOPs, system documentation and training records.

The output from this phase is a concise Risk Management Statement that captures the corrective actions to be taken and any remaining non-compliances. This document provides a documented rationale for both the actions that have been taken and are planned, as well as for the residual risk stemming from any non-actions. It thus ensures management buy-in to both the managed risk and the planned resource and cost.

### ***Close-out***

Once the planned actions have been carried out, the Risk Management Statement needs to be up-dated to reflect the current system status.

## Capabilities

ABB has a comprehensive delivery capability with regard to 21 CFR Part 11. We are active in the following aspects of dealing with the rule:-

- ❑ Training, ranging from brief awareness training for large audiences to 2-day interactive workshops dealing with all aspects of the rule
- ❑ Setting up company / site wide compliance projects, including the creation of rule interpretation, strategy, training, and planning
- ❑ Carry out initial assessments and prioritisations and writing action reports
- ❑ Investigate and formulating corrective actions
- ❑ Implementing compliant solutions, including SOP writing, technical solutions, system up-grades, and system replacement
- ❑ Project management of all 21 CFR Part 11 and validation related activities

Please refer to appendix 4 for a client list applicable to these services.

## 7. MICROSOFT EXCEL SPREADSHEET COMPLIANCE

### Validated Status and 21 CFR Part 11 Issues

MS Excel spreadsheets, although useful and easy to use, are currently difficult to use in a compliant manner for regulated studies and manufacturing. Spreadsheets are commonly used for a range of purposes in the Quality Control and manufacturing environment, for example:-

- ❑ Statistical calculations, regressions, extrapolations, etc.
- ❑ Standard calculations
- ❑ Generation of analytical sample tables for export to analysis systems
- ❑ Report compilation
- ❑ Basic database functions

Using the standard Excel application it is possible to generate a spreadsheet template, which can be verified and validated at that moment in time. Because the files have inadequate logical access controls and do not generate a secure, automatic audit trail, it is not possible to guarantee the verified and validated status of an electronically stored spreadsheet, and hence the outputs from such spreadsheets can be called to question.

Excel spreadsheets, which are used for the generation of inspectable records, fall under the 21 CFR Part 11 regulation. This means that the application should have logical access controls, and should also generate a secure automatic audit trail capturing the original and new values, the name of the person making the change, and the time and date of the change. In addition the spreadsheets must be validated.

### The Solution

ABB offers a total service for Excel applications. This applies a proven three stage process, which addresses the compliance issues relating to the use and control of spreadsheets within your department or wider organisation.

Initially we compile a list of spreadsheets and capture their fundamental purpose, their inputs and outputs, and an overview of their functionality.

Secondly we determine whether any of the spreadsheets could be included as an extension to the use or functionality of existing systems, which are currently validated and compliant with the requirements of 21 CFR Part 11. For example, the generation of analytical sample tables and the execution of customised calculations can be undertaken by some LIMS systems, and in the manufacturing environment, the enterprise management system can be adapted to provide bespoke calculations and

statistical data analysis and reporting. Any decision to retire a spreadsheet and transpose the functionality to an alternative system would be based upon an analysis of benefits and relative costs.

Thirdly, the spreadsheets which still remain on the list are assessed for cGxP criticality using a check sheet approach. The non-critical spreadsheets are operated under the following regime:-

- ❑ Re-format the spreadsheet to lock out critical cells within the spreadsheet
- ❑ Document briefly the functionality of the spreadsheet
- ❑ Apply version based change control to the spreadsheet governed by global SOP
- ❑ Verify the functionality of the spreadsheet (manually check calculations, etc.)

The cGxP critical spreadsheets are created and operated under the following regime:-

- ❑ Define and apply a spreadsheet development and testing lifecycle for the generation of new cGxP critical spreadsheets
- ❑ For existing spreadsheets review the spreadsheet and lock out critical elements of the spreadsheet
- ❑ Load and configure the Data Compliance System (DaCS) bolt-on security pack. This is a software package written by Wimmer Systems and provided by ABB, that enables Excel applications to become 21 CFR Part 11 compliant by the addition of access controls and an electronic audit trail. The DaCS package also has some electronic signature capability
- ❑ Prepare a system specification document (combined user requirements and functional specification) identify cGxP critical elements of the spreadsheet
- ❑ Prepare and execute a combined IQ / OQ document relating to the Excel application and the DaCS bolt on security pack
- ❑ Prepare and execute a combined IQ / OQ document, which tests and documents the spreadsheet's fitness for purpose when compared to the system specification document. Ensure that all cGxP elements of the spreadsheet are addressed

ABB can provide additional information relating to this service, please request our Excel Spreadsheet Validation Solution brochure.

## 8. TRAINING

ABB Eutech provide a wide range of courses, which at the latest count totalled 75 standard courses. These are delivered by in-house experts with relevant experience, either at the client's premises or at one of our offices. In addition, client tailored courses can be put together to suit particular demands.

Training courses are provided in the following areas:-

- Foundation courses for graduate engineers
- Intermediate courses for process engineers
- Intermediate courses for mechanical engineers
- Intermediate courses for control / electrical engineers
- Intermediate courses for project engineers
- Advanced courses for safety engineers
- Advanced courses for senior engineers
- Advanced courses for validation engineers
- Advanced courses for senior project managers

Please refer to Appendix 5 for a list of our standard validation courses. In addition, more specialised courses can be offered or standard courses can be combined to suit. As part of our training portfolio we also conduct brief awareness training to wide audiences, typically lasting between one and two hours. We will also be happy to assist you with putting together company wide training schemes.

All courses come with comprehensive course binders, which include copies of all presentation slides, exercises and reference material. Training certificates and course synopsis are issued. Courses are generally designed to be interactive to maximise learning efficiency.

A separate training brochure, which describes each course in detail, is available upon request.

## **9. APPENDIX 1: COMPUTER BASED SYSTEMS EXPERIENCE**

### ***ERP / MRP / Inventory Systems***

- ❑ Avanté, BASE10, BPCS, Morris Warehouse Management System, MoveX, MRP Customer fulfilment, OPUS Warehouse Management System, Oracle Manufacturing, Propak, SAP R2 1.0 to R3 4.6d, etc.
- ❑ Bespoke inventory and MRP systems

### ***LIMS***

- ❑ Agilent, Applied Biosystems, Autoscribe, Beckman Coulter, Labware, ThermoLabsystems, etc.

### ***CDS***

- ❑ Agilent, Beckman Coulter, PerkinElmer, ThermoLabsystems, Trivector, Waters, etc.

### ***Instrumentation Interfacing***

- ❑ CSOLS, Labtronics, etc.

### ***Instrumentation Software***

- ❑ DCS
- ❑ Maintenance and Calibration
- ❑ NIR –TOPNIR
- ❑ Various SCADA, etc.

### ***Mass Spectrometers***

- ❑ ABS (PE) Sciex LC / MS
- ❑ Agilent GC / MS
- ❑ Waters Masslynx LC / MS, etc.

### ***HPLC's***

- ❑ Agilent, Gilson, PerkinElmer, Spectraphysics, Varian, Waters, etc.

### **GC's**

- Agilent, PerkinElmer, Varian, etc.

### **Macromolecule Analysis and Separation Systems**

- Gel Permeation Chromatography
- Laser Light Scattering and Diffraction Systems
- Viscometers Capillary Electrophoresis, etc.

### **Spectrometers / Spectrophotometers**

- Infrared Spectrometers
- Near Infrared Spectrometers
- UV/Visible Spectrophotometers, etc.

### **General Instruments**

- Autotitrators
- Autoclaves
- Density Meters
- Dissolution Testers
- Fridges and Deep Freezes
- Laboratory Washers
- Liquid Nitrogen based Cryogenic Systems
- Moisture Meters
- PH Systems
- Recirculating Baths and Chillers
- Stability Monitoring Chambers
- Various Analytical Balances, etc.

### **Clinical Trials Management Systems**

- Clinsoft (formally Domain), Clintrial, FW Pharma -Initiator Pro, etc.
- Bespoke systems

### **Document Handling**

- Back Office, Documentum, etc.

- ❑ Email systems (Lotus Notes, Microsoft Outlook)

### ***Databases***

- ❑ Base 10, DB400, MS Access, ODBC, Oracle rdbms, SQL Server, etc.

### ***Process Control Hardware***

- ❑ DCS / Scada: ABB, Emerson, Invensys, Siemens, etc.
- ❑ PLC: ABB, Allen-Bradley, Eberle, Siemens, etc.
- ❑ Mainframe: AS400, Compaq Alpha, HP, RS6000, SGI, SUN, VAX, etc.

### ***Architectures***

- ❑ 2 tier & 3 tier client server systems, multiply redundant clusters, Novell and Token Ring Networks, TCP/IP, etc.
- ❑ Bespoke embedded systems, complex systems interfacing (bespoke), legacy architectures

### ***Operating Systems***

- ❑ OS400, Unix (SunOS, HP Unix, Ulrtix, TRU64), VMS, Windows 3.11 to 2000, Windows NT, etc.

### ***Programming Environments***

- ❑ Assembler, Basic, C, C++, COBOL, Fortran, PASCAL, SQL+, Various 4GL (ABAP/4, Oracle Developer 2000 etc), Various PLC/DCS (ABB, Allen-Bradley, Siemens, etc.), VBA, etc.

## **10. APPENDIX 2: FACILITY AND MANUFACTURING SYSTEMS VALIDATION EXPERIENCE**

Examples of our facility and process equipment validation experience includes but is not limited to:-

### ***Types of Process***

- Aseptic
- Bulk (including multi-product)
- Creams
- Oral Dosage
- Terminal Sterilisation, etc.

### ***Packaging***

- Form, Fill, Seal Packaging
- Labelling Systems
- Leak Tester Instrumentation
- Strip Packaging, etc.

### ***Oral Dosage***

- Blending
- Capsule Filling
- Check Weighing
- Dispensing
- Granulation
- IBC Washing Facilities
- Process Dryers
- Tablet Coaters
- Tablet Pressing
- Vacuum Transfer, etc.

### ***Aseptic/Terminal Sterilisation***

- Depyrogenation Ovens
- Equipment Autoclave Sterilisation

- Form, Fill, Seal
- Freeze Drying
- Product Sterilisation Autoclaves
- Stopper Autoclave Sterilisation
- Vial Capping, Filling, Washing, etc.

### ***Facilities***

- Finishes
- Interlocks
- Mastic
- Utilities, etc.

### ***Utilities***

- Clean Steam Generation
- Compressed air
- HVAC
- Nitrogen
- Purified water
- Site steam
- Water for Injections, etc.

### ***Cleaning***

- Clean-in-Place Systems
- Sterilisation-in-Place Systems, etc.

### ***Other***

- HFA Propellant Supply & Recovery Systems
- Medical Devices
- Medical Gases
- Micronisers
- Inhalation Filling Systems
- Inhalation Manufacturing Systems
- PSA and Liquid Nitrogen Systems
- VHP Chambers, etc.

## 11. APPENDIX 3: TYPICAL CLIENTS

The following is a list of typical clients we have provided validation services for. The list is not comprehensive and is constantly being added to.

- 3M HealthCare
- Abbot Laboratories
- AstraZeneca
- Avecia
- Aventis
- Beaufour Ipsen
- BioProducts Laboratories
- Boots Pharmaceuticals
- Bristol-Myers Squibb
- Clinical Trial Services
- Daon
- Delta Biotechnology
- Elan Pharmaceuticals
- Eli Lilly
- GlaxoSmithKline
- GlaxoWellcome
- Hoechst Pharmaceuticals
- Hoffman la Roche
- Knoll Pharma Chemicals
- Lonza Biologics
- Medeva
- Napp Laboratories
- Norton Healthcare
- Novartis
- Nycomed Amersham
- Pfizer
- PPL Therapeutics
- Rhône-Poulenc Rorer
- Schering Plough
- Seton Healthcare
- Solvay Duphar
- Speywood Biopharm

## 12. APPENDIX 4: 21 CFR PART 11 TYPICAL CLIENTS

ABB has delivered 21 CFR Part 11 services as follows:-

### **Seminars**

ABB Consultants have presented at numerous (approx. 25) seminars organised by ISPE, Vision in Business, IIR, etc.

### **Training**

Formal training courses are delivered both directly to life sciences manufacturers and suppliers as well as through IIR. Training has been provided for:-

- |  |   |
|--|---|
| <input type="checkbox"/> Alpharma                  | <input type="checkbox"/> Kvaerner         |
| <input type="checkbox"/> Applied Cytometry Systems | <input type="checkbox"/> Lonza Biologics  |
| <input type="checkbox"/> AstraZeneca               | <input type="checkbox"/> PerkinElmer      |
| <input type="checkbox"/> Avecia                    | <input type="checkbox"/> PPL Therapeutics |
| <input type="checkbox"/> Bristol-Myers Squibb      | <input type="checkbox"/> Roche            |
| <input type="checkbox"/> Daon                      | <input type="checkbox"/> Simon-Carves     |
| <input type="checkbox"/> Elan Pharmaceuticals      | <input type="checkbox"/> Tyco Control     |
| <input type="checkbox"/> Fluor Daniel              | <input type="checkbox"/> Yokogawa         |
| <input type="checkbox"/> Jagger & Jagger           |   |

### **Compliance Programmes, Assessments, Remediations, Etc.**

Significant validation projects directly related to 21 CFR Part 11 have been carried out for the following clients. This list is not comprehensive and is constantly expanding.

- |   |  |
|---|--|
| <input type="checkbox"/> Aventis              | <input type="checkbox"/> GlaxoSmithKline   |
| <input type="checkbox"/> AstraZeneca          | <input type="checkbox"/> Lonza Biologics   |
| <input type="checkbox"/> Beauford Ipsen       | <input type="checkbox"/> Norton Healthcare |
| <input type="checkbox"/> BPL                  | <input type="checkbox"/> Pfizer            |
| <input type="checkbox"/> Daon                 | <input type="checkbox"/> Roche             |
| <input type="checkbox"/> Elan Pharmaceuticals | <input type="checkbox"/> Schering-Plough   |

### 13. APPENDIX 5: VALIDATION TRAINING COURSES

The following is a list of current training courses that are directly applicable to validation.

<b>Course Title</b>	<b>Type</b>	<b>Duration</b>
Introduction to GMP	Foundation	½ day
GMP for Engineers	Foundation	½ day
Introduction to Computer System Validation	Foundation	½ day
Introduction to Laboratory System Validation	Foundation	½ day
Introduction to Business System Validation	Foundation	½ day
Introduction to 21 CFR Part 11	Foundation	½ day
Introduction to Equipment and Facilities Validation	Foundation	½ day
Introduction to Cleaning Validation	Foundation	½ day
Equipment Cleaning and Cleaning Validation	Intermediate	3 days
Equipment and Facilities Validation	Advanced	1 day
Purified Water System Validation	Advanced	1 day
Computer System Validation	Advanced	1 day
Laboratory Information Management System Validation	Advanced	1 day
GAMP 4	Advanced	1 day
21 CFR Part 11 Compliance Management	Advanced	1 day