This article presents practical risk-based advice regarding the implementation and management of computerized aspecis of a Building Management System.

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Position Paper:
Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments

by the ISPE GAMP® Forum, Special Interest Group

Building Management Systems (BMS) have evolved over many years, along side the development of Heating, Ventilation, and Air Conditioning (HVAC) and other building system technologies. Increasingly, BMS technology has adopted control system architectures and philosophies to satisfy the need for advanced automation. The consequence has been that BMS is widely deployed throughout healthcare companies with modern day solutions being based on standard software and hardware design. Further, a BMS provides standard inbuilt functionality, based on many years of building automation solutions. As such, a BMS is often an effective solution to cost conscious building management strategies. The implementation of a modern day BMS brings several benefits to organizations including, but not limited to:

- effective control of building related processes and equipment
- real time visibility of building management system performance
- early warning of process deviations
- predictive maintenance planning
- centralized and/or remote control of facilities and equipment
- optimization of utility costs
- secure management and storage of process and equipment performance data
- implementation of standardized building management strategies
- availability of state of the art and expandable technologies
- effective system management and support

The requirements pertaining to the use of BMS within regulated environments has been debated within the healthcare industry for many years with differing views remaining today. Several reasons are cited for this discussion, the commonly recurring themes being:

(i) BMS are used to control, record, monitor, and alarm a variety of processes of varying risk to the attributes of the manufactured product (e.g., purity, safety, quality, and efficacy).
(ii) Product characteristics vary widely, and therefore, similar BMS implementations may have different product risk.

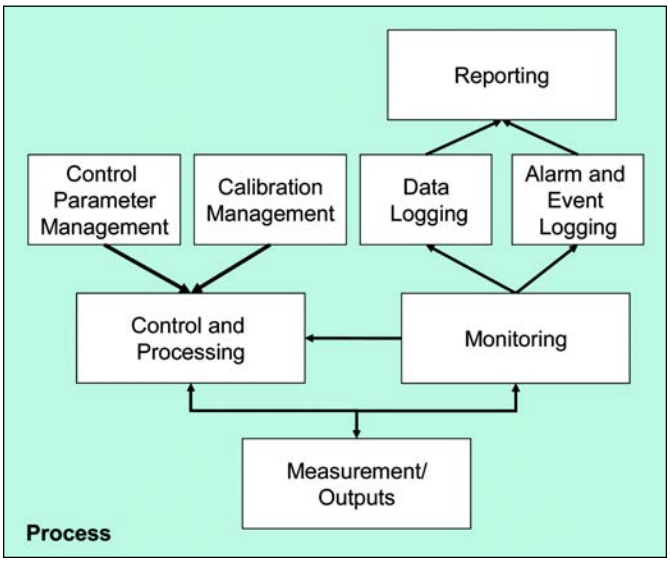

Figure 1. BMS functional model.

(iii) ability to readily detect product attributes downstream of the process
(iv) BMS often cover both regulated and non-regulated processes concurrently.
(v) BMS can sometimes be difficult and expensive to validate, especially when deployed centrally, utilizing older technology, evolved over a period of time
(vi) There are a number of different implementation strategies that impact the criticality of the BMS (e.g., use of independent monitoring systems)

A number of topical issues are considered by this position paper including:

(i) the need to validate BMS controls when validated/calibrated independent monitoring is in place
(ii) relationship between BMS risk and process/product risk
(iii) good design practices for new BMS
(iv) good Engineering Practice
(v) mitigation options for existing BMS
(vi) electronic record implications

The ISPE GAMP® Forum has developed this position paper to provide practical risk based advice regarding the implementation and management of a BMS within regulated healthcare industries. In drawing its conclusions, this position paper attempts to utilize and build on existing guidance currently available within industry, in particular ISPE Baseline® Guides.

This position paper focuses on the computerized aspects of BMS; however, the principles and issues raised by this position paper also may be beneficial when considering associated equipment (e.g., HVAC and other examples). Within the context of this position paper, the term 'process' relates to environmental control and monitoring, storage condition control and monitoring, and utility production, etc. The examples used in this position paper relate to environmental control.

It is recommended this position paper is considered within the overall context of the ISPE GAMP® Good Practice Guide: Validation of Process Control Systems.

BMS Scope and Definition

BMS may be used as a collective noun for a range of computerized systems including Programmable Logic Controllers (PLC), Supervisory Control and Data Acquisition Systems (SCADA), Distributed Control Systems (DCS), Outstations/Controllers and Instrumentation.

BMS may be deployed and managed centrally as a large network of systems that may comprise different vendor products, or as a low complexity standalone system.

The type of computerized system deployed and the scope, size, and complexity of the system will determine the level of difficulty in demonstrating that the system is fit for purpose.

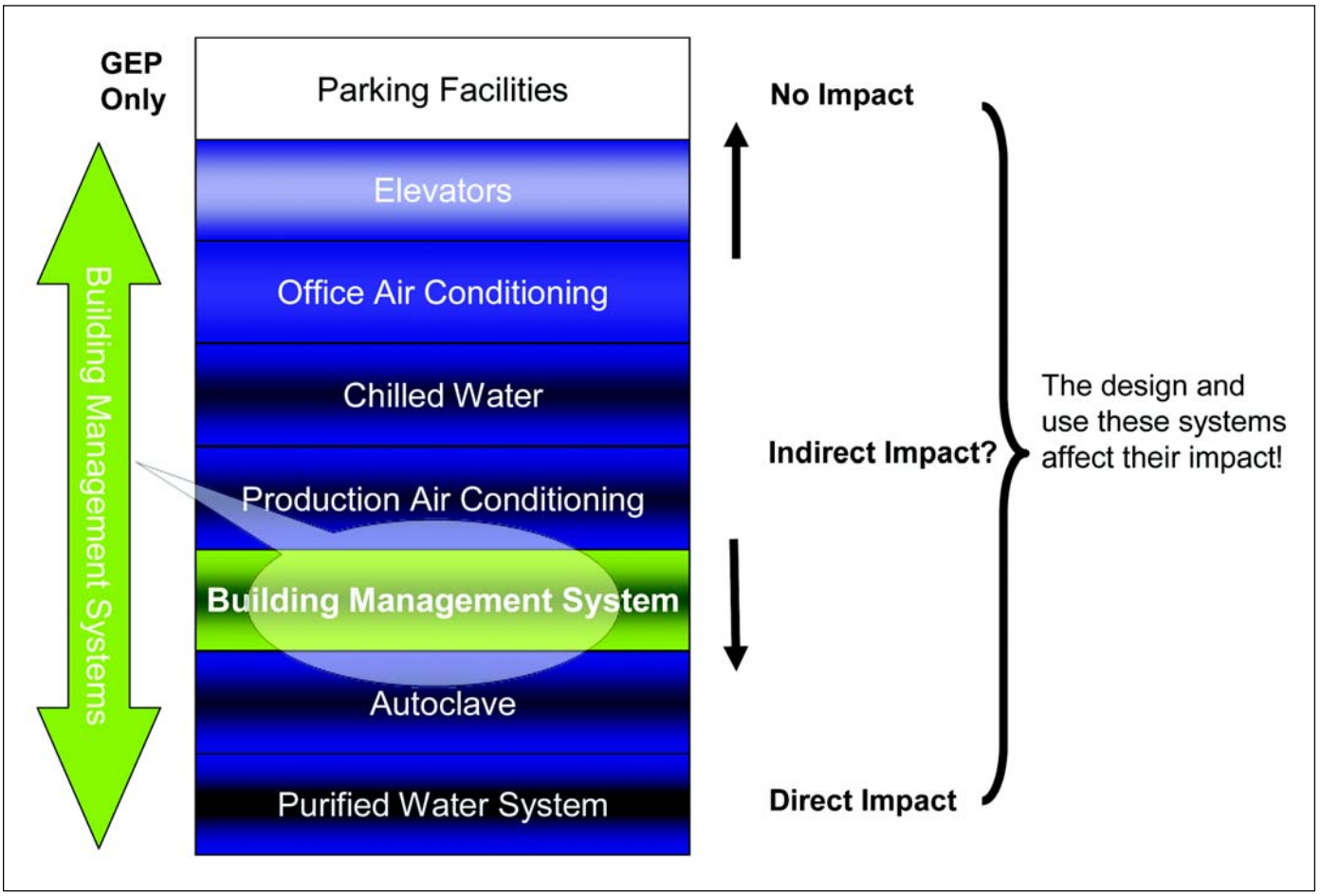

Figure 2. Adaptation of the ISPE Commissioning and Qualification Baseline® Guide Impact Spectrum.

Some of these issues are discussed later; however, initially this position paper focuses on a functional model of the BMS rather than its physical architecture - *Figure 1.*

Instrumentation and Devices

Instrumentation and devices communicate measurements and status information to the control and monitoring logic usually in the form of digital and analogue inputs. Such information is interpreted by the control logic in order to deduce control actions that are used to refine the process control. The installation, calibration, and tuning of such instrumentation is critical to the process control and monitoring.

Control

Control is typically provided by assembling standard control functions, e.g., control loops (P&ID or Ratio) and Start/Stop functions, into the required control scheme. Control and calibration adjustment parameters are inputs to the control scheme that establish process characteristics, process timings, and responsiveness of the control scheme.

Monitoring

Feedback from instrumentation influences the control scheme that will respond, in order to maintain process parameters within configured limits. Integrated and/or independent monitoring functions scale and check inputs against pre-configured statuses and limits, setting alarm conditions when deviations are detected.

Control Parameter Management

Control Parameter Management enables users to change control parameters in order to achieve the desired characteristics of the process, e.g., temperature and humidity setpoints, tolerances, time spans, alarm limits, dynamics. Such parameters are usually entered via centrally/locally located graphical user interfaces or local/remote devices. Control parameters are usually configured and tested during initial system implementation and modified following process change.

Calibration Adjustment Parameters

Calibration adjustment parameters are established and configured during periodic calibration of instruments.

Data Logging

Data logging (historical and point in time) enables the capture and recording of process events and data in order to enable process optimization, investigation, or monitoring. Critical data often forms part of regulated records such as batch records.

Alarm and Event Reporting

Alarms typically warn of pending, actual, and continued deviations from process limits. Events typically provide indication that a process step or condition has been achieved (e.g., start-up complete). Alarms and events may be used to indicate the need for maintenance and/or to report process deviations. Alarms and events may be logged in addition to display and/or printing. Alarm annunciation and reporting may take several forms depending on the purpose and priority of alarms (e.g., screen alarms, email, pagers, buzzers, printouts).

In terms of core functionality therefore, the BMS is no different to any other process control system. The nature of the processes controlled and monitored and their impact on the manufactured product is therefore what defines the BMS criticality. As can be seen from the list below, these processes vary in risk to product:

- Production Facility Heating, Ventilation, and Air Conditioning
- Office Heating, Ventilation, and Air Conditioning
- Laboratory Heating, Ventilation, and Air Conditioning
- Water Purification
- Cold Storage Facility Control and Monitoring
- Fire and Security Alarm Systems
- Energy Management

A basic premise of this position paper is therefore established; *"The criticality of the BMS is dictated by the impact of the process parameters being controlled by the BMS on product purity, safety, quality, and efficacy, not the functionality of the BMS itself."* A blanket statement of whether BMS should or should not be validated is therefore invalid.

It is essential that the impact of the BMS controlled process on product attributes is clearly determined by a team of knowledgeable people that should include Quality Assurance and Engineering.

Definitions

The definitions below are derived from ISPE Baseline® Guide, Volume 5 Commissioning and Qualification and ISPE GAMP® 4.

Good Engineering Practice (GEP)

Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate, cost-effective solutions.

Process Validation (PV)

Establishing documented evidence which provides a high degree of assurance that a specific process consistently produces a product meeting its pre-determined specification and quality attributes.

Qualification Protocol

An individual detailed document that describes the system under consideration, the testing plans, the acceptance criteria, and the test results that ensure that a system is installed and operates in accordance with predetermined specifications.

Regulatory Insight

Having established that the process should be the focus of

risk assessment, it is possible to review regulatory citations over a number of years in order to identify regulatory concerns associated with typical processes controlled and monitored by BMS.

US FDA Warning Letters

Table A summarizes example citations from US FDA Warning letters. While not all of the Warning Letters listed indicate the use of a BMS, the processes and equipment referred to are typical of those associated with BMS.

When reviewing regulatory citations, care should be taken because the context within which the citation is raised is not always apparent. Several of the citations indicate the importance of monitoring key (environmental) parameters against predetermined limits such as temperature, humidity, and differential pressures. Although predominantly focused on

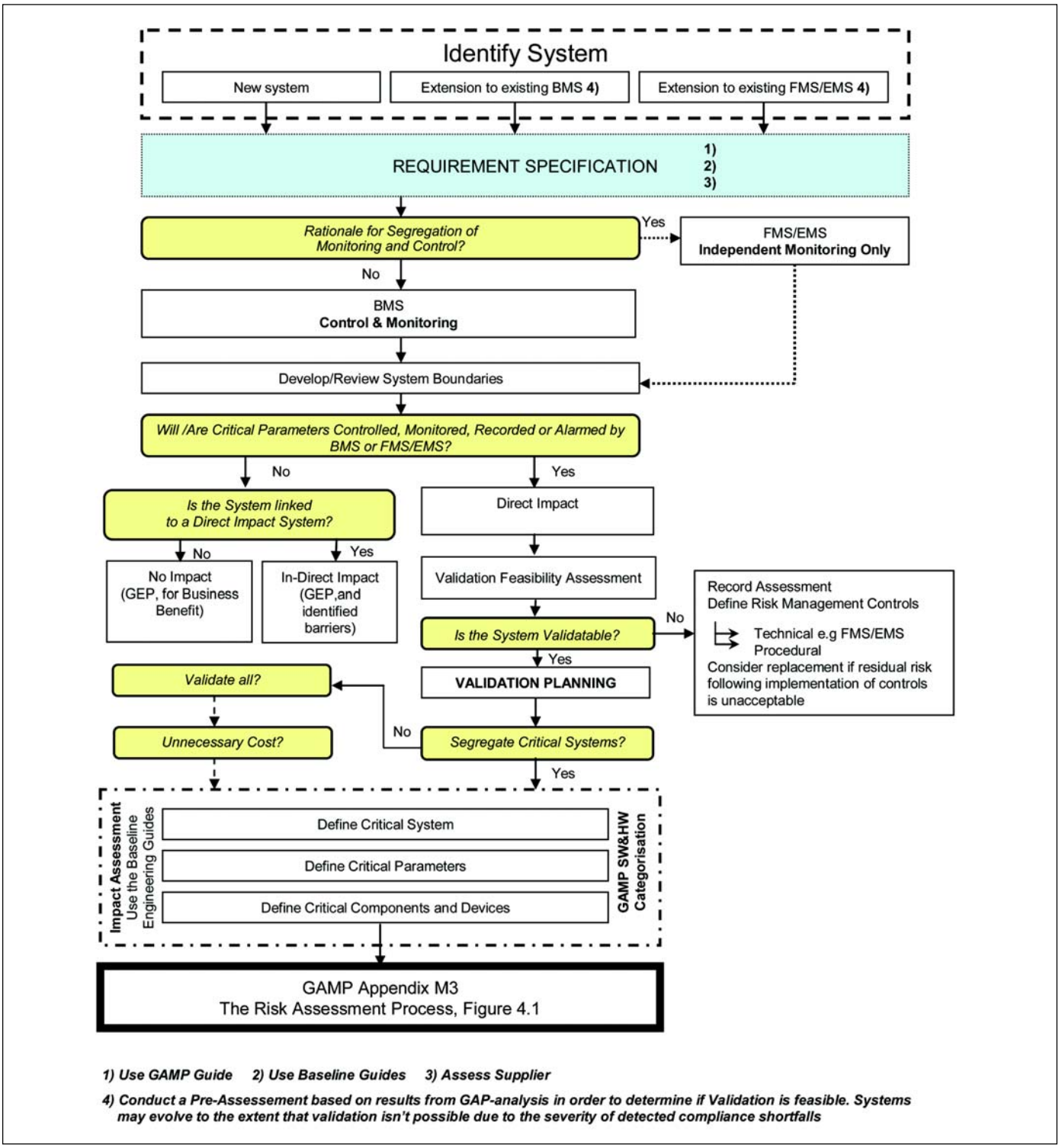

Figure 3. Decision tree.

monitoring, some of the citations indicate a lack of validation/qualification of controls although the criticality of the cited systems to product attributes is not clear from the citation.

Although access to specific European regulatory observations is restricted, anecdotal evidence from industry forums such as ISPE GAMP® Forum suggests that a number of companies have been challenged by European regulators about control of their BMS. Table B provides a summary of regulatory citations from the UK Medicines and Healthcare Product Regulatory Agency (MHRA), published February 2003. Although these observations reflect a fixed period in time, they serve to demonstrate that processes controlled and monitored by a BMS, and where implemented, independent monitoring systems are considered important by regulatory authorities.

The MHRA inspection findings reiterate the importance of monitoring critical (environmental) parameters while also demonstrating the importance of sterility assurance and cross contamination risks.

By raising issues relating to temperature, humidity, differential pressure, containment, and sterility, it might appear natural to conclude that, as a BMS often controls equipment that maintains such parameters, the BMS must be critical itself. However, the criticality of the BMS can be determined only through a risk assessment that considers the consequence on product attributes of failure of a parameter. The probability of impact and ability to detect such a failure also must be considered. ISPE GAMP® 4, Appendix M3 provides guidance on risk assessment.

Review of Existing Industry Guidance

The ISPE Baseline® Guides provide guidance on a number of BMS related issues. Table C, Summary of Current BMS Guidance Related documents, highlights some of these issues.

The extracts reviewed are mainly based on Environmental Control and Monitoring Systems (e.g., HVAC), as much industry discussion emanates regarding these systems. As with the review of regulatory citations, some key messages can be derived from the guidance:

- It is important to monitor and where necessary log critical parameters.
- Aseptic processes should be considered as direct impact.
- Consideration should be given to validation of direct impact systems.
- Independence of monitoring systems from control may simplify validation considerations.
- Monitoring systems may range from manual, hand held monitoring devices through to computerized Environmental Monitoring Systems (EMS).
- The selected monitoring method should be based on criticality of monitored parameters with respect to product attributes.

Figure 2, reproduces a figure from the ISPE Baseline® Guide, Commissioning and Qualification. The Baseline® Guide diagram largely relates to processes; however, a BMS is a computerized system used in the control and/or monitoring of such processes. As such, a BMS may better be considered as a sliding scale of impact. Clearly, the diagram indicates the need for increasing Quality Assurance rigor as process criticality increases. As such, where a BMS is used to control and/or monitor such processes, the criticality of BMS components increases in line with process criticality. As with all computerized systems, the extent of the BMS criticality is determined by the influence of the BMS on critical product attributes.

Citation	Clause (where stated)	Warning Letter Date
"Qualification and control of the ambient temperate and accelerated temperature stability rooms is inadequate ....."	211.166	July 01, 1999
"The alarm system that communicates, records, and controls alarms such as air balance and temperatures for production, warehouse and testing areas lacked validation documentation"	Not stated	January 2001
"No evidence that your firm investigated temperature failures that occurred for the incubators and refrigerators"	211.22(a)	January 16, 2001
"There is no written procedure in place for, nor is there any testing performed, for the environmental monitoring ....."	211.160(b)	
"Failure to validate equipment for example ..... Failure to document the rationale behind established alarm times to monitor the specified differential air pressures within the manufacturing areas"	211.168	March 02, 2001
"You have failed to validate the HVAC system used to control temperature and relative humidity in your manufacturing and warehouse areas". "No formal specifications for temperature or humidity have been established for these areas." "You were noted to have portable chart recorders for monitoring of temperature and humidity in Suites 1 and 2 and one recorder was noted in the warehouse." "A wide range of temperatures and humidity was noted in our review of the data from the monitored areas. ...."		August 14, 2001
"IQ and OQ which support .... production .... The list of deviations include ... replacement of HVAC systems and its control system." "IQ and OQ which supports coating ..... list of deviations and resolution plan include failing acceptance criteria for temperature and pressurization flow direction ..... updating control system ... converting to a... control system" "IQ and OQ which supports coating ..... list of deviations and resolution plan include failing acceptance criteria for temperature, HVAC alarm and interlock testing ....."		February 15, 2002
"No documentation of the validation of the air handling system or the water system used in production"	211.42	October 10, 2002

Table A. US FDA regulatory citation examples.

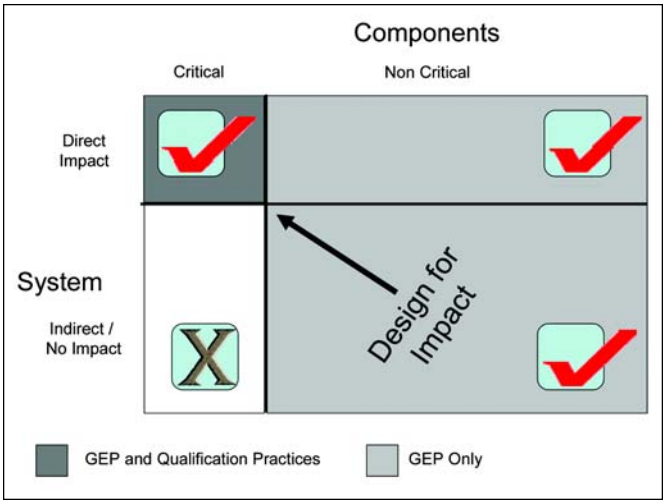

Figure 4. ISPE Baseline® Guide, Commissioning and Qualification – System/Component Criticality.

Risk Assessment

Review of regulatory citations and industry articles has illustrated the importance of risk assessment to determine the criticality of BMS components and functions and where implemented, independent monitoring systems. Figure 3 describes the decisions to determine the appropriate strategy for new and existing systems.

The key to the risk assessment is in understanding what the critical process parameters are. In the context of this position paper, critical process parameters are those parameters that have a high probability of affecting product attributes if they deviate from stated limits for a defined period of time. A functional risk assessment in accordance with ISPE Baseline® Guide to Commissioning and Qualification and GAMP® 4 will determine the consequence of functional failure, probability of impact, and ability to detect product impact. When conducting the risk assessment, there are many considerations that need to be made when determining the risk, some of which are listed below:

- criticality of the product (e.g., final product, intermediate, bulk)
- product characteristics (e.g., is the product hygroscopic)
- probability of a process parameter deviation (e.g., temperature, humidity, airflow) impacting product attributes (e.g., if product temperature is critical to stability, how likely is a deviation in air temperature to affect product temperature for a sufficient duration to affect stability)
- probability of a critical parameter deviation being detected before it could reasonably affect product attributes
- probability of a simultaneous failure of control and monitoring functions
- Is data from a component of the system used to demonstrate compliance with a registered process?
- Is data from a component of the system recorded as part of the batch record, lot release, or other GMP record/documentation?

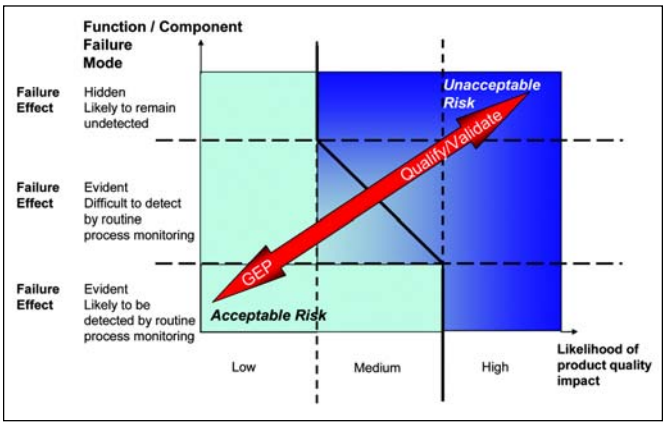

Figure 5. GEP vs. qualification/validation.

When conducting the risk assessment, it is important that individual components and functions of the system are assessed (e.g., alarm annunciation and reporting, instruments, outstations, data historian, network) within the context of their use (e.g., maintenance management, GMP compliance,). The criticality of the BMS, like any other process control system, is dependent of the criticality of the individual components within the system. As illustrated in Figure 4, qualification should be considered in addition to Good Engineering Practice for critical components of a 'Direct Impact' system.

When determining whether or not to qualify aspects of the BMS and any associated monitoring system, it is important to consider the relationships between the process being controlled, equipment (e.g., HVAC) and the computerized aspects of the BMS. It is important to understand the role of the BMS and associated equipment in establishing and monitoring process parameters and ultimately the impact of such process parameters on product attributes. It is important that each component of the overall computerized system be considered including automated and non automated components and that criticality is not assumed simply by association (e.g., aspects of the process are critical therefore the equipment and automated controls must be critical). Some examples of the relationship between product, process, equipment, and BMS are illustrated below:

- consequential impact (e.g., a raise in temperature may not directly impact product; however, the resultant heat profile may give rise to changes in humidity or particulates)
- parameter relationships (e.g., room differential pressure may not be an accurate reflection of air change rates)
- monitoring strategies (e.g., not all critical parameters may be covered by the monitoring system, such as environmental recovery rates, air change rates, air flow patterns)
- criticality of controlled equipment (e.g., HVAC) may not infer criticality of a BMS (e.g., HEPA filter may be critical, but is not necessarily controlled or monitored by the BMS)
- relationship between control parameters and product (e.g., deviation from control parameter may not impact product quality within a reasonable timeframe)

Validation of process endpoints must be considered, such as

environmental conditions as prescribed by international standards such as ISO 14644 and US Federal Standard 209E.

It is likely as with all systems that any validation effort will be focused on critical functions and components only and that the approach to validation of critical components will be scaled according to size, complexity, and standardization of the component.

Change Control

Change control is essential to any system. Changes to the control strategy must be subject to appropriate GEP and/or qualification practices. In particular, it is important that critical process characteristics are proven following change to control schemes.

Implementing New Systems or Enhancing Existing Systems

User Requirement Specifications (URS) are important irrespective of the GMP criticality of any system. For a complex, centralized BMS, there may be several "users" including engineering, system owners, data owners, and QA. It is important that the needs of all stakeholders are captured in the URS (see ISPE GAMP® 4, Appendix D1, Production of a User Requirement Specification). The URS must clearly define the relationships between the BMS (and independent monitoring systems where implemented) and the process(es) being controlled and monitored.

It is important that each requirement be categorized in order to define whether the requirement is safety critical, GMP critical (Direct Impact), business critical, or otherwise. The categorization of the requirements will help determine the most appropriate approach to implementation each requirement, i.e., GEP or validation.

Figure 5 illustrates that the decision to apply GEP or qualification/validation is determined by combining the likelihood of product impact with the ability to detect, and where possible, correct failure. Guidance on approaches to GEP, qualification, and validation can be found in the following guides:

- ISPE Baseline® Guide Volume 5, Commissioning and Qualification
- ISPE GAMP® 4
- GAMP® Good Practice Guide: Validation of Process Control Systems

Irrespective of the criticality of any system, the principles of validation are important in terms of:

- understanding system operation and capability
- understanding and managing system vulnerabilities and constraints
- verifying continued performance
- managing and verifying the impact of system change
- understanding and managing system accountabilities
- enabling recovery from system failure and disaster

Critical GMP Deficiences 02/04			
CATEGORY	RANKING	NO.	
Sterility Assurance	1	6	
Contamination Risk - Non microbial	2	4	
Design and maintenance of premises	3	4	
Environmental monitoring	4	4	
Contamination Risk - Microbial	5	3	
Serious GMP Deficiences 02/03 Third Country Manufacturers			
CATEGORY	RANKING	NO.	%
Contamination Risk - Non-microbial	1	25	16.3
Contamination Risk - Microbial	2	17	11.1
Design and maintenance of premises	3	13	8.5
Environmental monitoring	5	8	5.2
Serious GDP Deficiences 02/03			
CATEGORY	RANKING	NO.	%
General storage - temperature control and monitoring	1	66	32.2
Cold storage - temperature control and monitoring	3	34	16.6
Premises, equipment, calibration	4	17	8.3

Table B. MHRA, BMS related inspection trends.

Specifying New BMS Functionality

The design of the BMS will determine the ease with which the BMS can be implemented, quality assured, and managed in its operational life. Requirements specifications, design and operational controls may consider the following items in Table D.

Where new (greenfield) systems are implemented, some of the issues raised by this paper may not be relevant. New systems should incorporate, where relevant, the design considerations highlighted by this position paper. Further, business benefits rather than compliance benefits may be achieved through the validation of new BMS. Such business benefits may include:

- verification and consistency of control strategy
- increased clarity of system operation and support responsibilities
- improved system maintainability
- defined system enhancement strategy and capability

Existing Systems

As with new systems, risk assessment will determine the need to implement additional Quality Assurance measures for existing systems. A Gap Analysis should be conducted against company standards in order to determine shortfalls. The risk associated with such shortfalls should be documented and appropriate corrective actions taken. It should be recognized that it may not be possible or practical to fully address all identified shortfalls and some degree of operational history may be used to determine adequacy of system operation and control. Typical shortfalls may include:

- Systems may not have been developed to current quality system expectations (supplier and manufacturer quality

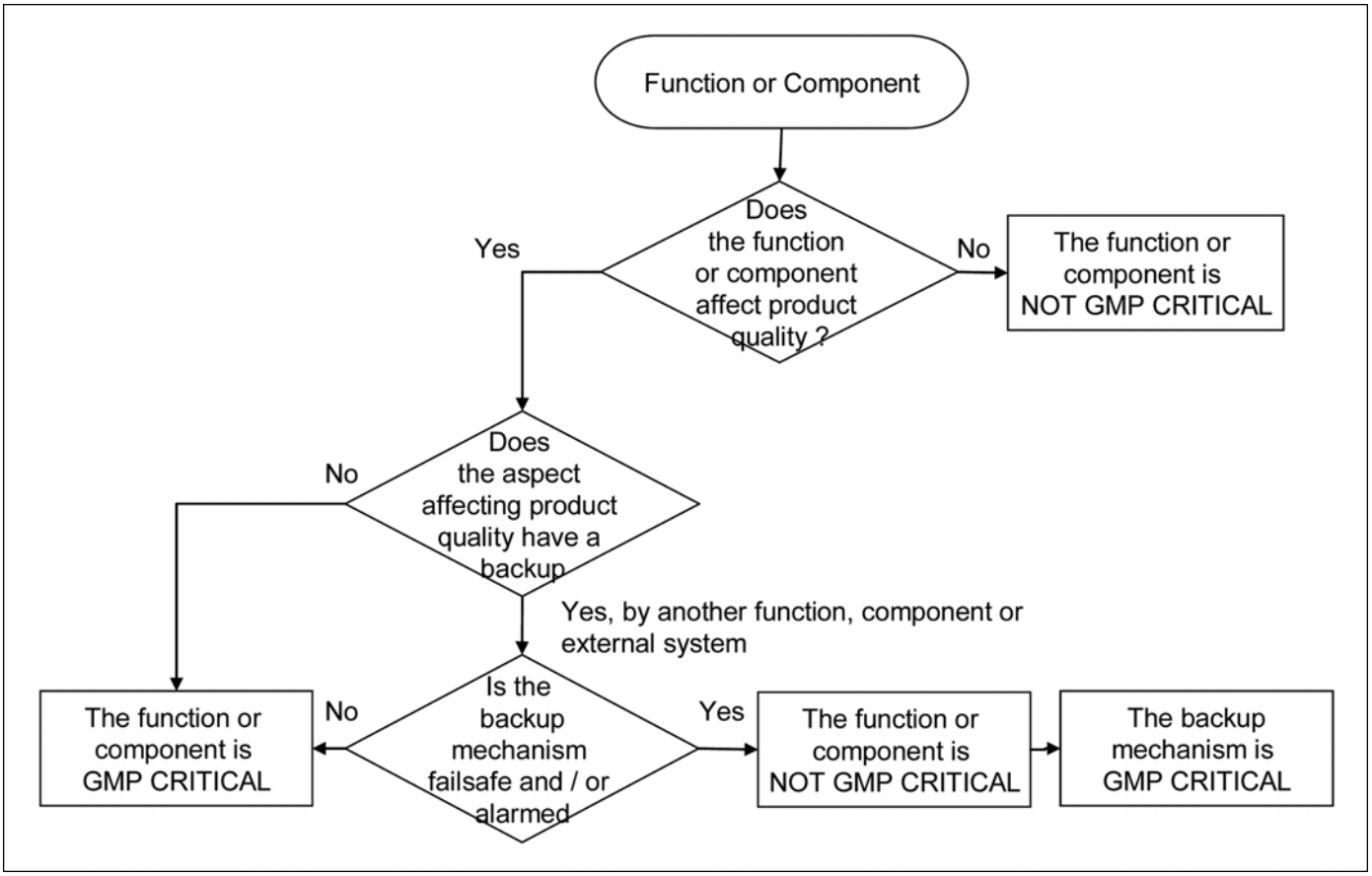

Figure 6. GMP impact and backup systems.

standards).
- Old technologies may be in place that do not allow for implementation of current control requirements.
- Original design may be difficult to modify.
- The scale of technology upgrade required may not deliver acceptable cost/benefit returns.

In such cases, mitigation controls including procedural and where cost effective, technical controls should be considered. Such controls may include:

- redesign (where practical)
- implementation of appropriate automated and/or manual monitoring regimes at a frequency commensurate with risk (including where appropriate validation and calibration)
- implementation of available logical security features (e.g., password controls, review and reorganization of security access rights)
- introduction of physical security controls where possible (e.g., locked cabinets, tamper evident labels, etc.)
- implementation of procedural security measures where technical controls are inadequate (e.g., periodic password change, periodic review of control parameter and alarm settings, control of access to programming devices, periodic review of I/O override settings)
- re-commissioning of areas of the system in accordance with ISPE Baseline® Commissioning and Qualification Guide
- review and adjustment of calibration schedules
- regular system backup

The degree and nature of mitigation controls will obviously depend on the current status of the BMS.

Defining BMS Alarm Strategies

BMS alarms are used to provide information for a variety of purposes including notification of events, pending and actual equipment failures, control limit excursions, loss of controlled conditions. It is important to understand the purpose of all alarms in order that processing and response to such alarms is commensurate with the information being conveyed. For example, an alarm notifying actual loss of critical controlled conditions will warrant a different response to an alarm notifying engineers of the need for equipment maintenance and calibration.

The alarm strategy should consider:

- purpose of each alarm
- priority of each alarm derived from the purpose
- routing of the alarm based on priority
- segregation of high priority alarms from lower priority alarms
- requirements for retention of alarm history

The priority of alarms also will determine who reviews and responds to alarms. For example, where alarms indicate possible product attributes issues, they may need to be investigated by production and Quality Assurance departments. Investigation of such alarms is enhanced when product attributes related alarms are clearly differentiated from other alarms such as maintenance alarms. Such differentiate can be achieved by highlighting product attributes related alarms, routing product attributes related alarms to a dedicated printer or logging device, use of independent monitoring system or otherwise.

Review of Electronic Records and Electronic Signatures

Where the BMS (and/or associated monitoring system) is determined to be GMP critical, an assessment of the impact of electronic records and electronic signatures should be made. A BMS (or associated monitoring system) holds data for a variety of reasons including business management, engineering maintenance, and GMP decision making. The context within which such records are used determines whether they are regulated electronic records or otherwise.

European (Chapter 4, Annex 11, PIC/S), US (21 CFR Part 11), and Japanese (MHLW Guideline) regulations and guidance should be considered as appropriate when determining management controls. Table E defines typical data held by a BMS (and associated monitoring systems) and rationales for electronic records compliance determination or otherwise. The requirements for electronic signatures used within BMS are no different than for any other computerized system.

The risks associated with potential BMS electronic records should be determined in parallel with the BMS functional risk assessment.

Electronic records and electronic signatures considerations should be defined in BMS User Requirement Specifications and verified during design and test activities.

A BMS may be maintained remotely by the BMS supplier or specialist maintenance contractor. Remote access to the system raises questions about the open or closed nature of the system. Controls need to be established that ensure:

- Remote access sessions do not increase vulnerability of the IT infrastructure.
- Security codes are managed by the pharmaceutical organization.
- Remote access sessions are authorized and monitored by

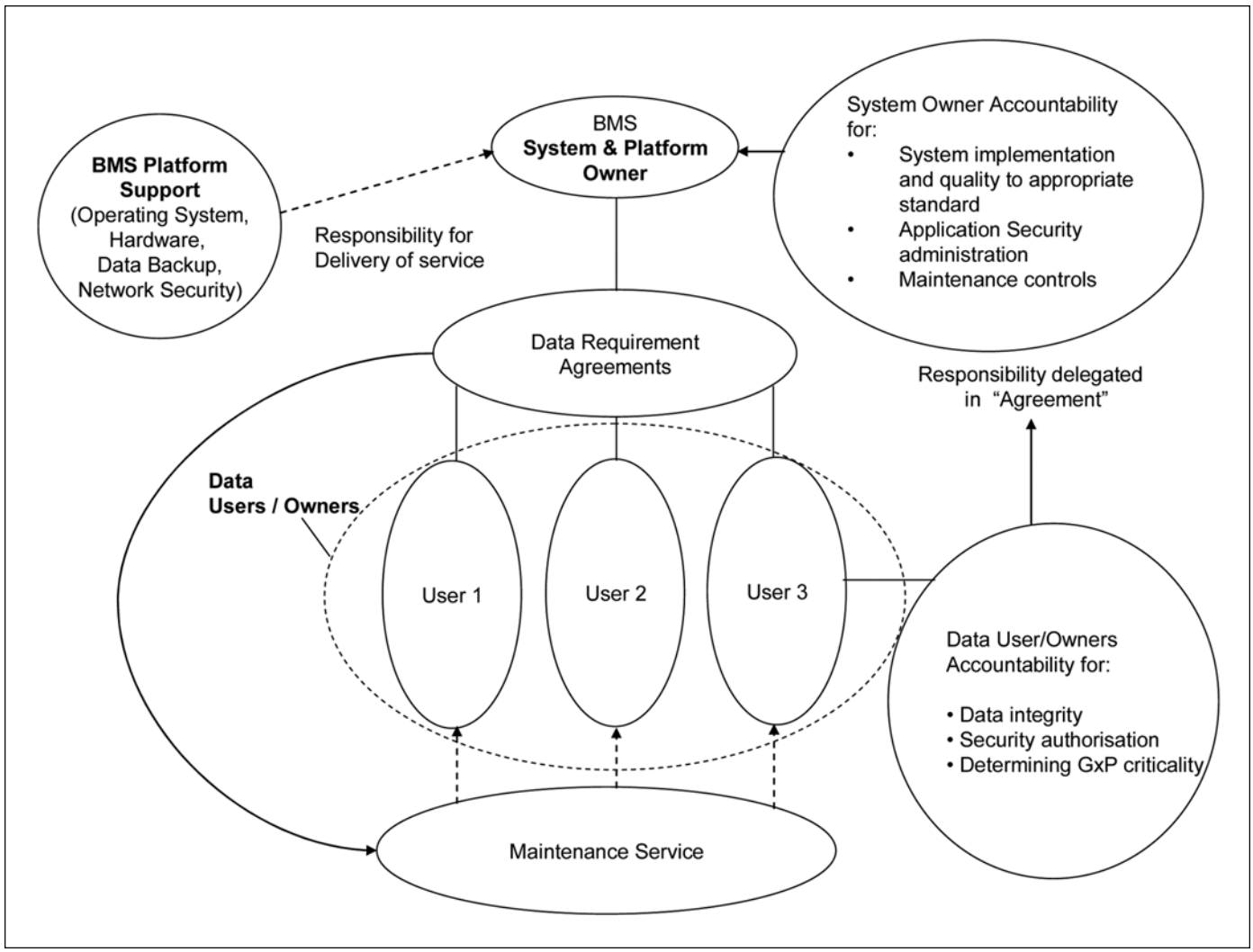

Figure 7. Governance relationships.

the pharmaceutical organization.
- Security audits are conducted to ensure that access controls are not violated.
- Procedures are in place to manage changes and maintenance.

Supplier Relationships

BMS suppliers are integral to achieving appropriate compliance. As with all computerized systems, suppliers may have developed systems prior to the establishment of Quality Management Systems. Suppliers must review current systems and consider practical remediation actions to confirm the quality of systems currently marketed. It is acknowledged that it may not be practical to retrospectively establish design and test documentation for older systems. However, where older systems are still supported, historical performance data should be established to provide a degree of assurance as to the quality of such systems. Such performance data shall be largely based on support records including:

Document	Key Principles	Inference
ISPE Baseline® Guide, Volume 1: Bulk Pharmaceutical Chemicals, Section 6.8 HVAC	Instrumentation should be provided to monitor and record critical room parameters and alarms. It may be possible to monitor, record, and alarm with portable or other instrumentation which is not a part of the HVAC control system in order to avoid validation of proprietary software. It is good practice to monitor the performance of equipment such as fans, coils and control components, but it is not a regulatory requirement, as long as critical parameters meet acceptance criteria. Critical parameters should be monitored, either continuously through the HVAC control or process control automation, or frequently by manual methods. Many commercial HVAC (DDC) control systems provide adequate control, data handling and alarming capability, as long as the system can be validated for critical parameters	Monitoring of critical parameters is important. Monitoring system could be BMS, EMS, portable equipment, chart recorders as appropriate. Avoid controls validation (Bulk Pharmaceuticals). Critical parameters should be monitored at a frequency relevant to criticality of parameters. Monitoring system could be BMS, EMS, portable equipment, chart recorders as appropriate. Component performance monitoring is a GEP issue, not regulatory issue. Where possible to validate HVAC (DDC) for control, data handling and alarming of critical parameters, independent monitoring may not be necessary.
ISPE Baseline® Guide, Volume 2: Oral Solid Dosage Forms, Section 2.4 Extent of Validation	Systems are considered critical, and should be validated when they are either in direct physical contact with the drug product or used to measure, monitor, control or record a critical parameter. Support systems, such a heat transfer systems, electric power and non-process contact water are not critical and need not be validated. The monitoring and control of critical parameters that these support systems affect, however, should be validated	Validate Direct Product Impact Systems. Validate Critical Parameter Monitoring Systems. Support systems do not require validation, however, Good Engineering Practice should be applied.
ISPE Baseline® Guide, Volume 2: Oral Solid Dosage Forms, Section 6.6 HVAC	Instrumentation should be provided to monitor critical room parameters and alarms. It is possible to monitor, record, and/or alarm with portable or other instrumentation, which is not a part of the HVAC control system. Many commercial HVAC (DDC) control systems provide adequate control, data handling, and alarming capability, as long as the system can be validated for critical parameters. However, some commercial grade sensors often are less desirable than industrial grade sensors for critical parameters, from a life cycle cost standpoint, driven by reliability, drift, repeatability, and maintenance cost.	Critical Parameter Monitoring is important (this may be independent automated or manual monitoring). Use of commercial HVAC control systems for critical parameter monitoring may be beneficial if the system can be validated. Quality and accuracy of sensors is dependent on the risk of what they are being used for.
ISPE Baseline® Guide, Volume 3: Sterile Manufacturing Facilities, Chapter 5 HVAC	[5.8.2] ..., it is the monitoring and documenting system that provide "GMP Critical Parameter" data to production staff, hence these systems are direct impact and require qualification studies... It may be preferable that the monitoring and documenting of these "GMP Critical Parameters" should be isolated from any HVAC (Building Management System: BMS) control systems, to avoid qualification complications. [5.8.10] By its nature, the HVAC system serving aseptic manufacturing suite must be a "Direct Impact System", i.e. its failure to perform may directly affect final product attributes. Therefore, qualification, testing, and commissioning, in line with Good Engineering Practice, needs to be considered carefully.	Critical parameter monitoring should be treated as direct impact. Critical Parameter monitoring should be validated. Independent monitoring may avoid complications of BMS validation. Aseptic environments should be considered as direct impact.
ISPE Baseline® Guide, Volume 3: Sterile Manufacturing Facilities Chapter 8 Control and Instrumentation	[8.7.1] Control System Choice HVAC industrial nature in clean room applications may not justify use of PLC or DCS based solutions. Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems. [8.7.2] HVAC Control Systems As the application's scale, complexity, and remote monitoring demands increase, the use of BMS rapidly becomes more cost-effective.	The type of BMS applied is not essential. Business benefit may be derived from using BMS as the scale of the process increases.

Table C. Summary of current BMS guidance related documents.

- reported faults
- risk assessment of reported faults (e.g., potential consequence of failure of reported faults)
- system vulnerabilities (e.g., shortfalls against current industry expectations)
- availability of patches for known faults

BMS suppliers provide support services enabling fault rectification and system enhancement. Such services are provided by remote or on site support. Control and traceability of support services, in particular system modifications, is important. Suppliers are able to enhance client systems and procedures by providing documented, control mechanisms that ensure BMS changes are reviewed, approved, and documented.

Monitoring Systems

The importance of monitoring systems has been established by this position paper and other referenced material. Wingate, in his book *Validating Computer Systems*, uses Figure 6 to demonstrate how backup systems can affect the criticality of the functions

Requirements Aspect	Design Considerations	Comments
System Partitioning	Physically segregate GMP and non GMP BMS	Avoids conflict between GMP and non GMP functions and I/O. Enables boundaries to be put around GMP critical aspects of BMS.
	Logically segregate GMP and non GMP functionality and I/O	Avoids conflict between GMP and non GMP functions and I/O. Enables boundaries to be put around GMP critical aspects of BMS. Must be able to demonstrate that there are no conflicts between GMP and non GMP functions and I/O.
	Segregate (physical or logical) GMP and non GMP databases	Avoids conflict between GMP and non GMP aspects of the system. Not always possible or desirable for operational reasons, e.g., viewing multiple databases.
	Independent local network for BMS	Segregates critical aspects of the system and avoids conflict with non-GMP operations. Security is also easier to manage.
Alarm Handling	Alarm Management strategy defines alarm prioritization that clearly differentiates product quality alarms from maintenance alarms, tolerance alarms and system alarms	Critical process alarms are clearly differentiated from other alarms. Process alarms easily identified. Defined within Alarm Management Strategy
	Separate alarm printouts/logs for product quality alarms	Those alarms requiring Quality Assurance review are differentiated.
Security	Outstation security controls	Prevents inadvertent modification of the control logic and/or critical control parameters.
	Restricted access to maintenance functions.	Minimizes risk of false readings, e.g., through forced I/O settings.
	Workstation multilevel security access.	Ensures that roles can be differentiated and appropriate controls applied, e.g., Engineering Administrator, Quality Assurance, Users, Data Stakeholders.
	Ability to synchronize security settings across the BMS infrastructure.	Changes to one Workstation reflected across all workstations in order to ensure consistency of access from different points.
Instrument Failure Detection	Detection of instrument failure, isolation, manual override.	Enables validation of data input/output and ensuring integrity of process control and monitoring.
Communication Failure	Detection of data transfer failure	Ensures integrity of process control and historical data capture. Ensures integrity of data timestamping.
Data storage failure	Detection of data overload following communications failure or similar events	Ensures that critical events and data are recorded in accordance with design.
Planned Enhancement Capability	Built in expansion to allow for easy addition of control and monitoring points	Easier validation/GEP of upgrades. Reduces pressure to combine GMP and non GMP functionality.
	Backwards compatibility to enable controlled upgrade	Easier to maintain validated/GEP status following upgrade.
Testing	Simulation Tools	Enable setting of I/O and status conditions to facilitate controlled testing (note these features can also be detrimental to validation if not provided under appropriate access control).
Documentation Tools	Software tools to enable documentation to be created (also part of baseline of the system. Auditing of future differences against change control records)	Enables ease of documentation and record creation and verification of differences between current and new versions of BMS.

Table D. BMS requirements/design/operational considerations.

within the main system. With respect to BMS, an independent monitoring system would be such a backup system.

Monitoring of critical parameters is essential to ensuring that process performance is established and maintained. Validation/testing/calibration of monitoring systems is important to ensuring:

- accuracy of critical data
- timely notification of potential process deviations
- organization of critical and non critical process performance data

Data Type	Use	Electronic Records Determination (Direct Impact, Indirect Impact, No Impact)	Comments
HISTORICAL DATA LOGGING			
Critical Process Measurements	Support regulatory decision, e.g., batch release Support regulatory investigation, e.g., product adulteration	Direct impact, if used for batch release and investigation Indirect impact, if used for maintenance purposes	Potential to be inspected by regulatory authorities
Non Critical Process Parameters	Used to determine equipment performance and maintenance requirements	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
Energy usage profile	Determine alternative energy strategy or report energy usage	No impact	None
Equipment Failure and performance status	Condition Based Monitoring	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
ALARM AND EVENT LOGGING			
Critical Parameter Deviations	To determine process deviations	Direct Impact, if alarm logs are retained in electronic history files to support future investigation or used in batch record. Indirect Impact, if alarm logs used for maintenance.	If alarms simply annunciate and are then printed, no electronic record exists. If alarms are saved to removable storage media, then such media should be managed to prevent unauthorized change.
Equipment Failure and performance alarms	To determine need for maintenance	Indirect Impact	Indication of maintenance requirements does not necessarily indicate a process failure or product impact
System Events	To determine system performance	Indirect Impact	Indicates system status, e.g., communications failure, I/O failure, disk storage failure. Requires investigation and backup data to verify process performance during failure.
CALIBRATION PARAMETER MANAGEMENT			
Calibration adjustment settings	To ensure accuracy of instrument and equipment feedback.	Indirect or No Impact	GMP decisions are not made on calibration adjustment parameters. Change control or operational procedures should be used to manage calibration adjustments. Calibration adjustment parameters should be secure from unauthorized or inadvertent change.
CONTROL PARAMETER MANAGEMENT			
Critical process setpoints, control actions and alarm limits	To establish required control scheme	Indirect Impact	Parameters should be subject to change control/configuration management. Parameter should be secure from inadvertent or unauthorized change. Regulated decisions are made on process performance rather than input parameters. Audit trails may bring business benefit
Non critical Process setpoints, control actions and alarms	To establishing required control scheme	No impact	Non GMP or Indirect Impact processes
CONTROL			
Control logic	To ensure consistent and accurate performance of process to stated specification	Indirect Impact, control logic is software that should be validated or subject to GEP to demonstrate that the system is fit for purpose.	Change control and configuration management should be adopted.
INSTRUMENTATION			
Any readings or records held by instruments are typically transient.	Readings and status of process sent to control logic	No impact, assuming measurements are transmitted to control and monitoring system and not retained and used within instrument i.e. they are transient in nature.	Instruments may be configured in order to establish operating ranges and control parameters. Such configuration should be subject to configuration management.

Table E. Electronic records rationales.

The above may be achieved by integrated or independent monitoring functionality and equipment. However, cost or historical technology issues may warrant the implementation of independent monitoring systems such as EMS. The implementation of independent monitoring systems also may bring the added benefit in terms of minimizing the risk of simultaneous failure of control and monitoring functions. This consideration may be of particular importance when considering existing systems based on older technologies.

It is important with such systems that scan frequencies and measurement accuracy is appropriate to the process and product risks. Where current BMS instrumentation is not capable of meeting such accuracy or reliability requirements, the installation of independent instrumentation may be necessary.

When considering monitoring strategies, automated monitoring systems alone are not likely to demonstrate control of critical process parameters. For example, environmental control, periodic monitoring of airflow, environmental recover rates, non viable, and viable particulate levels may be achieved through manual procedures.

Where the IT infrastructure supporting the BMS has not been qualified, it may be beneficial to establish an independent qualified IT infrastructure to host the environmental monitoring system.

BMS Governance

Many BMS systems are large, complex systems controlling and monitoring a range of GMP and non-GMP processes and data. As such, unlike many other systems, defining a single point of contact for system administration, system ownership and data ownership may be difficult. Nonetheless, it is essential that a model be established that clearly defines the role and responsibilities for:

- platform configuration, maintenance, and support
- system configuration, maintenance, and support
- system use
- data access and management

The model illustrated in Figure 7 is an example of a networked BMS solution. The actual model implemented within an organization will be dependent on the defined roles and responsibilities within the organization. However, the model illustrates the need to consider different roles and responsibilities for the BMS's development, operation, and support. Such roles will include both internal and external organizations.

These BMS management, operation, and maintenance roles should be appropriately documented, for example in a Service Level Agreement between the Engineering Department and other functions in order that all parties understand the potential consequence of their actions on other areas of the system. In particular, it is important that security profiles, configuration management, and change control systems are established in order to minimize the potential impact of a given group of users on another group of users.

Maintenance and Operational Controls

Maintenance and operational control requirements for the BMS are no different to any other computerized system; however, there are some special considerations that warrant inclusion in such procedures:

- provision of system overview
- identification of system and data owners and definition of system and data change authorities
- Changes to controlled and monitored processes and equipment need to consider BMS, including a BMS maintenance strategy.
- System faults and anomalies should be recorded and investigated.
- Controls should be in place to manage and document external support activities, including remote access support (e.g., records of on site and remote support activities must be documented), including potential "open system" controls.
- Change control or equivalent operation controls should be in place to manage changes to alarm limits, alarm messages, graphics, control schemes, data logging.
- Operational data change procedures should be in place (procedural or automated) e.g., set-points.
- Changes to BMS do not always propagate throughout the system. Procedural controls need to be in place to ensure changes are implemented at all locations, e.g., security changes to workstations.
- disaster recovery and business continuity (guarding against data loss)
- risk assessment for acceptable downtime and recovery rates

Good Engineering Practice

The application of GEP differs considerably from organization to organization. GEP has been established for many years and requires the robust specification, design, construction, commissioning, testing, and handover of systems in order to ensure that they are fit for their intended use.

GEP shall ensure that systems are appropriately documented and maintenance organizations are trained in system design and operation.

ISPE Baseline® Guides refer to the need for documented design, design review, commissioning plans, and test records. In this sense, GEP is not significantly different to qualification other than in the rigor applied to the development of documents and extent of Quality Assurance input during the commissioning and test process. This said, the Baseline® Guide to Commissioning and Qualification recognizes the importance of the Quality Assurance role. Dependence on GEP should, therefore, be viewed as the application of professional practices to ensure that systems satisfy their predefined specification and not as an opportunity for inadequate design and testing of systems.

Conclusions

This position paper has illustrated some of the complexities in managing BMSs and the issues faced when determining the most appropriate Quality Assurance strategy for the

BMS. The key points raised by this paper are summarized as:

- Validation/qualification/GEP of existing systems may be difficult or not cost effective due to long term evolution in the absence of appropriate quality management controls.
- Strategic planning of BMS use is essential to clarity of BMS benefits and GMP impact.
- Risk assessment is essential to determining criticality of BMS and any associated monitoring systems (manual or automated).
- Risk assessments must focus on the probability that a BMS controlled process will impact product attributes.
- Validated and/or calibrated independent monitoring systems can reduce the reliance on BMS for GMP decision making and enable a balanced cost/benefit approach to BMS Quality Assurance.
- Consideration should be given to validation/qualification of potentially high criticality aspects of the BMS controls (e.g., aseptic environmental controls).
- GEP should be applied as a minimum Quality Assurance standard for indirect and direct impact BMS systems. GEP represents a professional engineering approach to assuring a system is fit for intended use.
- Documented governance model is essential to control operation, support, and the development of BMS.
- Replacement of older aspects of the system to use current technologies and meet current industry standards may not provide an appropriate cost/benefit balance.

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