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GAMP 5 – Enabling Innovation

by Sion Wyn

The new GAMP 5: *A Risk-Based Approach to Compliant GxP Computerized Systems* provides pragmatic and practical industry guidance that aims to achieve compliant computerized systems that are fit for intended use in an efficient and effective manner, while also enabling innovation and technological advance. The revised Guide describes a flexible risk-based approach to compliant GxP regulated computerized systems, based on scalable specification and verification. A robust quality risk management process based on ICH Q9 principles is central to the approach. GAMP 5 also contains new information on outsourcing, electronic batch recording, end user applications (such as spreadsheets and small database applications), and patch management.

Changing Environment – Regulatory and Industry Initiatives

The pharmaceutical industry is responding to the challenge of significantly improving the way drug development and manufacturing is managed. New concepts are being developed and applied, including science based risk management approaches, a focus on product and process understanding, and the application of Quality by Design concepts.

Many of these ideas are defined and described in the FDA 21st Century Initiative, new ICH documents, such as Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System, ISPE's Product Quality Lifecycle Implementation (PQLI) initiative, and various supporting industry consensus standards, such as ASTM E2500 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*.

As these new ideas and ways of working are being established, the industry will for some time be in a *period of transition*.

GAMP Guidance must evolve to meet the needs of the changing environment and integrate fully with ISPE initiatives, such as PQLI and the revision of the ISPE C&Q Baseline® Guide. There is both a need and an opportunity to make activities related to all types of computerized systems efficient, effective, and focused on patient safety.

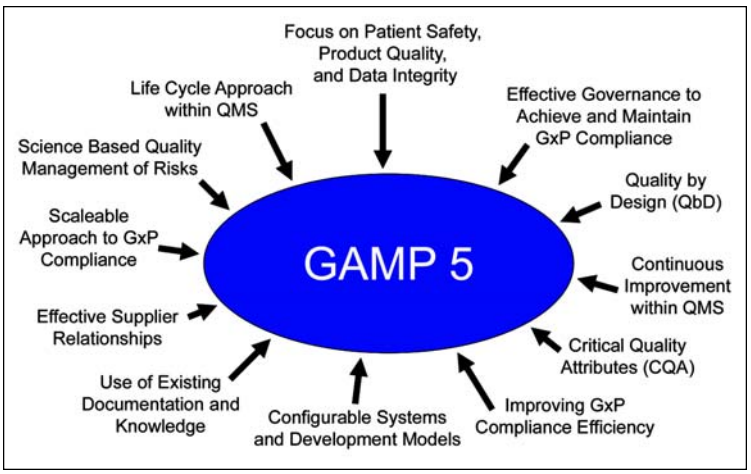

Figure 1. Drivers for GAMP 5.

New and Innovative Approaches

Where a computer system is regarded as one component of a wider manufacturing process or system, particularly in an integrated Quality by Design environment, specific and separate computerized system validation may not be necessary. This environment requires both complete product and process understanding and that the critical process parameters can be accurately and reliably predicted and controlled over the design space. In such a case, the fitness for intended use of the computer system within the process may be adequately demonstrated by documented engineering or project activities together with subsequent Process Validation or continuous quality verification of the overall process or system. The same principle applies to the adoption of Process Analytical Technology (PAT).

These innovative approaches are available and useable now if the appropriate pre-requisites are met. While acknowledging that not all regulated companies will be in a position to, or will choose to, fully embrace the new approaches immediately, GAMP 5 is intended to encourage the adoption of such approaches and in no way to be a barrier.

Improving Quality Practice

During the period of transition, the industry continues to need practical guidance based on current good practice – giving practitioners the tools to do the job today, while building a bridge to new approaches. GAMP 5 aims to describe current good prac-

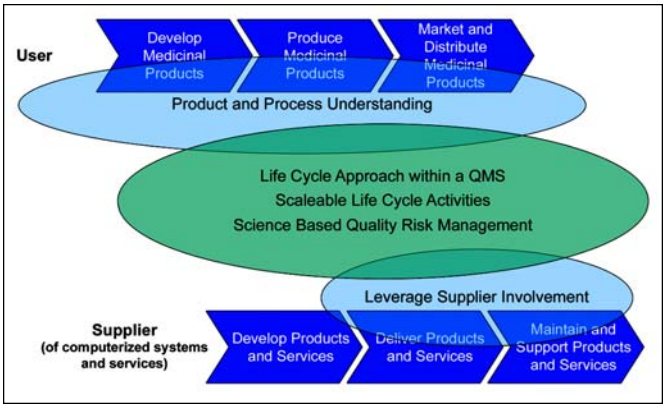

Figure 2. Key Concepts of GAMP 5.

tice in order to satisfy the needs of the majority of practitioners involved with computer systems, while also enabling new and innovative approaches, e.g., for process systems in a Quality by Design environment. These innovative approaches and the application of principles to specific system types will be explored in detail in subsequent documents.

In the meantime, key aspects supportive of ISPE PQLI and ASTM E2500 are addressed immediately to make current activities as effective and efficient as possible. These include:

- focusing on aspects critical to the patient
- avoiding duplication of activities (e.g., by fully integrating engineering and computer system activities so that they are performed only once)
- leveraging supplier activities to the maximum possible extent, while still ensuring fitness for intended use
- clarifying the roles of Subject Matter Experts and Quality Assurance
- scaling all lifecycle activities and associated documentation according to risk, complexity, and novelty
- clarifying that traditional linear or waterfall development models are not the most appropriate in all cases

These are reflected in Key Concepts upon which GAMP is based, and in the detailed contents - *Figure 2*.

GAMP 5 is deliberately flexible with regard to terminology – focusing on value-added activities and avoiding unnecessary activities is the main intent, and different regulated companies and suppliers may choose to use a wide range of different terms. In line with the principles of ASTM 2500, GAMP 5 adopts *specification* and *verification* as overall terms describing specific life-cycle activities, but does not discard the general lifecycle validation framework to reflect current industry practice for companies that decide to maintain these practices rather than applying the new concepts.

Extended Scope and Application

Coupled with these initiatives in development and manufacturing, a wide and ever-increasing range of local and global networked computerized systems are being used throughout the product life cycle. Many of these are fundamental to GxP activities.

Accuracy and integrity of records and data is essential throughout the product life cycle, from research and development through pre-clinical studies, clinical trials, production and quality control to marketing. The GAMP Good Practice Guide: *A Risk-Based Approach to Compliant Electronic Records and Signatures* provides further guidance on this topic, and should be read in conjunction with GAMP 5.

Achieving compliance and fitness for intended use for all GxP regulated systems in a pragmatic and efficient manner is essential. GAMP 5 aims to address the need to safeguard public health, product quality, and data integrity while at the same time enabling innovation and technological advance.

Focusing on Patient Risk

While previous GAMP guides provided an overall life cycle framework for systems and controlled equipment, they recognized that the practicalities are different for different system types. As a result, a series of Good Practice Guides were produced to support the understanding of these differences and provide more practical detail.

Many pharmaceutical companies undertake complex, time consuming and expensive qualification practices. There are aspects of qualification that can add value in terms of ensuring the equipment and systems are fit for intended use, but there are other aspects that often do not add this value. Some of the prescriptive and rigid conventions and practices that surround qualification as often practiced can detract from its overall value. GMP regulations provide the basis for the activities that are called qualification, but no specific requirements that relate to how qualification is practiced.

By focusing on the risk to the patient and leveraging the expertise of the supplier and subject matter experts based on Good Engineering Practices, verification is considered as a set of integrated activities that can replace the activities previously called IQ and OQ. Regulated company IQ and OQ activities may then be omitted or limited to an assessment of the supplier's activities and documentation, and if necessary, performing mitigation activities to close gaps. This eliminates much of the costly duplicated testing which does little or nothing to protect the patient.

Finally, the overall performance and fitness for intended purpose can be ensured through Performance Qualification or Verification, which focus on critical-to-quality attributes. Overall, this will demonstrate that the equipment or system is performing satisfactorily for its intended purpose, the process with which it is involved is controlled, and the risks to the patient have been effectively managed, thus meeting the regulatory requirement for validation.

It is important to select the right tool for a specific need, such as design review, inspection or testing (e.g., Commissioning, Qualification, IQ, or OQ). The term verification is

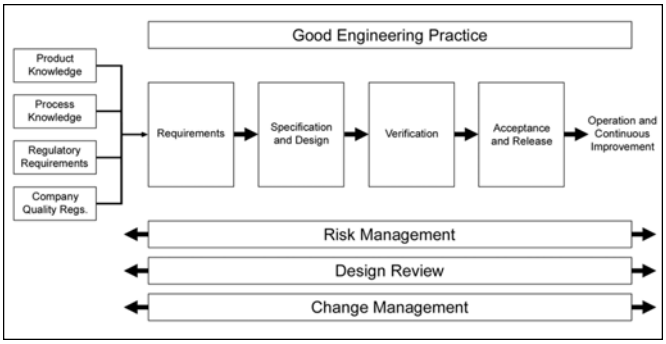

Figure 3. The specification, design, and verification process.

used in ASTM 2500 and aims to promote flexibility in choosing the right approach - *Figure 3*.

A science- and risk-based approach is inherent in the thinking behind verification, where the level and extent of verification is based on scientifically-assessed risk to the patient from specific processes, equipment, and systems. This is directly in line with the principles described in ICH Q8, Q9, and the forthcoming Q10 documents for the development, quality risk management, and quality management of pharmaceutical products throughout their life cycle. It is, of course, still appropriate to create a plan describing and justifying the approach taken to ensure the equipment is fit for use in a GxP regulated environment, and to have a report available providing the necessary evidence to support this claim.

Different Types of Computerized Systems

For integrated manufacturing systems or equipment where a computer-based system is part of the overall functionality, a specific and separate computerized system validation may not be required.

For example, where the computer controlled equipment can be regarded as one component of a wider manufacturing or process control system the verification can be an integrated part of the overall process validation effort. The verification of fitness for intended use may be adequately demonstrated by documented integrated engineering or project activities together with subsequent Process Validation – and the overall approach may be defined based on each regulated company's policies and preferences.

Validation is the common term used in regulations worldwide to describe a process that demonstrates that systems are fit for intended use. Some computerized systems are intimately involved in many regulated business activities outside the manufacturing area, and are critical for the health and protection of the patient. Examples include the collection of clinical trials data, the management of donor details in blood collection, the recording of adverse events and complaints, the release of product for sale, and the recall of defective product.

Such IT systems have no direct correlation with the manufacturing and release of the product. Consequently, there is no direct parallel with the manufacturing process and associated process validation. Acceptance of the system is dependent on the satisfactory completion of a functional test, such as the traditional OQ or equivalent tests, prior to a controlled cut over into the live environment. (Some further testing, e.g., stress or performance testing, may be necessary which some organizations call PQ but it is not an activity parallel to the PQ testing of controlled process equipment).

The principles described in ASTM Standard E2500 should be interpreted with attention to the special characteristics of particular systems, and suitable verification that the critical-to-quality requirements of the system have been met should be completed before the computer system can be approved for use in a GxP-regulated environment.

The ideas that led to the development of ASTM E2500 are applicable to all computerized systems. GAMP 5 describes a process which follows the same principles:

New and Revised Material

Particular emphasis is given in GAMP 5 on providing a cost effective approach to compliance and demonstrating fitness for intended use. To support this, new and updated guidance is given on the following aspects:

- a complete system life cycle approach as part of a Quality Management System (QMS), from concept to retirement
- a scaleable approach to achieve and maintain GxP compliance driven by novelty, complexity, and risk to patient safety, product quality, and data integrity
- clarifying the role of the Quality Unit, and introducing the roles of Process Owner, System Owner, and Subject Matter Experts.
- in the GMP environment, stressing the importance of clear requirements based on a thorough understanding of the science and of the Critical Quality Attributes (CQAs) of the development and manufacturing process and drug products, to facilitate the adoption of a Quality by Design (QbD) approach
- the leveraging of supplier documentation and knowledge, wherever possible, and subject to satisfactory supplier assessment to avoid unnecessary duplication
- improving efficiency by promoting practical and effective interpretation of GAMP guidance
- maximizing use of documentation from activities such as development and commissioning as verification evidence
- the importance of effective governance to achieve and maintain compliance
- identifying opportunities for process and system improvements based on periodic review, root-cause analysis, and Corrective and Preventive Action (CAPA)

New information is provided in specific appendices on the following topics of special interest to industry:

- alignment with ASTM E2500
- organizational change
- outsourcing
- electronic batch recording
- end user applications such as spreadsheets and small databases
- patch management

- the requirements of the system should be clearly defined
- requirements critical to the health and protection of the patient (critical-to-quality requirements) have been identified and the risks identified and controlled
- the principles of GEP are applied throughout
- the testing carried out and documented by the supplier should be leveraged as much as possible
- the critical-to-quality requirements are appropriately verified and reported by the regulated organization in line with regulatory expectations

It is also recommended that a plan describing and justifying the approach taken, and a report supporting the claim that the system is fit for intended use, are created.

Performed in this way, the process described above for computerized systems meets all the GxP regulatory expectations for validation.

Terminology

Since GAMP 5 covers both systems involved in manufacturing of pharmaceuticals and systems for other critical types of IT applications, this Guide uses terminology that enables appropriate selection of the relevant life-cycle activities, depending on the specific context.

Some organizations have already taken the decision to adopt the term "verification" and apply it to both computer and control systems. Others have indicated that they will stay with the words "qualification," but adopt the principles described in the ASTM Standard 2500. Still others have changed to verification for controlled process equipment, but retained "qualification" for computer systems.

The GAMP Community of Practice aims to strongly support and promote innovation. GAMP Guidance is neither mandatory, nor prescriptive, but aims at enabling innovation in a compliant and cost effective manner.

Descriptions of current industry practices in GAMP 5 should not be read as constraining in any way the development and adoption of other approaches. Individual companies should and will decide what terms and precise approach they will use.

GAMP 5, like previous versions of GAMP, supports good quality management practices. The enhanced focus on science and the increased focus on risk to the patient are important to the future of the pharmaceutical industry. GAMP will continue to support evolving good practices for the pharmaceutical industry at large, its regulators, and suppliers.

GAMP 5 is scheduled to be released at the ISPE Conference on Manufacturing Excellence, 25-28 February 2008 in Tampa, Florida, US. Please visit www.ISPE.org/manufacturingexcellence for more information.

About the Author

Sion Wyn, Director, Conformity Ltd., is an acknowledged expert in computer system validation and compliance and international regulations in this field. He is currently assisting the FDA with its re-examination of 21 CFR Part 11, and is a member of the team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He is the technical content expert for the FDA's ORA Virtual University on-line training modules on computerized systems validation and compliance. He has received the FDA Group Recognition Award for work on Part 11. Wyn is the editor of ISPE's *Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems,* and is a member of the ISPE GAMP Council and the GAMP Europe Steering Committee. He has extensive experience in all aspects of computer systems validation and compliance, including managing validation projects, validation planning, specification and testing of systems, performing site and system compliance audits, writing SOPs, performing 21 CFR Part 11 assessments, and supplier audits. Wyn's expertise as a specialized computer validation consultant covers all stages of the lifecycle approach to validation of computerized systems and most system types including MRPII, manufacturing execution, electronic document management, EBRS, process control and monitoring, environmental monitoring, manufacturing equipment, and laboratory systems. At Conformity Ltd., Wyn provides computer validation and compliance consultancy to the pharmaceutical and other regulated healthcare industries. Wyn received the 2006 ISPE *Professional Achievement Award*, which honors an ISPE Member who has made a significant contribution to the pharmaceutical manufacturing industry.