Current Good Validation Practice

by Brian Collins and Kieran Sides

This case study presents how a site validation policy was developed using a modular validation approach and incorporating the latest FDA initiatives, as well as principles from ISPE's Commissioning and Qualification Baseline® Guide, GAMP® 4, and the GAMP Good Practice Guide: Validation of Laboratory Computerized Systems.

Editor's Note: In August of 2006, the Havant site validation approach was formally honored with a Wyeth Corporate Best Practice Award.

Introduction

Wyeth Pharmaceuticals approached Validation in Partnership Ltd. with the requirement to develop a site validation policy that would complement existing quality standards while changing the existing culture from one of multi-factory standards to one of more centralized control. The goal for this change was to present a more unified approach to regulatory compliance and respond to a number of recent and pending industry initiatives. The new policy would need to satisfy the following:

- facilitate the continuity of the focused factory management
- ensure 100% buy-in from department heads and the shop-floor
- be manageable, transparent and maintainable
- add minimum overhead
- fulfill all current regulatory requirements
- comply with the principles of ISPE's Baseline® Guide on Commissioning and Qualification[1]
- embrace all foreseeable industry and regulatory trends

The 'trends' to be accommodated were those appearing in the latest guidance from the regulatory agencies and industry advisory bodies, in particular:

- the FDA's regulatory initiative: "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach"[2]
- the FDA's guidance on Process Analytical Technology (PAT)[3]
- rumors of a Quality Systems approach to inspections by the FDA[4]

It was also to later embrace:

- GAMP 4[5] and the GAMP Good Practice Guide: Validation of Laboratory Computerized Systems[6]

More recently, there has been talk of minimizing the amount of paperwork and repeat work generated by validation departments by assigning more work to vendors and by eliminating the necessity for requalification and revalidation.

Although only needing to satisfy the requirements set down by the EMEA and PIC/S, corporate standards being issued from the USA were imposing requirements specifically designed to satisfy the FDA as well.

Overview

Up to a few years ago, Wyeth's history at its UK Havant site had been one of unparalleled commitment to the daily demands of its customer base. The name became synonymous with the epitome in fast-tracking the installation and start-up of new processes.

Inevitably, with this focus, against a background of high activity, it was realized that the level of documentation to support such new introductions would benefit from a more rigorous approach to meet the current expectations of the regulatory agencies and the company's own internal requirements.

The development of a sensible, workable, economic validation policy compliant with all current and foreseeable initiatives, and providing a springboard for the future would certainly be difficult, but not too daunting. The introduction of such a system while managing the changing routines of a pharmaceutical business with a culture of decentralized management and comprising the manufacturing and packing of a dynamic portfolio of some 250 products would, unarguably, present something of a challenge.

The answer seemed to lie in a modular validation approach designed to minimize the impact of change and the exposure of surplus information, while optimizing the level of control and ease of inspection. The solution is illustrated in Figure 1.

Please note that, while submitting this illustration, it is acknowledged that the termi-

Continued on page 82.

nology applied to the activities shown differs through the industry. Similarly, it is appreciated that the division of qualification/compliance activities is handled differently between the various qualification stages from company to company. Therefore, the titles of the documents and activities referred to in this article should not be assigned any undue significance – it is their content and satisfactory completion in the correct sequence that matters.

The validation policy described is applied to all the hardware and software systems employed in a manufacturing process that are categorized as cGxP impacting, a category assigned to any system that can affect product quality. However, there are a series of crucial activities that must be formally undertaken before any such assignation is possible. They are not considered part of the validation approach, because they are not specific regulatory requirements, but without them, all ensuing validation work would be unfounded. As such, they are referred to as validation foundations.

Validation Foundations

The justification for all validation work is derived from the outcome of those activities shown in the top left hand corner of Figure 1, which comprise:

- Process and Production Rationales
- User Requirement Specifications
- Compliance Reviews
- System Definitions
- System Impact Assessments

And the deliverables determined are mapped through to provision using:

- Traceability Matrices

An expanded view of this section is shown in Figure 2.

Process and Production Rationales

The start point is a Process Rationale, which is written during process development to evaluate risks to product quality and to formally document the process critical parameters. Comprising a variety of sources, such as technology transfer documents, the Process Rationale then forms the basis of a series of risk assessments, which are performed while the User Requirement Specification(s) and the detail of the full scale production model are being developed. This iterative process is documented in a Production Rationale, which provides a step by step analysis of the proposed production

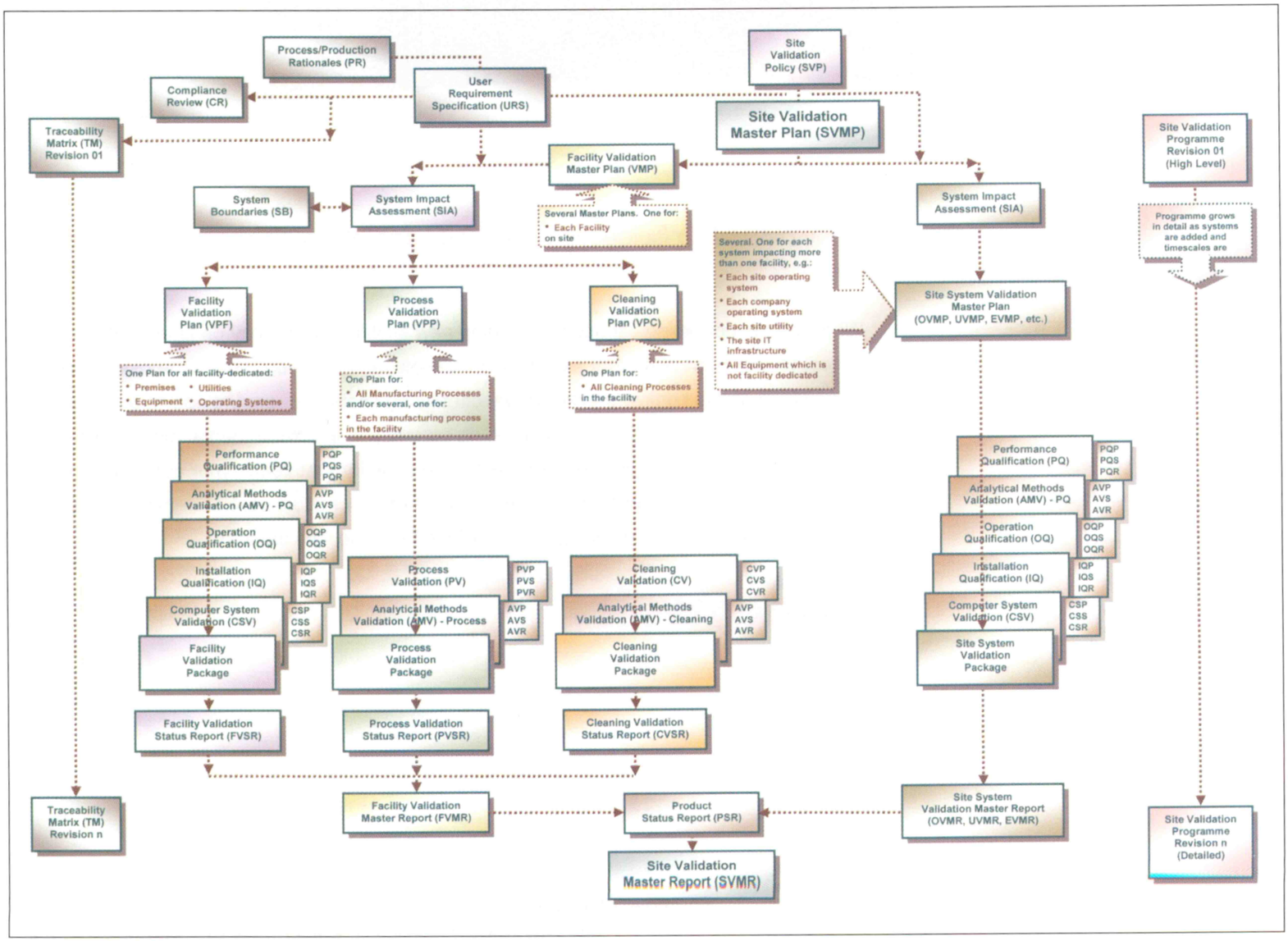

Figure 1. Validation policy overview.

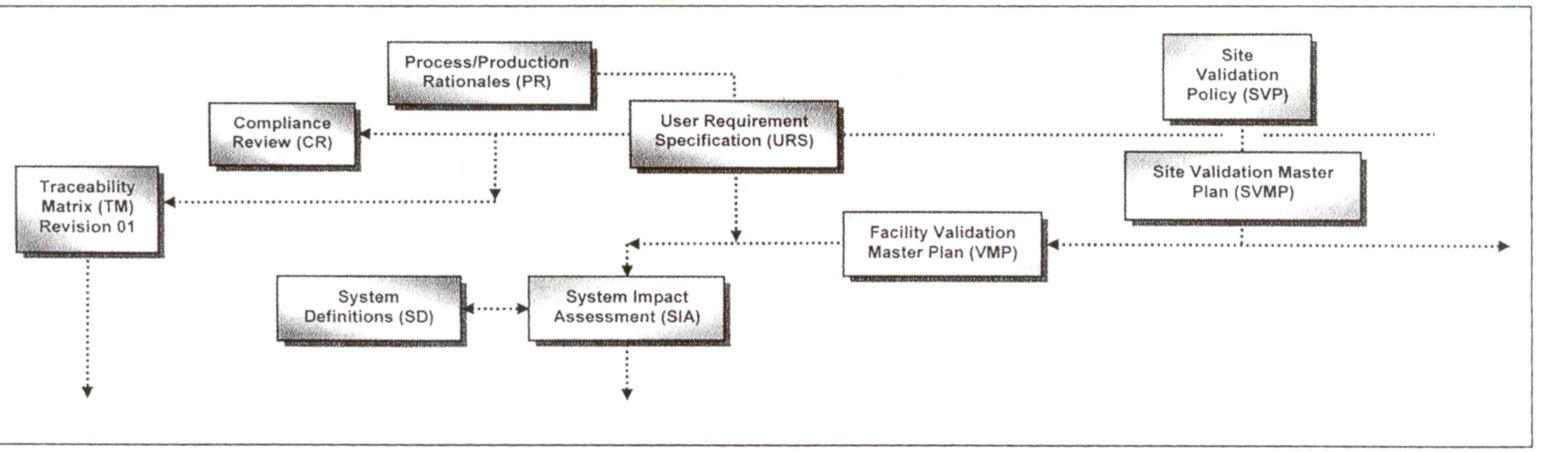

Figure 2. Validation foundations.

process and a compilation of all parameters that may have an impact on the quality of the finished product. One Production Rationale can be generated for each individual product or for several products of the same type. The hardware and software process systems are the obvious focus for this, but there is a tendency to overlook other key aspects of the manufacturing process. Every step, from the arrival on site of raw materials and components, to the departure of finished product, needs to be considered. The way ingredients are specified, procured, transported, off-loaded, handled, sampled, analyzed, stored, dispensed, and charged all can have an adverse effect on quality unless properly controlled, as can in-process sampling, handling, analysis, and subsequent finished product storage and despatch.

Uninformed reactions to regulatory initiatives, such as PAT, can be counterproductive, and in certain cases, result in catastrophic failure of the quality system. Without the fundamental blueprint provided by the Process and Production Rationales, additional in-process analytical steps installed to demonstrate compliance and control may inundate the manufacturer with data providing more questions than answers. In extreme cases, this supplementary data, which cannot be ignored, has led beyond confusion and back to the drawing board, as companies have been forced to admit they did not understand their processes well enough to control them.

Continued on page 84.

The finally agreed Production Rationale, which should reference all supporting development reports, provides a complete list of all product quality impacting parameters at every step, and where possible, identifies all set-points and ranges of tolerances. It is equally important that the non-critical parameters also are identified and the justification for their lack of criticality is documented. Simply omitting these from the rationale begs the question of whether they were even considered at all.

The rationale deliverable is a justification for every subsequent process control measure, whether it be by facility, utility or equipment qualification, automation validation, calibration, in-process monitoring, Standard Operating Procedure (SOP), or training. All static and dynamic attributes of the process are included. A parameter such as equipment product contact parts is assigned to Installation Qualification for verification, whereas the standing time for an off-loaded drum of material becomes the subject of an SOP. The charging of an ingredient into a mixing vessel, if a manual operation, is controlled by approved SOP, training, and calibrated time piece, where appropriate. Dynamics such as mixing speed are covered by Operation Qualification. Thereafter, they are monitored and trended, either by a suitably independently validated and maintained automated system or by manual measurements at specified intervals by qualified individuals trained in approved SOPs and using calibrated test equipment.

If another product of similar type is later introduced for manufacture using the same process, the Production Rationale is revisited to incorporate the new product and make any necessary adjustments to the operating ranges of the process parameters.

As with all the documents referred to in this article, once approved, Production Rationales must be governed by the site change control system. System Impact Assessments will rely on these rationales to provide the parameters for qualification checking and testing, and where applicable, the ranges or operational limits.

User Requirement Specifications

The importance of the role played by User Requirement Specifications (URSs) cannot be stressed enough. They provide a home for all the known requirements of all stakeholders and are generated as a precursor to procurement of all facilities, utilities, equipment, and operating systems. The modular approach to the validation documentation system also is favored here with non-detailed Project URSs providing the master control over more detailed System URSs. Compiled as tender documents, they provide all the information necessary for prospective vendors to satisfy all the hardware, software, and documentation requirements of the Quality, Production, Engineering, and Maintenance departments. The URS covers not only the current requirements of GMP, GAMP (other GxP compliance issues, as appropriate), the registered process(es), and corporate standards, but is expanded to become a receptacle for all required deliverables.

There may be several ways in which to satisfy a particular business need so the URS is not unnecessarily restrictive. Wherever possible, designers are permitted to offer the most cost-effective and compliant solutions. In cases where there is scope for interpretation, URSs are accepted as iterative, becoming more prescriptive as the design is developed.

There are numerous URS formats in use throughout the industry, and there are good and bad elements in all. The format adopted for the Havant site was developed with an automated documentation process in mind, which is described further on. The URS groups the requirements according to the phases of the project life cycle during which they are to be delivered with separate sections for the design, vendor assessment, construction, factory testing, installation, commissioning, operation, training and maintenance phases of the project. Each individual requirement is given a unique identifier and a suffix, the suffix denoting the origin (cGMP, GAMP, Process, HSE, etc.), e.g., *"5.3 Certification exists to demonstrate that all contact part materials correspond to the approved design requirements [cGMP]."* This would appear in the list of items to be verified at the Installation Phase. Each requirement is written as a clear and unambiguous deliverable that is lifted verbatim into a subsequent document as a predetermined acceptance criterion. This eliminates any later confusion arising from a misinterpretation of the requirement.

A URS is generally subject to constant development prior to procurement, but it also can be affected by changes agreed throughout the design and construction stages. With this in

mind, the URS has an integrated change control mechanism to facilitate amendment. Even after the installation of a system has been qualified, there may be changes necessitated by unforeseen circumstances that will impact the URS. As all validation protocols import their acceptance criteria from the URS, the Site Change Control System ensures these modifications are captured and it is updated.

Compliance Reviews

A Request for Proposal is issued to prospective vendors and the proposed designs submitted are checked for compliance with the user requirements. This is the role played by the Compliance Review. It performs the same function as the Enhanced Design Review in the ISPE Baseline® Guide on Commissioning and Qualification,[7] and what some refer to as Design Qualification. The EMEA suggests this 'could' be the first stage of validation[7] and intimate that the compliance of the design with cGMP should be documented.[8] The FDA, on the other hand, does not require a formal review at design stage to verify regulatory compliance, which is contradictory to the very essence of the meaning of validation.

The reason we validate is because we cannot test quality into the end product. Unfortunately, the regulators seem to have diluted this message. If we follow the letter of the law, qualification is not required until an installation is complete, which is way too late for any non-compliances to be rectified. In the real world, where projects are generally behind schedule, the discovery during Installation Qualification that the design was not all it should be, is far more likely to lead to a compromise in standards than the necessary alterations. For pure economy alone, it makes more sense to identify and eradicate potential shortcomings on the drawing board than actual faults on site.

Each individual user requirement is verified as a deliverable of the proposed design by recording the precise location within the design package where the vendor's intention to comply is documented. Only then can an order be placed.

It is recognized that design development is the domain of the vendor so the Site Change Control System is not invoked until the commencement of Installation Qualification. Prospective vendors are audited to verify that adequate change controls will be employed to safeguard the user requirements as the design is developed and components are procured.

Although performed at proposal submission stage, the Compliance Review incorporates a similar means of change control to the URS, ensuring that all subsequent changes to the user requirements are formally accepted by the vendor. Audits of the two change control systems at intervals prior to the commencement of Installation Qualification will confirm the vendor's sustained commitment to compliance with the URS.

System Definitions

A System Impact Assessment will determine whether or not validation is needed, but before this can occur, the full extent

Continued on page 86.

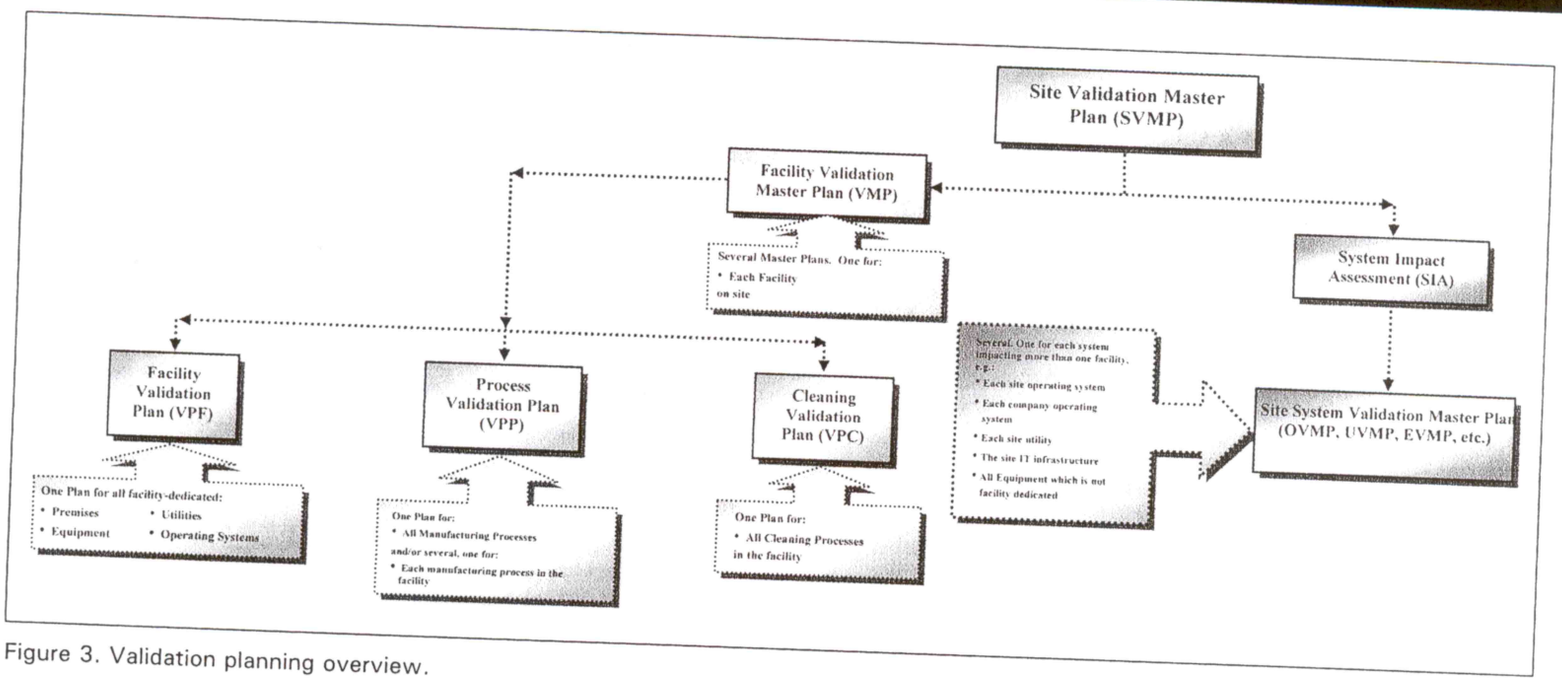

Figure 3. Validation planning overview.

of the system has to be known. A System Definition document not only identifies the physical boundaries of the system, but also provides a complete description of the static and dynamic attributes of the system. It constitutes a key ingredient of the modular approach to validation, as the descriptions in validation plans and protocols can be minimized, supported by a simple cross-reference. For something as complex as an automated Clean-in-Place system with numerous interfaces with other systems, the finished document would contain a schematic diagram, marked up to identify the start and finish points, a detailed specification of the installation and functionality, and an index identifying the references, versions, and locations of all other pertinent documentation, back-up software programs, etc. For simpler, stand-alone systems such as a refridgerator or a pH meter, a vendor's brochure may suffice.

System Impact Assessments

With the system fully defined, the next risk assessment is performed, which is the System Impact Assessment (SIA). This is when the decision is made whether or not the system needs to be qualified. The SIA is referred to as the Impact Assessment in ISPE's Commissioning and Qualification Baseline® Guide.[9]

The criteria provided by ISPE and the Production Rationale are used to determine if Good Engineering Practice (GEP)[10] standards alone will suffice or if they need to be supplemented by the appropriate validation phases. It can be tempting to ease up on the documentation standards for systems exempt from qualification, but one day the use of a system may be changed such that it can impact on product quality and needs to be qualified. It may not be possible to qualify a system lacking the necessary supporting documentation.

Every SIA includes a matrix, which maps the system/systems covered against its/their critical parameters, as defined by the relevant Production Rationale(s). The SIA is revisited each time there is an amendment to a Production Rationale, this revisit being prompted by the Site Change Control System and its inbuilt risk assessment. For example, if the scope of an existing manufacturing process is extended to cover the introduction of an additional product, any changes required to the operational limits of any of the process parameters will be passed on to the SIA. In response to the revised SIA, the duly amended Traceability Matrix will project where an evaluation is required of the impact on the existing qualification package.

Traceability Matrices

Traceability Matrices are now in common use, plotting the projected delivery of every single user requirement to ensure nothing is overlooked. Most companies use them prospectively to define precisely where each requirement will be verified as satisfied. But they also can be used retrospectively to identify exactly where the fulfillment of a requirement is actually documented. They are used mainly to demonstrate control of the current GxP requirements, but, if the URS is properly structured, there is no reason why individual matrices should not be compiled for all other requirements, such as health, safety and environment, or corporate standards.

If more than one Traceability Matrix is generated, there also should be a master overseeing them, which, retrospectively, would verify that all individual matrices had been brought to a satisfactory conclusion.

Validation Policy

The Site Validation Policy presents the complete approach to validation across the site.

Validation Master Plans

The Site Validation Master Plan (SVMP) identifies all the types of products categorized in the site inventory as cGMP impacting, a category that applies to all medicinal products for human use. It also lists all the individual Validation Master Plans (VMPs) generated for the site. As indicated in Figure 1, a VMP is produced for each facility on site, and for each 'site system', i.e. a system serving more than one facility (site utilities, site and company operating systems, site IT infra-

structure, and equipment systems that are not facility-dedicated). The SVMP then identifies, for each product, which VMPs are impacted during any stage of its manufacturing process. An expanded view of this section is shown in Figure 3.

Validation Plans

Each Facility VMP introduces three types of Validation Plans (VPs); one for the facility, one for the manufacturing processes and products accommodated therein, and one for the associated cleaning processes. The modular approach presented here would be less beneficial to a single product facility for which it may be feasible to omit the VPs by incorporating their contents into the Facility VMP.

System descriptions in the VMPs and VPs need be nothing more than cross-references to the System Definition documents. This enables any change, other than one impacting a critical parameter, to be accommodated and documented without the need for a revision to the plan.

The Facility VP covers all the facility-dedicated systems, which include the premises (the facility itself and the various rooms) and all the equipment, utilities, and operating systems located within the facility. It acknowledges the 'site systems' serving the facility, but simply cross references to their VMPs for any detail, and it makes no mention of manufacturing or cleaning processes at all. The plan then introduces the phases of validation it controls and contains the traditional matrix plotting systems against their assigned qualification and/or validation phases. The phases covered by a Facility VP are the same as those of a 'site system' VMP, as can be seen in Figure 1.

The Process VP details the manufacturing process for each product produced and/or packed in the facility. It groups the products in families according to their production or packing processes and identifies both the facility-dedicated systems and the 'site systems' impacting these processes. If a facility is subject to an ever-changing production schedule, it may be appropriate to modularize the approach further and generate separate Process VPs for individual manufacturing or packing processes to minimize revisions to the plan.

Although identifying all the hardware and software systems involved in each process, the Process VP merely directs the reader to the Facility VP or the 'site system' VMP for further details. It then provides an overview of the validation phases it covers, i.e., Process Validation (PV) and Analytical Methods Validation (AMV), and a matrix showing the assignment of these phases to the products and processes included in the plan.

The Cleaning VP details all possible permutations of product family campaigns for each of the production or packing processes operated within the facility and considers all opportunities of potential cross-contamination, including those involving products not categorized as cGMP impacting. The plan identifies all the equipment to be cleaned and all the systems to be used in the cleaning processes, the facility-dedicated systems, and the 'site systems.' However, it simply points to

Continued on page 88.

the Facility VP for further details of the facility-dedicated systems and to the appropriate VMP for each 'site system.' It also contains an introduction to the Cleaning Validation (CV) and Analytical Methods Validation (AMV) phases covered and a matrix assigning these phases against the various processes.

This modular validation planning ensures a minimization of the impact of any site changes, such as the installation of an additional compressor to increase the capacity of the Site Compressed Air System. Even though the system may serve numerous facilities and processes across the site, the only plan requiring a revisit would be the Site Compressed Air System VMP. Similarly, the introduction of a new product, the operational limits of which are within those already tested for its product family, would require nothing more than an inventory update. There would be no need to revisit the Cleaning VP, Process VP, IQ, or OQ, and there would be no urgency to produce the three consecutive replicate batches required to validate the process; they would simply fall in line with the production schedule.

Validation Program

Annex 15 to the EU Guide[11] specifies that a VMP should contain data on *"planning and scheduling."* True to the modularity of the approach, the validation program is generated and maintained as a separate document with recognition provided by a simple cross reference from the SVMP. With a product portfolio like the one at Havant, the production schedule would otherwise render the upkeep of the SVMP impossible. A formal validation program should indicate the appropriate sequence of all validation activities covered by the VMPs and VPs, but it should always have plenty of slack built in as there is nothing more ridiculous than deviations being raised during a validation project simply because timelines have not been met. The generation of such deviations is completely pointless as they cannot possibly be resolved, merely accepted.

The program is not just a regulatory requirement, but it is also an essential validation control document. As such, all additions and removals are subjected to the Site Change Control System.

An evolutionary approach to the development of detail within the validation program as the life cycle develops is particularly important for a new or expanding site. Many projects have ground to a halt or been forced to proceed with unapproved or unrepresentative plans as a result of trying to define all the detail at the outset, when such detail is simply not available. This is one of the primary factors in modularizing the validation package in terms of VMPs and VPs, such that the level of detail presented in each is appropriate to the level of knowledge available at the time it is generated. A similar end point could be achieved through the continued revision of a single plan, from an initial high level approach, as represented by our Site VMP, to a detailed approach, as represented by Site System VMPs and Facility, Process, and Cleaning VPs. However, the final provision of such a plan does not lend itself to change, as even minor site modifications would necessitate the continuous revision and re-issue of what would be an extremely bulky text for approval. It is simple enough to provide a validation package to support a new site or facility, but considerably more difficult to produce a package that is easily maintainable over time.

Protocols and Reports

All protocols and reports, whether for a Compliance Review, Installation Qualification, or Process Validation follow the same modular pattern as indicated by Figure 4. Protocols are constructed such that each of the series of pre-requisites, checks and tests contained therein has its own objective, methodology, and acceptance criteria section. Each objective

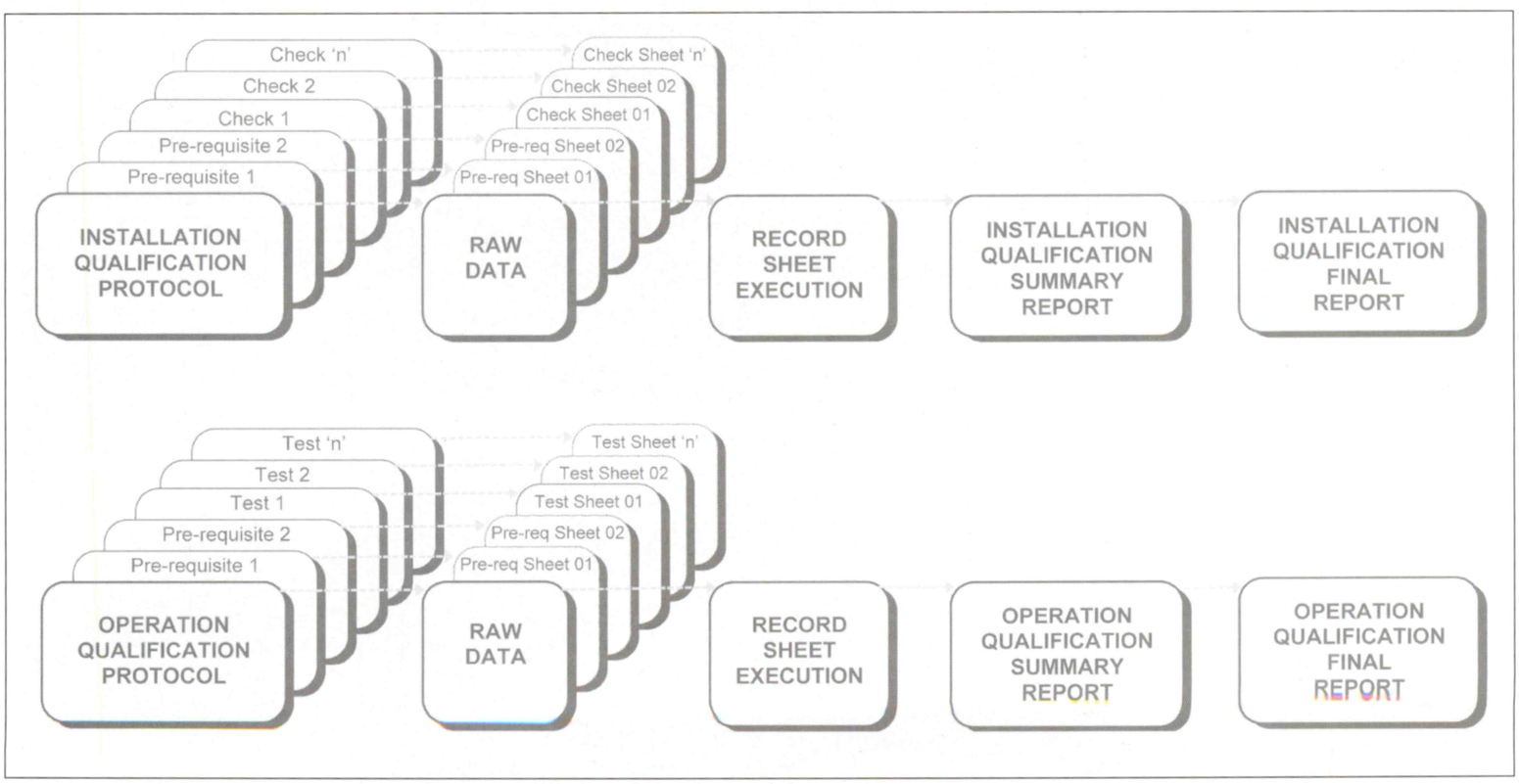

Figure 4. Qualification documentation pverview.

to provide documented evidence that a pre-requisite has en satisfied or that a check or test has been successfully mpleted. The methodology sections explain only the intent d not the step by step detail of the execution procedure. is is provided elsewhere, on stand-alone record sheets. The asons for this are several. For a complex OQ test, the heads department nominated to approve a protocol are unlikely be sufficiently acquainted with a system to be able to agree detailed test procedure, but they should be comfortably alified to approve the intent of the test.

There also may be various ways to execute a test. For stance, a test to verify the satisfactory operation of a high vel switch for a purified water system storage tank can be cluded in the protocol with only high level detail of how this st will be conducted. For example, it will be important that suitable quality of water is used and that the high level vitch is activated when the water in the tank reaches a edefined level (with tolerance). However, it may not be cessary to charge the water from the associated purified ater generation system or within a particular time period. he skill is to document the critical elements of the test ethodology at a high level in the protocol, and to clearly fine the supporting acceptance criteria. The detail of the lve sequences, interlocks, etc., required to safely realize the st on the plant can be derived following approval of the otocol as more detail of the installation and commissioning atus of the facility becomes available.

The most appropriate way of testing might not have been decided, but this is no reason to delay what can be a lengthy protocol review and approval process. Whatever method is eventually selected, the test acceptance criteria will be the same. When finally decided, the record sheet will prescribe the specific qualification steps to be followed in performing the test. The finished record sheet is then submitted to the most technically competent person to review the detail before approving it for execution. There is no need for a Quality department approval of the record sheet, as all the protocol approvers will see the completed sheet when reviewing and approving the report.

Separating the detail from the protocol in this way has a number of advantages, including reduced review and approval times. The most significant time (and cost) savings can be realized in respect to tests which protocol reviewers deem unnecessary or approaches with which they fundamentally disagree. In a traditional system, by this stage the protocol author would have already wasted valuable time trying to write a detailed test script, which is now redundant. In the model proposed here, such wastage is minimized.

When all the protocol record sheets have been executed and completed, a report is written to summarize their results. A Summary Report enables the next stage of validation to commence, even though there are outstanding minor deviations, and a Final Report is generated on their satisfactory resolution.

Continued on page 90.

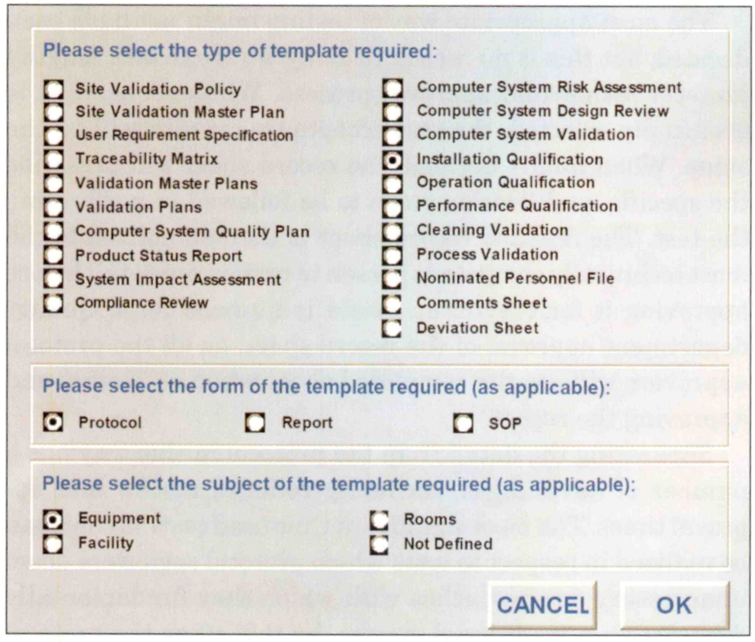

Figure 5. Automated document template menu.

With the current emphasis on Quality Risk Management (QRM),[12] it was wholly appropriate to embrace the concept of its scientific, risk-based framework within the validation approach. Although the message of QRM, and particularly PAT, is often focused on in-process control and analysis, the principles should be spread to cover any part of the process where enhancements can increase product quality.

Since 1987, the FDA's Guideline on General Principles of Process Validation[13] has stated "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." It was decided that QRM should now be applied, not just to the consistent production of product, but also to the production of the documented evidence. To this end, the entire documentation process illustrated in Figure 1 was automated to minimize the risk of human error, an ever present feature of paperwork systems.

Automated Document Templates

Microsoft Word templates were developed initially for all the validation documents to instantly generate Validation Master Plans and Reports, Validation Plans and Reports, Installation, Operation, and Performance Qualification (IQ, OQ, and PQ) Protocols, Computer System, Cleaning Validation, and Process Validation (CSV, CV, and PV) Protocols, and Record Sheets and Reports.

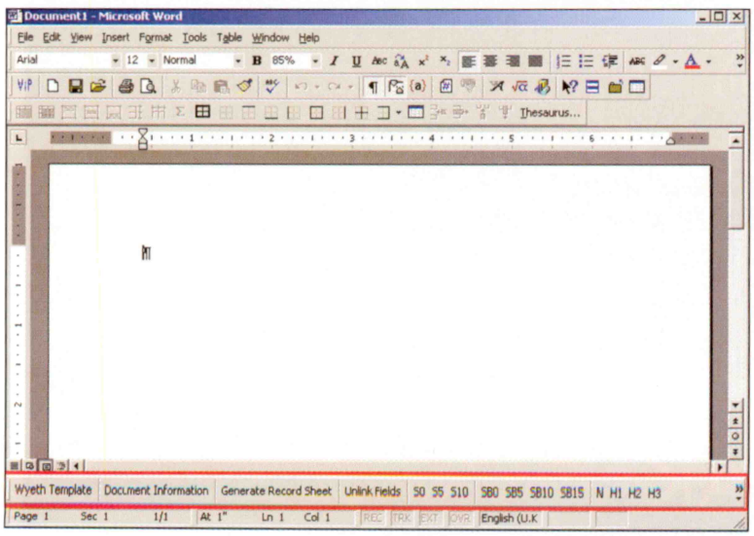

Figure 6. Automated document template toolbar.

The scope was then broadened to provide automated templates for the validation foundation documents, such as User Requirement Specifications, Traceability Matrices, System Impact Assessments, and Compliance Reviews. Finally, Computer System Validation (CSV) support documents, such as Quality Plans, Risk Assessments, Design Reviews, and Configuration Reviews also were automated, providing templates for both GAMP's System Development and System Implementation Life Cycles. These refer to the requirements specified in GAMP 4 Guide to Validation of Automated Systems and the more recent GAMP Good Practice Guide: Validation of Laboratory Computerized Systems respectively.

To create a document, the author simply selects the type of template required from a menu, similar to the example shown in Figure 5, and accessed via the purpose designed toolbar shown in Figure 6.

The selection of Installation Qualification prompts the author to choose between the Protocol or Report forms of the template and the subject matter, Facility, Rooms, or Equipment. The menu display changes depending on the type of template selected. For instance, a document of the chosen type, such as an Equipment System Installation Qualification (IQ) Protocol, instantly appears when selected. Selection of the Document Information button on the toolbar enables its personalization as the author is prompted to input the specific details requested in Figure 7.

This information is then automatically fed onto the document front approval page, into the header, and consistently throughout the document, wherever necessary. The templates contain as much boilerplate text as possible with the author only having to provide details of the system description, drawing, equipment and instrumentation specifics. The Equipment System IQ template is used for utility and equipment systems with separate templates provided for facilities and rooms. The IQ and OQ elements of computer systems are built into the Computer System Validation Protocol itself.

Rather than the author having to decide on the regulatory compliance criteria for IQ protocols, each template already contains all the acceptance criteria required to satisfy the FDA and EMEA. These are grouped under logical headings and the author merely deletes those not applicable. These acceptance criteria are provided courtesy of Validation in Partnership's in-house regulatory database, which affords immediate access to all the regulatory requirements of the FDA and EMEA.

Once the IQ Protocol is generated, its system-specific Objectives, Methodologies, and Acceptance Criteria for all the prerequisites and checks to be executed during the qualification are each translated into stand-alone Pre-requisite Sheets and Check Sheets, also at the touch of a button - *Figure 4*. Each record sheet carries all the necessary Document Information from the protocol. Requiring only one pre-approval signature,

record sheets are ready for execution. They carry the exact rding of the objective and acceptance criteria, as extracted n the protocol, and the prescriptive step by step instruc-ns on how to complete the tasks. The automation ensures re can be no possibility of the all too common transcription ors from protocol to record sheet or vice versa.

Once the record sheets have been field-executed, the reports equally instantaneously generated via the menu. The hor is presented with a report prompting the appropriate ice from all necessary options. The report is generated as ner an Equipment System Installation Qualification ***Sum-ry*** Report (IQS) in the case of minor outstanding devia-ns, or a **Final** Report (IQR) if they have been resolved.

Traceability

evolving appreciation of the possibilities for the auto-ted templates led to the cementing of the entire validation roach. Individual user requirements are now automati-y lifted into the downstream documents that are used to ify their delivery. All items listed in the Installation Phase tion of a URS, that are destined for verification during dation, find themselves automatically transported into acceptance criteria section of the appropriate check in an Protocol. Those in the Operation Phase likewise become eptance criteria in OQ Protocols. The example given above ler ***User Requirement Specifications*** would become IQ eptance criterion *"Certification exists to demonstrate that contact part materials correspond to the approved design uirements [CGMP]. [URS Ref. 5.3],"* automatically main-ning the precise wording and its unique URS reference. se not requiring verification via the validation documen-on system can be automatically transported into equiva-t Good Engineering Practice system documents.

The requirements recorded in the various project life cycle ses of a URS are automatically lifted into:

- Compliance Review Protocol templates and beyond into executable record sheets
- Traceability Matrices to project the documented evidence of the delivery of each individual user requirement
- IQ templates and record sheets
- OQ templates and record sheets
- PQ templates and record sheets
- Process Validation templates and record sheets
- Cleaning Validation templates and record sheets

ther enhancements will see requirements being lifted Factory Acceptance Testing and System Acceptance ting templates.

The entire system of documentation comprising the tem-te menu in Figure 5 is fully supported by SOPs, which ude examples of all document types and also personnel ning/assessment sections.

Validation Maintenance

is too often the case, especially when using an outside tracting organization, a manufacturing facility is com-

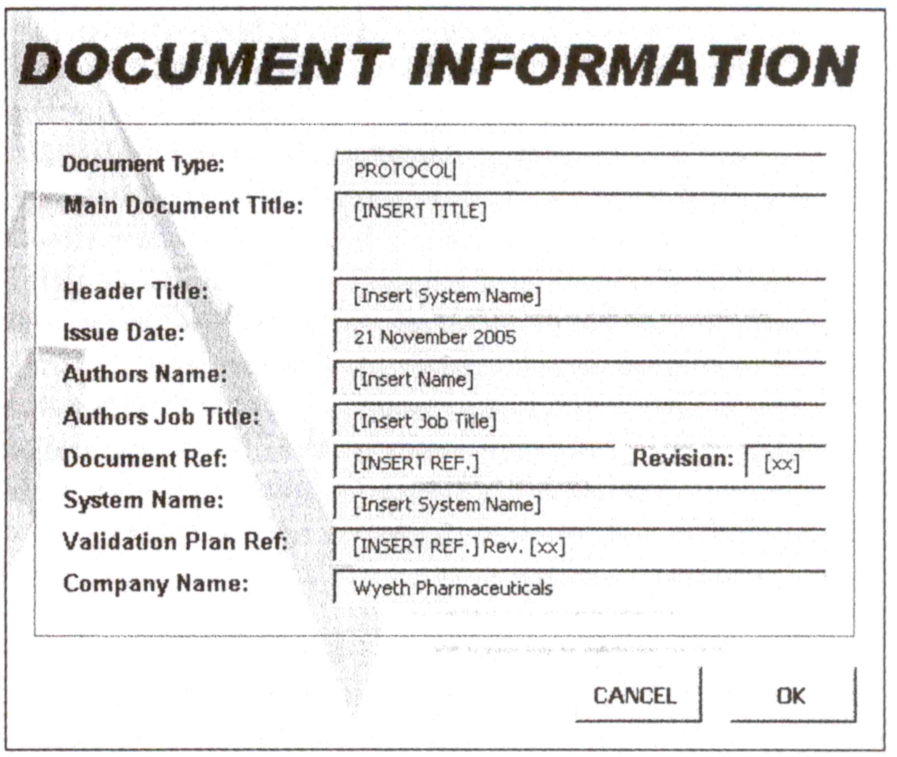

Figure 7. Document information prompt table.

pleted and the qualified package is inadequately handed over to the user. By this stage, timescales are so tight that nobody has noticed. The contractors are looking toward their next project and the user is desperate to complete the process validation work and start filling the shelves with product.

Operators are trained in approved production and cleaning SOPs; the analytical methods are validated; QC personnel, schooled in sampling techniques, are waiting in the wings; the validation documentation is safely in the hands of the Quality department and the project support information is tucked away with Engineering and Maintenance who are wading through the mountain of instruction manuals and putting the finishing touches to the maintenance and calibration SOPs. All that stands between where we are now and routine production are the process and cleaning validation stages. All that stands between where we are now and the slippery slope to non-compliance, that is.

Most of us are so glad to get through to the process validation stage relatively unscathed that one major interface is overlooked. Maintenance personnel have absolutely no idea what part they have to play in the upkeep of the facility's validated state, because nobody has thought to tell them. They know precisely what to do to keep the process systems up and running, because the system vendors have imparted all this knowledge. But what about the flow velocity in the purified water system? Unless instructed to ensure the same critical parameter requirements tested and verified at OQ are retested and reverified following maintenance, the system will be subjected to only the vendors recommended checks and a steady drift into non-compliance is inevitable.

This is yet one more reason for keeping record sheets separate to protocols to enable the maintenance of the qualified or validated state of a system. Agreement reached by the appropriate involvement at the validation stage can lead to the Maintenance department providing the necessary assurance. Instructed in which IQ checks and OQ tests need to be performed in response to preventive or breakdown maintenance, copies of the corresponding approved blank record

Concludes on page 92.

sheets can be executed and completed by maintenance personnel as a matter of routine. This documentation, combined with data generated during trending of critical parameters will provide the necessary justification for not requalifying or revalidating the system. Unless results determine otherwise, all that is required is an occasional audit. With record sheets completed by Maintenance filed with the originals completed by Validation, the history of a particular test and the current state of validation can be effectively demonstrated.

Three monthly summary reports of critical parameter trending following OQ, combined with the upkeep assured by Maintenance and the Site Change Control System, provide an invaluable and readily available source of input into Annual Product Reviews.

Engineering Files

Traditionally, there has been a tendency to keep project documentation referred to during IQ and OQ with the validation documents themselves to ensure they can be retrieved during an audit, but with the appropriate controls in place, this need not happen. The Engineering department should be the home for all documentation provided by system vendors. With appropriately structured system files, there should be no need for any of it to reside in the Quality department. Secure in the knowledge that strict documentation control systems are exercised, IQ, OQ, and CSV protocols should merely refer to the locations and references of supporting documentation.

Summary

The response to the remit set for the site validation policy has resulted in a living system that has fulfilled all criteria and evolved into an economical, manageable, auditable, and maintainable validation system that has won corporate recognition and been praised during recent regulatory authority audits.

References

1. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.
2. Pharmaceutical cGMPS for the 21st Century - A Risk-Based Approach, FDA, Concept Paper, 21 August 2002 (progress documented in Pharmaceutical cGMPS for the 21st Century - A Risk-Based Approach, FDA, Second Progress Report and Implementation Plan, September 2003.
3. FDA Guidance for Industry, PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004.
4. Later emerging in FDA Draft Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2004, and FDA Compliance Program Guidance Manual for FDA Staff, Drug Manufacturing Inspections, Program 7356.002, 2/1/2002.
5. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems,* International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.
6. *GAMP® Good Practice Guide: Validation of Laboratory Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, April 2005, www.ispe.org.
7. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, Section 7, p. 75, www.ispe.org.
8. Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice, Qualification and Validation, Page 5, July 2001.
9. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, Section 3, p. 27, www.ispe.org.
10. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, Section 4, p. 33, www.ispe.org.
11. Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice, Qualification and Validation, July 2001.
12. ICH Draft Consensus Guideline, Quality Risk Management, Q9, Released for Consultation on 22 March 2005.
13. FDA Guideline on General Principles of Process Validation, May 1987.

About the Authors

Brian Collins is the Validation Manager at Wyeth Pharmaceuticals in Havant, UK. He has a Bachelor of Pharmacy (Hons) from the University of Bath and is a Registered Pharmacist in the United Kingdom. He has more than 19 years of experience within the pharmaceutical industry with roles encompassing laboratory analysis, product development, production operations, and validation. His latest role started with a new canvas to develop a team, site policy, and validation process to consolidate validation activities into a manageable and maintainable system. Collins can be contacted via e-mail at: collinbr@wyeth.com.

Wyeth Pharmaceuticals, New Lane, Havant, Hampshire, PO9 2NG, United Kingdom.

Kieran Sides has more than 16 years of experience in the qualification and validation of facilities, utilities, equipment, and systems associated with the life science industries, mainly pharmaceuticals. For the last 10 years, he has been a compliance consultant with Validation in Partnership Limited, a specialist validation and GxP compliance service provider based in the UK, during which time he has spent three years as the course tutor for the validation module of Manchester University's Pharmaceutical Engineering Advanced Training (PEAT) Programme. Sides can be contacted by telephone at +44 (0)1625 572777 or by email at: Kieran.sides@vipltd.co.uk.

Validation in Partnership Ltd.,Adelphi Mill, Grimshaw Lane, Bollington, Cheshire, SK10 5JB, United Kingdom.