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Published on IVT Network (www.ivtnetwork.com)

JVT Volume 27, Issue 6 – December 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
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BIOPHARMA EQUIPMENT DESIGN, QUALIFICATION AND MONITORING MODEL

INTRODUCTION

The commissioning and qualification approach for biopharmaceutical manufacturing equipment has been an established process for decades. The risk-based approach categorizes each as a direct impact or a non-direct impact system [1], where non-direct impact systems are typically only commissioned, and the direct impact systems require both commissioning and qualification activities. This article provides a structured framework for professionals to apply a patient focused approach, in line with current regulator thinking, applying scientific principles while developing a qualification plan for critical aseptic parenteral manufacturing equipment and systems. The proposed model [Figure 2] can bring equipment qualification activities under the lifecycle paradigm, a well-accepted development and qualification practice in the industry. With the emergence of single use systems and small batch sizes fit for emerging new biopharmaceutical therapies [2], such considerations can help in accelerating design, commissioning and qualification to support biologic product launches.

Quality by Design (QbD) acceptance has progressed from the time of FDA's encouragement and the ICH Q8 (R2) [3] adoption. The development and manufacture of drug substances (ICH Q11, 2012) [4], analytical procedure development (ICH Q14, 2018) [5], and clinical studies (ICH E8 (R1), 2019) [6] are some recent examples where QbD has been incorporated [Figure 1].

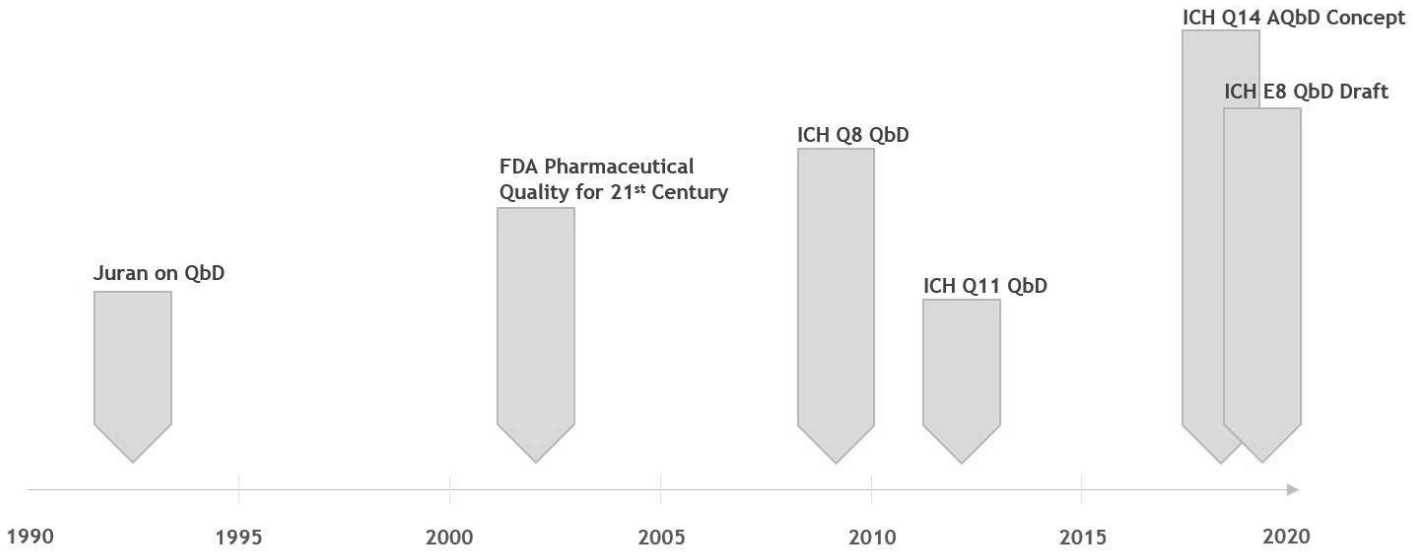

Figure 1: Quality by Design Timeline

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The planned changes to computer software assurance for production and quality system software guidance from FDA [7] provides the insight that regulators thinking has changed. The direction is that documentation generation should be pursuant with the patient risk. The proposal includes opportunity for unscripted purposeful testing that can simulate a real scenario to determine the real impact during use. The approach allows manufacturers to spend more time on early design stage critical thinking/experimentation while spending less time and effort on any nonvalue added downstream document generation exercises. Adopting a true QbD approach to equipment qualification can help the equipment vendors financially gain from the technical support provided during system design QbD experimentation exercise. The owner company can reduce the process development and tech transfer costs with the greater system understanding, supporting their quick to market efforts.

EQUIPMENT/SYSTEM VALIDATION ADHERING TO LIFECYCLE CONCEPTS

The current practice of determining equipment as a direct impact or a non-direct impact system is typically made at the beginning of the project, prior to completion of any experiments that can document the impact to your product or process. With structured experiments at equipment design and selection stage, there is an opportunity to prove that certain system parameter has minimal impact to the product/process, thus reducing the extent of downstream experimentation. For impactful systems on the other hand, the qualification requirements may be predetermined based on the data generated at design stage. Therefore, there are abundant opportunities to embrace the Quality by Design (QbD) concepts, when a science-based design objective with the patient in mind, design of experiments (DoE) to generate system understanding, and a preliminary system control strategy is developed upfront. The exercise supports FDA's expectation of having a justified equipment selection process for construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses. Equipment must be of appropriate design, of adequate size, and suitably located to facilitate operations for its intended use (§ 211.63). The upfront correction of functionality and variability of the commercial manufacturing equipment supports development of a process with reduced variability. Verifying that equipment is built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, functionality, and is properly connected and calibrated), and that the equipment is operated in accordance with the process requirements in all anticipated operating ranges is a guidance requirement. This should include challenging the equipment functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. The cGMP Section 211.180(e) requires that information and data be periodically reviewed to determine whether any changes to the established process are warranted. The 2011 FDA Process Validation guidance therefore introduced Stage 3, continued process verification [8]. Stage 3 continually assesses the variability to improve or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process characteristics.

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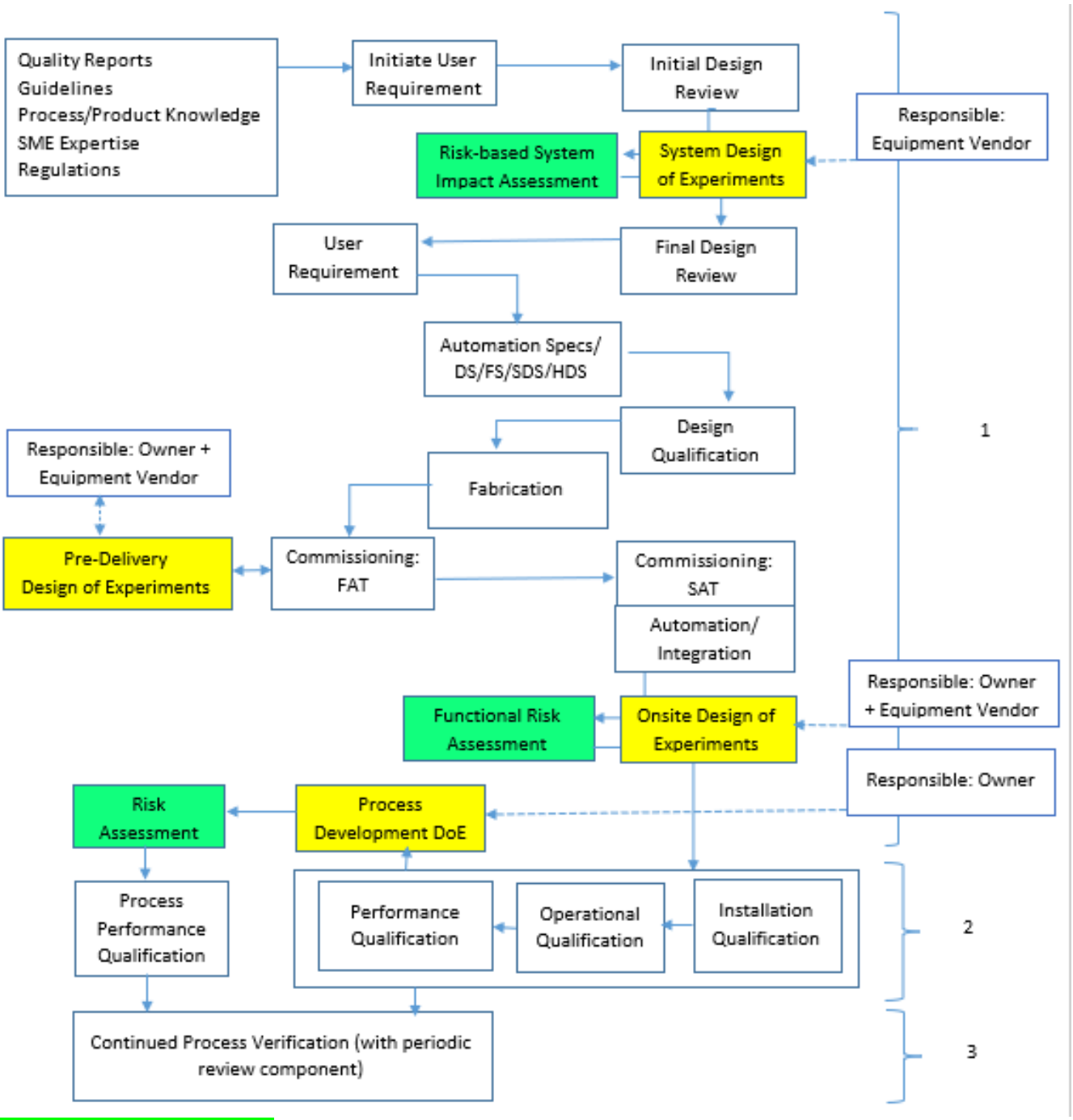

Data driven risk assessments.
Experiments to support science-based equipment design/functionality/parameter requirements and development of variability control strategy.

Figure 2: Lifecycle of Vendor Developed Automated Biopharma Systems

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ADDRESSING THE CURRENT CHALLENGES

The increased process automation in biopharma manufacturing lines necessitates the adoption of lifecycle stages, more particularly the full adoption of QbD design stage concepts. It has to be also noted that the 2011 process validation guidance requirements are relevant to processes that include automated equipment. Robotic process automation as part of the Industry 4.0 innovations is transforming aseptic fill finish lines and inspections. It supports in minimizing process variability, improving efficiency, enhancing repeatability, reducing human interventions, and lowering viable counts, and non-viable contamination with optimal movements. The biopharma equipment innovations with automation include high-speed aseptic processing, vial filling lines under isolators with connected freeze dryer, nested pre-sterilized syringe filling line featuring multiple robot arms, and fully automated vial inspection machines. Such highly automated systems require a structured experiment plan at early equipment selection/design stages.

Figure 3: BioPharma Manufacturing Technology Advancement

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Biopharma manufacturing is undergoing a transformational phase. Organizational product pipelines are more than ever increasing the number of biopharma products based on the recognised patient impact [9]. The regulator has introduced effective policies to re-shore domestic manufacturing [10], and naturally biopharma products have become the priority based on the perceived value and patient need. COVID has further highlighted the manufacturing capacity shortage, resulting in additional investments in biopharma capital projects. Therefore, industry deliberations, specific regulatory guidance, and internal procedural changes to integrate lifecycle concepts to automated systems may not catch-up with the current pace of facility commissioning and qualification in the biopharmaceutical manufacturing segment. Certain enhancements to existing equipment qualification programs can quickly identify and close any potential gaps that may arise while acquiring and qualifying state-of-the art highly automated systems.

The ASTM E2500 expectation is to select equipment, create a specification, and to design it based on patient risk. The current commissioning and qualification structure includes completion of a System Impact Assessment/System Classification (SIA). The first strategy is to enhance the existing SIA, to give the equipment qualification group an opportunity to perform preliminary product quality and patient safety related risk assessment related to the manufacturing systems and the corresponding design solutions. The additional product quality and patient safety related questions can identify potential risk factors earlier such that equipment design/controls can be selected and developed accordingly. The system impact assessment can very well be a risk-based system impact assessment (RBSIA).

The design review requirements in ASTM E2500 [11] are in line with the QbD expectations where manufacturing system is designed based upon knowledge of product, process, and other requirements. Further, the latest automated systems, where process analytical technology are employed need to follow ASTM E2474 requirements. Specification development and design activities should include focus on aspects identified as critical to product quality and patient safety. These critical aspects of the manufacturing system should be identified and documented by the subject matter experts (SME) with knowledge of its impact on the product quality and patient safety. In addition to equipment technical experts, this calls for involvement of SMEs with in-depth knowhow of product characteristics and needs generation of data to understand extent of variability that the manufacturing parameters can contribute to product quality attributes. The ISPE commissioning and qualification baseline guidance describes an approach for performing effective design reviews (DR) for the purpose of confirming if the design meets organizational and regulatory requirements and if it is aligned with organizational best practices [1]. The design review can also capture how the automated system can impact the specific product types and patient safety. The assessment will allow for early design changes to fit the product/process.

A high-level readiness checklist may be applied to assure that the automated systems have generated enough supporting evidence prior to initiating qualification activities. The checklist below [Table 1] is in line with ISPE Good Practice Guide [12] recommendations. The availability of extensive equipment performance data during the pre-qualification stage of the automated equipment in fact supports new technology transfer projects. Understanding of the processing parameters and its impact on the attributes can be utilized while developing the initial setup

parameters for the new product. The data driven optimization study can result in a reduced number of experimental batches at this stage. The involvement of the manufacturing science and technology group during automated equipment design, development, and qualification has therefore becoming critical.

Prerequisite	Status	Which study future will satisfy the requirement?
Equipment operating ranges stressed to the planned commercial ranges?	No	Verified as part of DoE at vendor site
Do we have adequate evidence to support the intended batch size range capacities with automation?	Yes	Verified as part of DoE at vendor site
Do we have evidence that the automated system delivers the expected sterility assurance goals?	No	Onsite Pre-Qualification Study
Has the initial identification of parameters that can impact quality/sterility attributes been complete?	Yes	Risk based system impact assessment
Have the critical component types and product range been identified?	Yes	User requirement specification
Does the automated system require integration with existing site systems (ex SCADA)? If yes, is there supporting data?	No	Onsite Pre-Qualification Study
Is a CQV plan and trace matrix available for the automated system?	Yes	CQV plan

Table 1: Example Readiness Checklist

The majority of biopharmaceutical organizations have effectively implemented the Stage 3 monitoring requirement from the decade old guidance requirement. Per FDA, once established, the qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The equipment and facility qualification data should be assessed periodically. Maintenance and calibration frequency is then adjusted based on feedback from these activities. A well-planned Stage 3 program can essentially integrate in the periodic equipment review requirements, thus eliminating the need for maintaining a separate periodic review program.

CONCLUSION

The trend review of US FDA warning letters from 2012 to 2019 indicates that 55% of the observations were data integrity related and out of that 45% were pertaining to production operations data [13]. Automated biopharmaceutical systems hence need to address during design phase, the potential risks with collection, governance, and maintenance of operations data. Special effort may be required at facilities with legacy lines to revise existing general standard operating procedures such that it can be applicable to the newly introduced automated manufacturing equipment. Enhancement of the existing system impact assessment (SIA) to a risk-based system impact assessment (RBSIA), performing structured experiments with the automated equipment as part of design

reviews (DR), and incorporating a readiness checklist can support the seamless commissioning and qualification of an automated biopharmaceutical manufacturing system. The proposed enhanced commissioning and qualification model supports science and risk-based decision making with respect to the manufacturing equipment, while meeting the FDA, ASTM and industry guidance expectations.

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