A CAI E-Publication:

POWER OF DESIGN REVIEW

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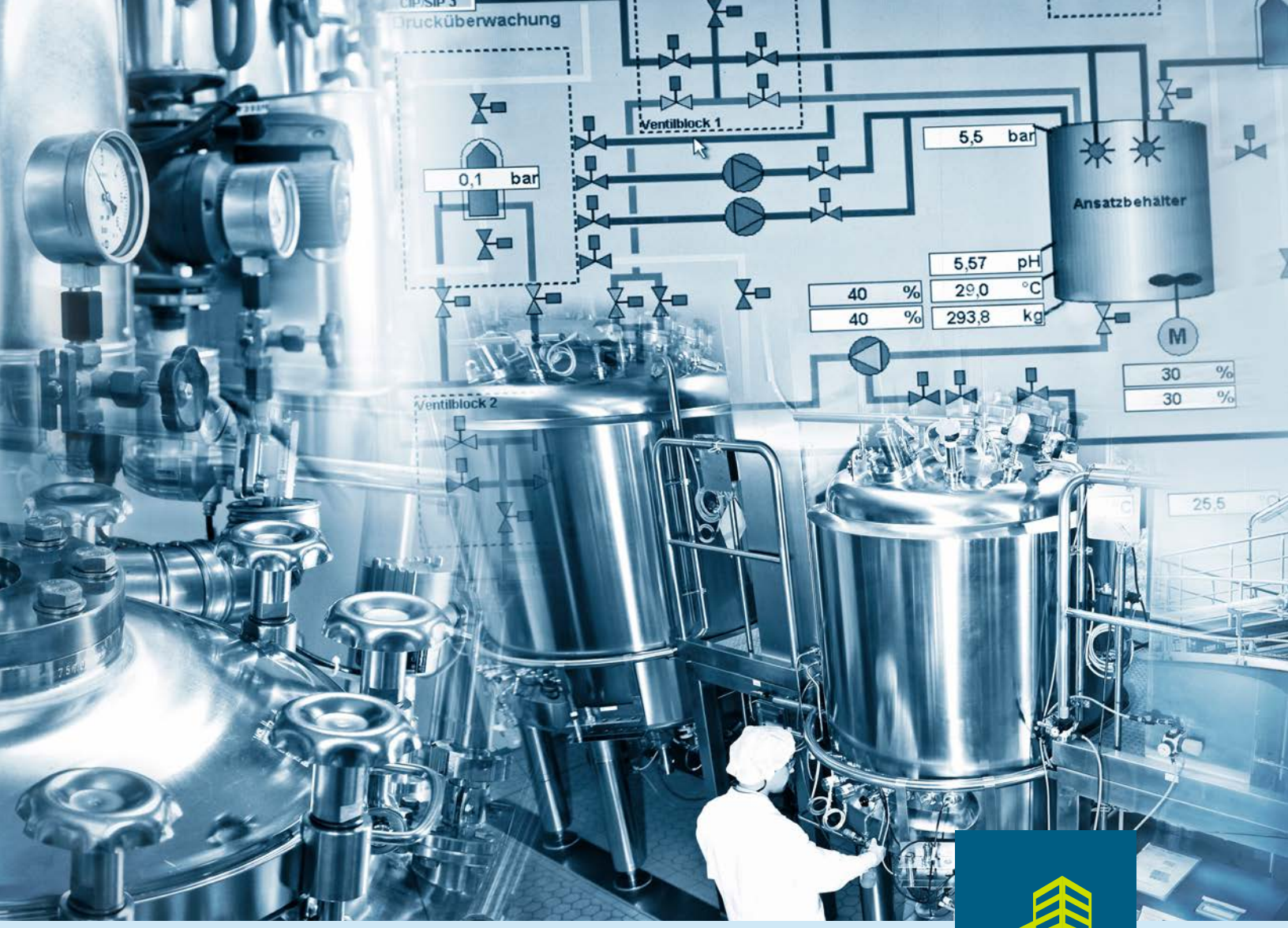

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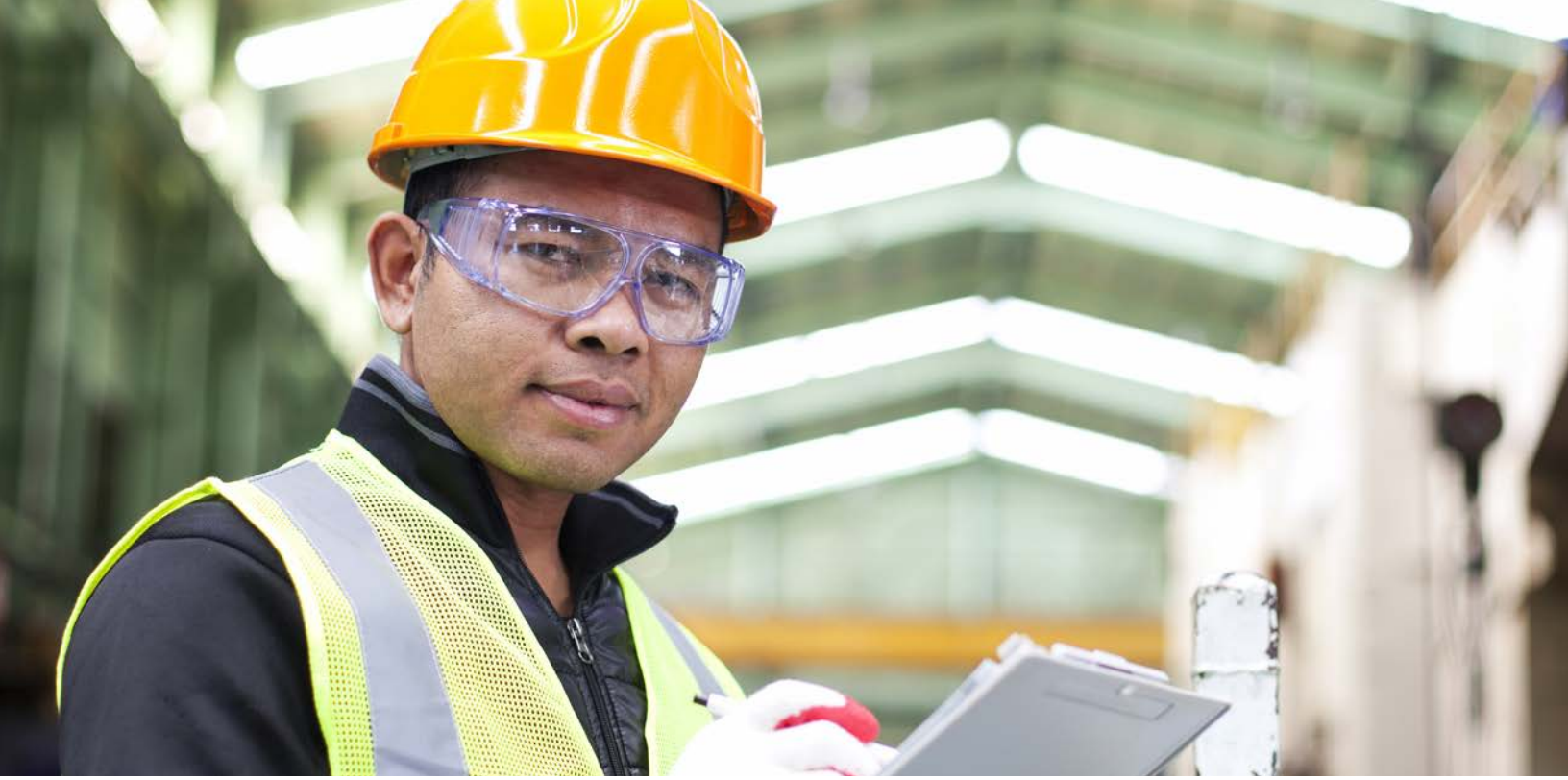


Design Review (DR) and Quality Risk Management (QRM) are considered current industry practice and are essential as enabling processes for verification of facilities, systems, and equipment. But what is Design Review? Why is Design Review underutilized in Commissioning, Qualification, and Validation projects? What are the risks of not performing Design Review? And more importantly, aside from regulatory expectations, what are the benefits of performing Design Review?

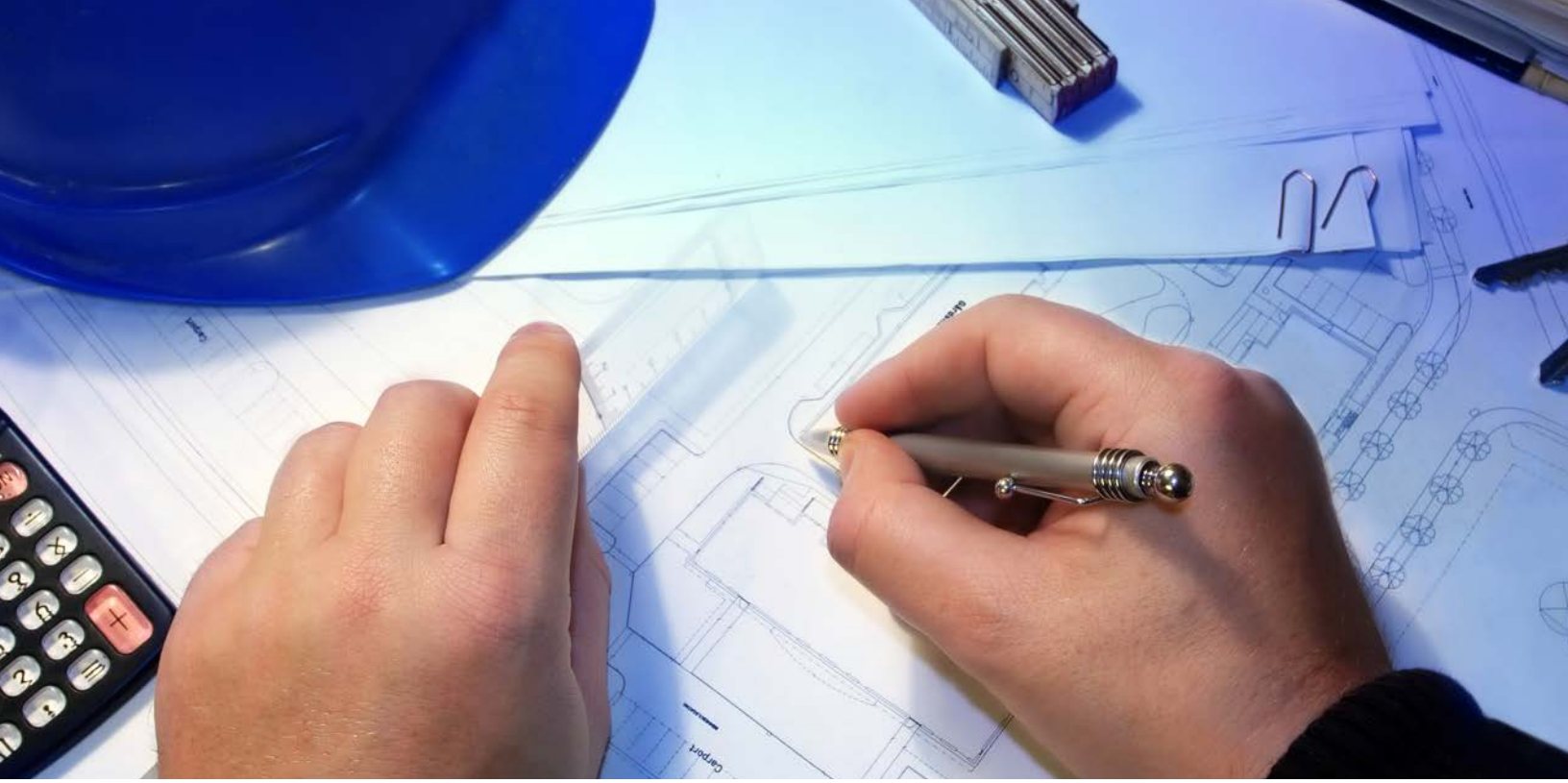
Design Review and cGMP

While it is true that Food and Drug Administration (FDA) Good Manufacturing Practice (GMP) regulations do not explicitly reference Design Review, regulatory guidance regarding Design Review as an aspect of Quality Risk Management (QRM) has evolved. Similarly, industry expectations regarding Design Review both as a component of Good Engineering Practice (GEP) and as an aspect of QRM have evolved. As a result, Design Review as an aspect of QRM-based integrated Commissioning and Qualification (C&Q) can be considered to be part of current Good Manufacturing Practice (cGMP), and thus, a regulatory expectation.

Industry Standards and Guidance for Design Review

ISPE Baseline Guide Volume 5, Commissioning and Qualification, 1st Edition, which represented the industry standard for CQV from its release in 2001 until adoption of ASTM E2500, includes "Enhanced Design Review" as a component of the Commissioning and Qualification (C&Q) process, but states that *"Enhanced Design Review (EDR) is not essential for compliance of manufacturing facilities regulated by the FDA. EDR is not referenced in any regulatory publications as regulations, rules, or guidelines."* However, the Guide also noted that design is referenced in GMP regulations and provided the caveat that DQ was referenced in guidance documents issued or in preparation by other regulatory agencies.

ASTM E2500, *Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,* first released in 2007 and revised in 2013, which represents the current industry standard for risk-based verification, considers Design Review to be one of four enabling processes for verification:



Design reviews should be performed as appropriate throughout the life-cycle of the manufacturing system. The design review process is a supporting process…

In 2008, ISPE issued Good Practice Guide 5, *Good Engineering Practice*, which includes Design Review as a defined project engineering procedure and states:

The regulated company should have a formal system for reviewing the design against objectives to ensure that adequate quality is delivered at optimum cost.

In response to ASTM E2500, ISPE published two documents in 2011: ISPE Guide, Science and Risk Based Approach for the Delivery of Facilities, Systems, and Equipment (ISPE FSE Guide), and ISPE Good Practice Guide 10, Applied Risk Management for Commissioning and Qualification (ISPE ARM GPG). The FSE Guide is ISPE's implementation of ASTM E2500, and the ARM GPG is a bridge document designed to facilitate the industry moving from Baseline Guide Volume 5 (1st Ed) to the QRM approach defined in ASTM E2500.

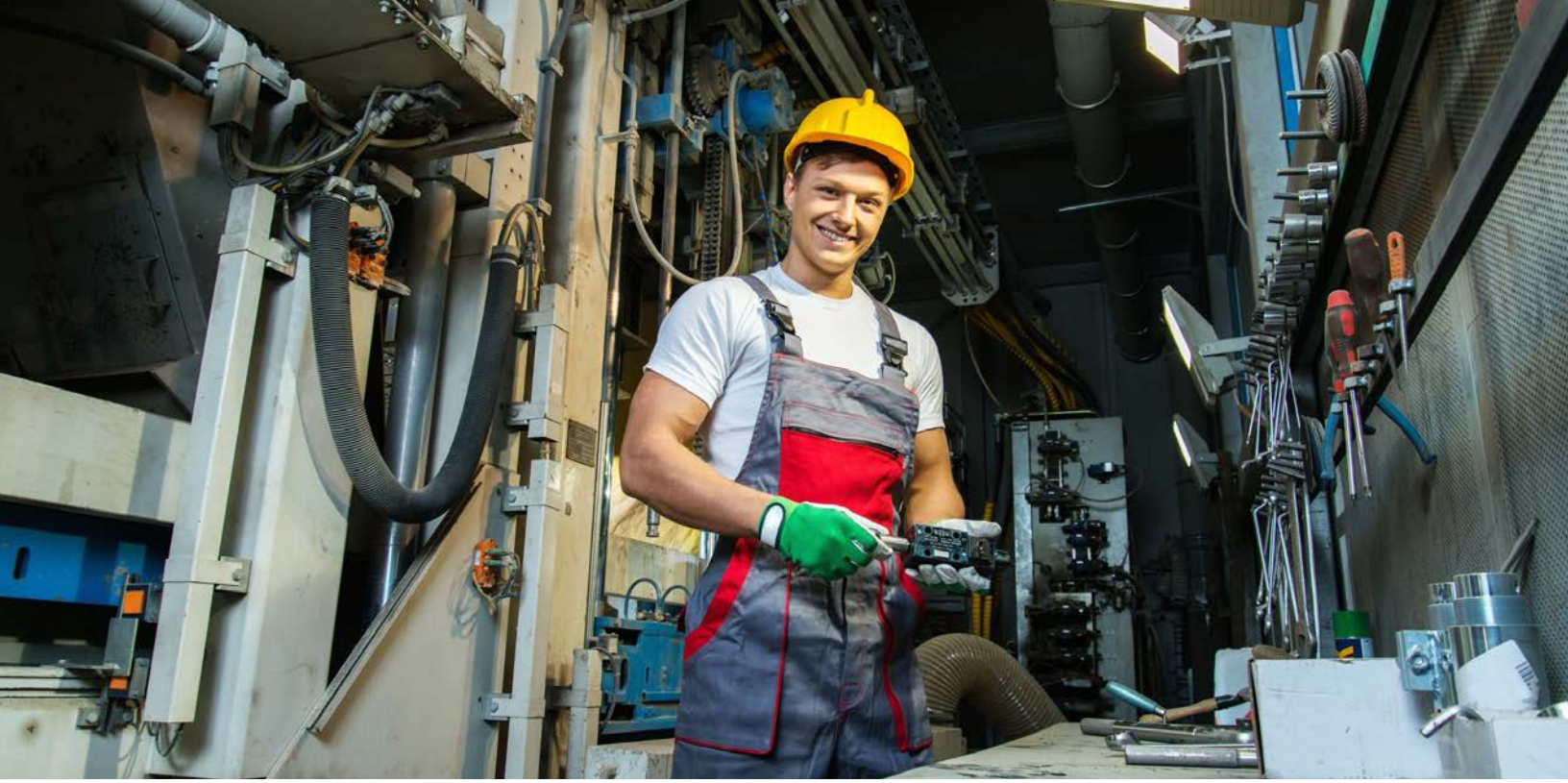
The ISPE FSE Guide states:

Design reviews and risk assessments should be conducted and documented following the requirements definition phase and each sequential phase of the design process. Design processes may need to be iterative; design processes may generate a range of design solutions in response to a single requirement. Risk assessments should evaluate the potential impact of design solutions on the product and process requirements. Design reviews in conjunction with risk assessments should be used to select the most appropriate design option.

ISPE ARM GPG states:

Throughout design development, Good Engineering Practices (GEP) should be applied to evaluate design alternatives and to review design specifications and submittals. These evaluations should ensure that product, process, compliance, and general user requirements have been incorporated into the design.

In addition, a review of the risk assessment results should be performed and enhancements made to the design as required until patient risks have been adequately controlled within the design.



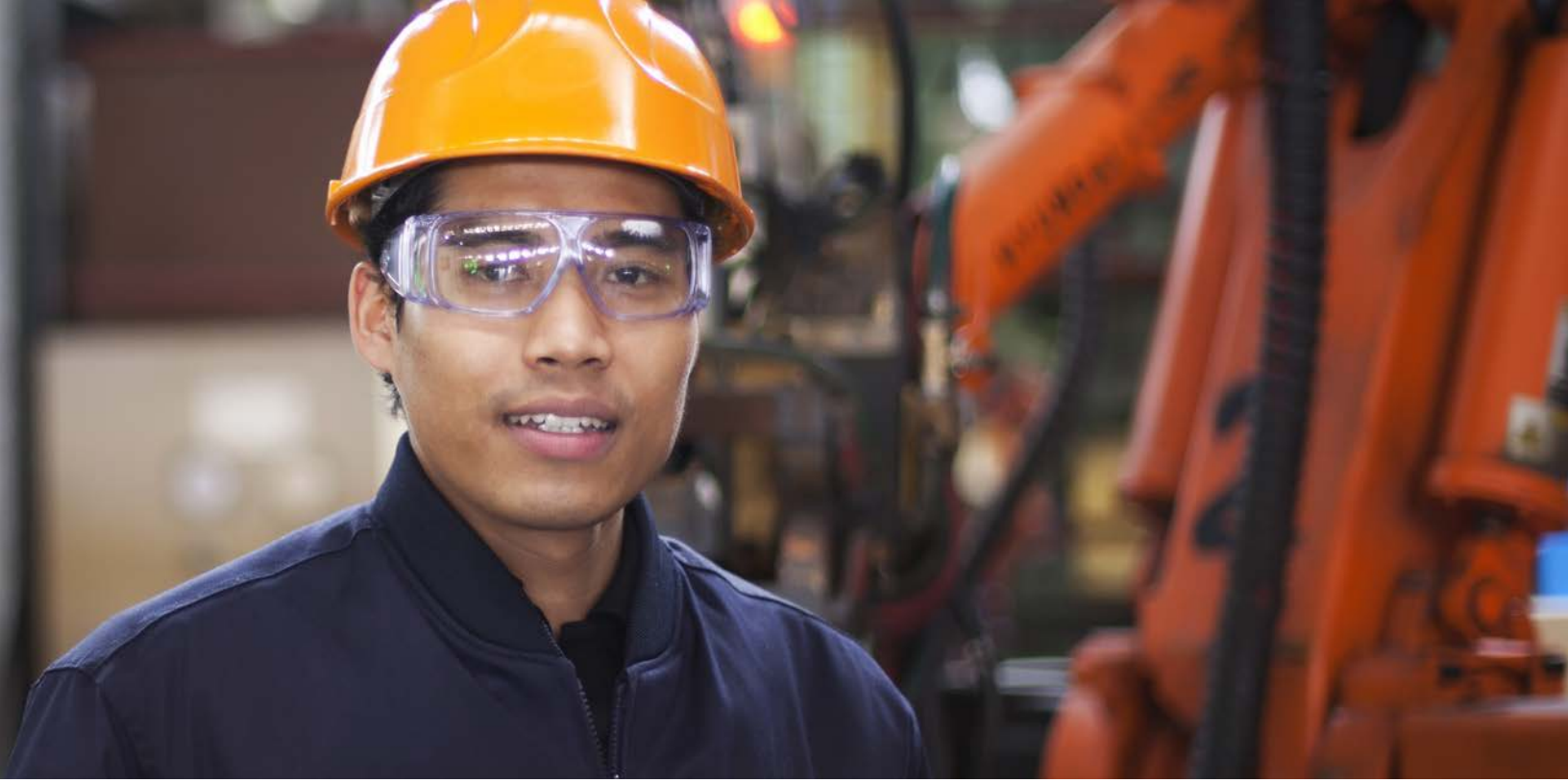
Note: ISPE will soon release the Second Edition of Baseline Guide Volume 5, which will supersede Baseline Guide Volume 5 (1st Ed), the ISPE FSE Guide, and the ISPE ARM GPG, all of which will be withdrawn upon release of Baseline Guide Volume 5 (2nd Ed). The revised Second Edition retires the EDR concept in favor of robust Design Review as a component of GEP (as currently described in the FSE Guide and ARM GPG), and DQ as an output of Design Review that consists of a review of process risk controls that are traceable to Critical Quality Attributes (CQA) and Critical Process Parameters (CPP).

What is Design Review?

Design Review is a current industry practice and a regulatory expectation as an aspect of cGMPs. But what is it? Per ASTM E2500, Design Reviews are "planned and systematic reviews of *specifications, design, and design development and continuous life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.*" Design Review can be considered from two perspectives: GEP and QRM.

From the perspective of GEP, the purpose of Design Review is to ensure that all requirements, including product and process user requirements and general user requirements, federal, state, and local regulatory code compliance requirements, are satisfied by the design; that health, safety, and environmental (HSE) risks are identified and appropriately mitigated by the design; and that business needs, energy efficiency, total cost of ownership, constructability, and other similar considerations are addressed by the design.

From the perspective of QRM, the purpose of Design Review is to ensure that product and process requirements are satisfied by the design, that Critical Aspects are appropriately addressed by the design, that risks to product quality or patient safety posed by the design are identified, and that unacceptable risks to product quality or patient safety are mitigated by the design.



Per the ISPE ARM GPG: *"The effort, formality, and documentation of these reviews should follow the ICH Q9 of being commensurate with the level of risk. Design review documentation may take the form of engineering meeting minutes or notes. For highly critical, novel systems, design reviews and stage approvals may be extensive and generate significant project documentation."*

What About Design Qualification?

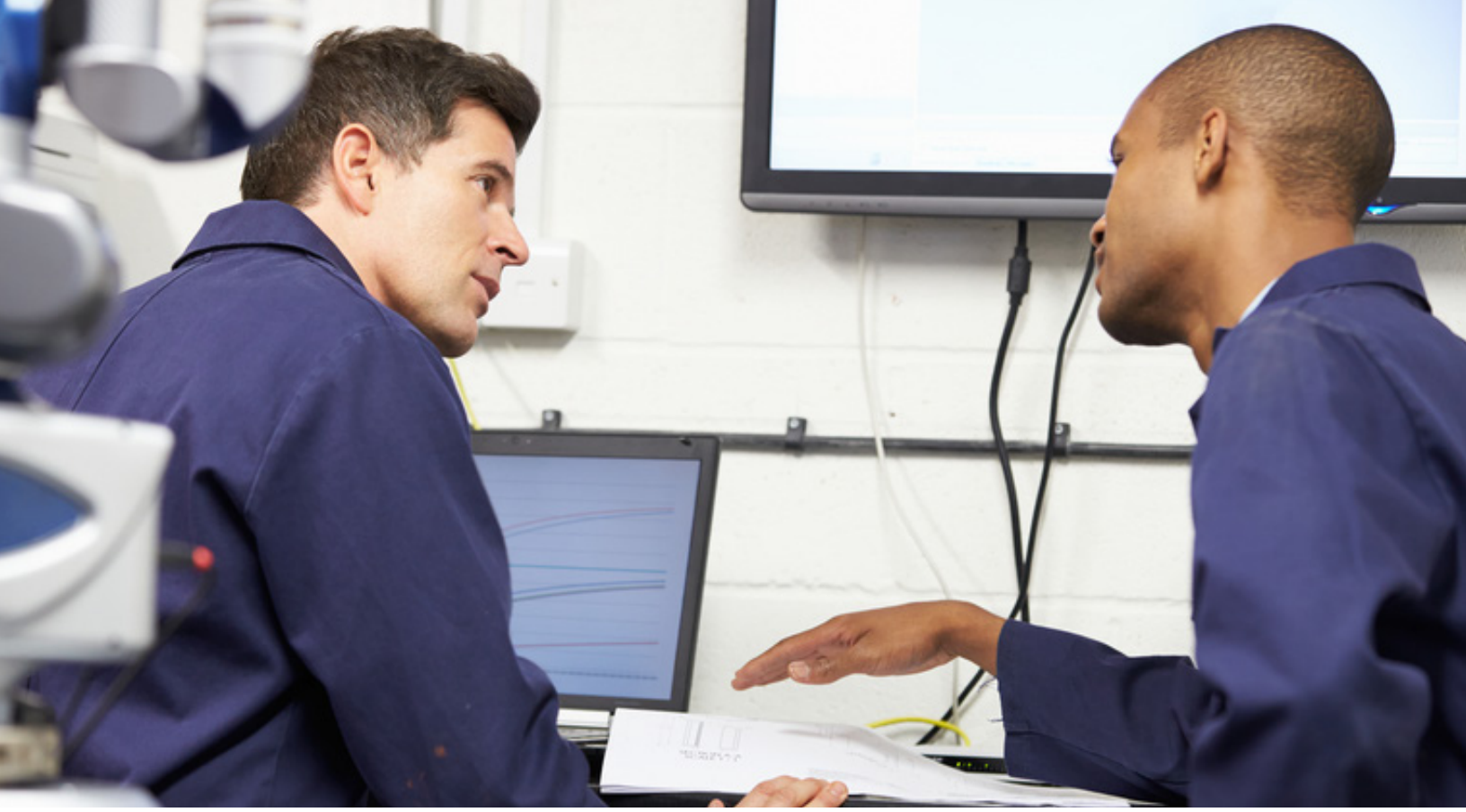
Design Qualification (DQ) is related to Design Review, in that it is an output from the Design Review process. DQ formally documents that the design satisfies Product/Process User Requirements (PURs), that the design of Critical Aspects of the system is fit for intended use of the system, and that identified process risks to product quality and patient safety are acceptably mitigated by the design.

Whereas Design Review is an iterative, Engineering (GEP) process that takes place throughout the lifecycle of a system and is conducted by a cross-functional team of appropriate Subject Matter Experts (SMEs), Design Qualification is a QRM activity, approved by the Quality unit, that takes place at a single point in the lifecycle of a system: Design Qualification is documented using the final, approved system design following completion of the Design phase.

Design Review as a Verification-Enabling Process

So, how does Design Review enable Verification?

To answer that question, let's first look at Verification. Per ASTM E2500, Verification is *"a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other."* As such, Verification, like Design Review, can be considered from the same two perspectives: GEP and QRM.



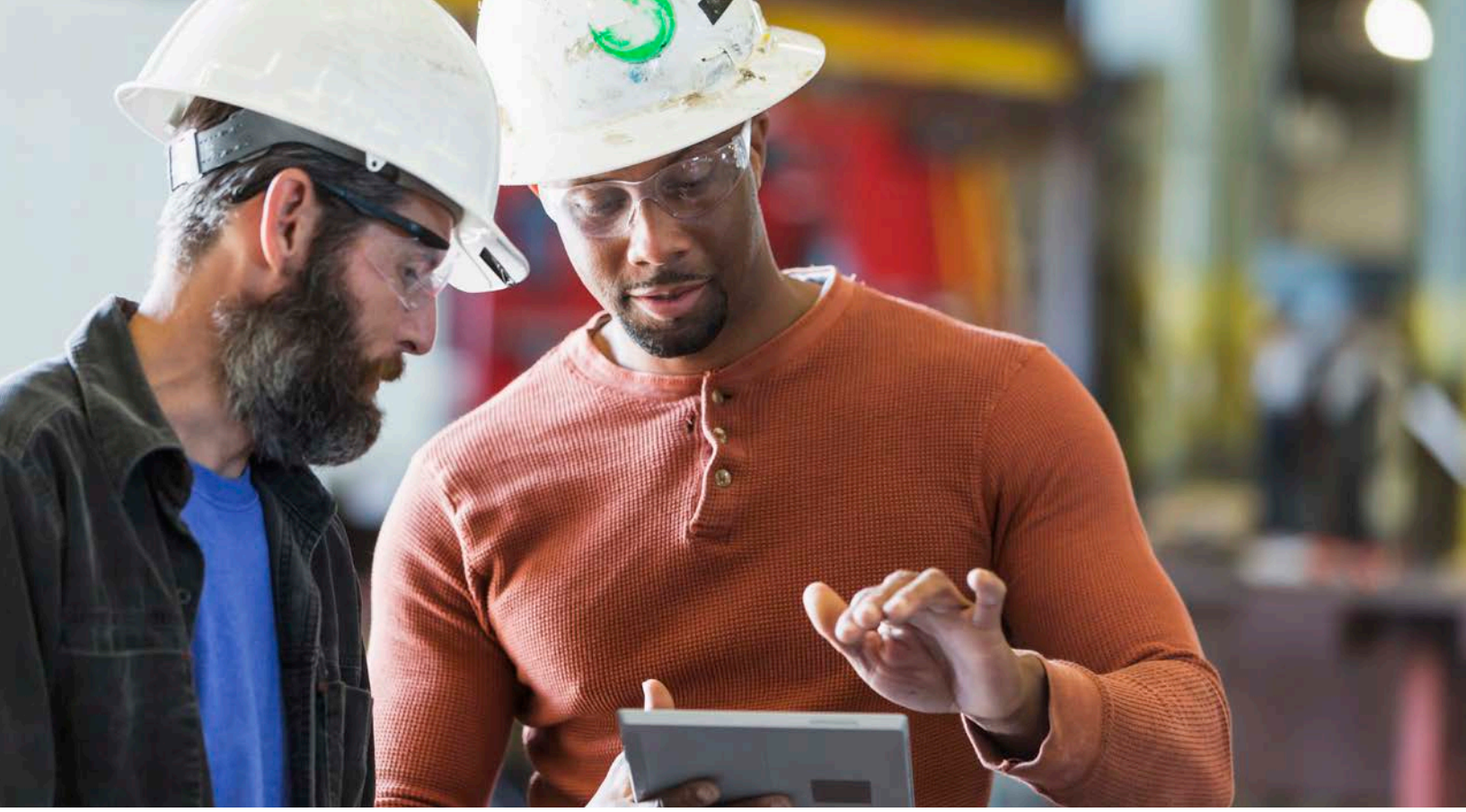
From the perspective of GEP, Verification includes fitness for intended use for all aspects of a system and encompasses both requirements that impact product quality, PURs, and requirements that do not, General User Requirements (GUR). From the perspective of QRM, Verification includes fitness for intended use for Critical Aspects of a system and encompasses PURs only. As with Design Review, the effort, formality, and documentation of Verification activities should also be commensurate with the level of risk.

First, Design Review helps prevent implementation of systems that fail verification testing by ensuring that the design satisfies user requirements prior to procurement or fabrication of the system. As a result, changes, re-designs, and rework during system commissioning are minimized.

Second, Design Review helps ensure that user requirements are well-defined and appropriate. In order to perform Verification, user requirements, and therefore the design aspects that satisfy those user requirements, must be specific, realistic, measurable, and verifiable. Verifying these aspects of the design through Design Review supports and facilitates verification of the system once implemented.

Third, and most importantly from the QRM perspective, Design Review supports definition of the process risk control strategy and identification of Critical Aspects of the system. Design Review identifies process risks to product quality posed by the design and determines the acceptability of those risks. Where identified risks are unacceptable, Design Review ensures that the design acceptably mitigates those risks. Thus, the features of the design that mitigate risk to product quality are identified as Critical Aspects, which combined with Risk Assessment, directly inform the verification strategy to ensure that testing is commensurate with risk.

Therefore, robust Design Review combined with Risk Assessment becomes the key enabler for implementing a science-based, risk-based verification of facilities, systems, and equipment.



Current Industry Design Review Practices

In practice, Design Review is often not performed, performed as an afterthought, or otherwise seen as a non-value-added hindrance to project progress.

Suppliers develop designs from an unclear design basis due to missing or inadequate user requirements, which prevents meaningful Design Review. In the absence of clear user requirements, suppliers follow their own procedures and design standards. In the absence of structured Design Review, suppliers follow their own change management procedures for continued design development.

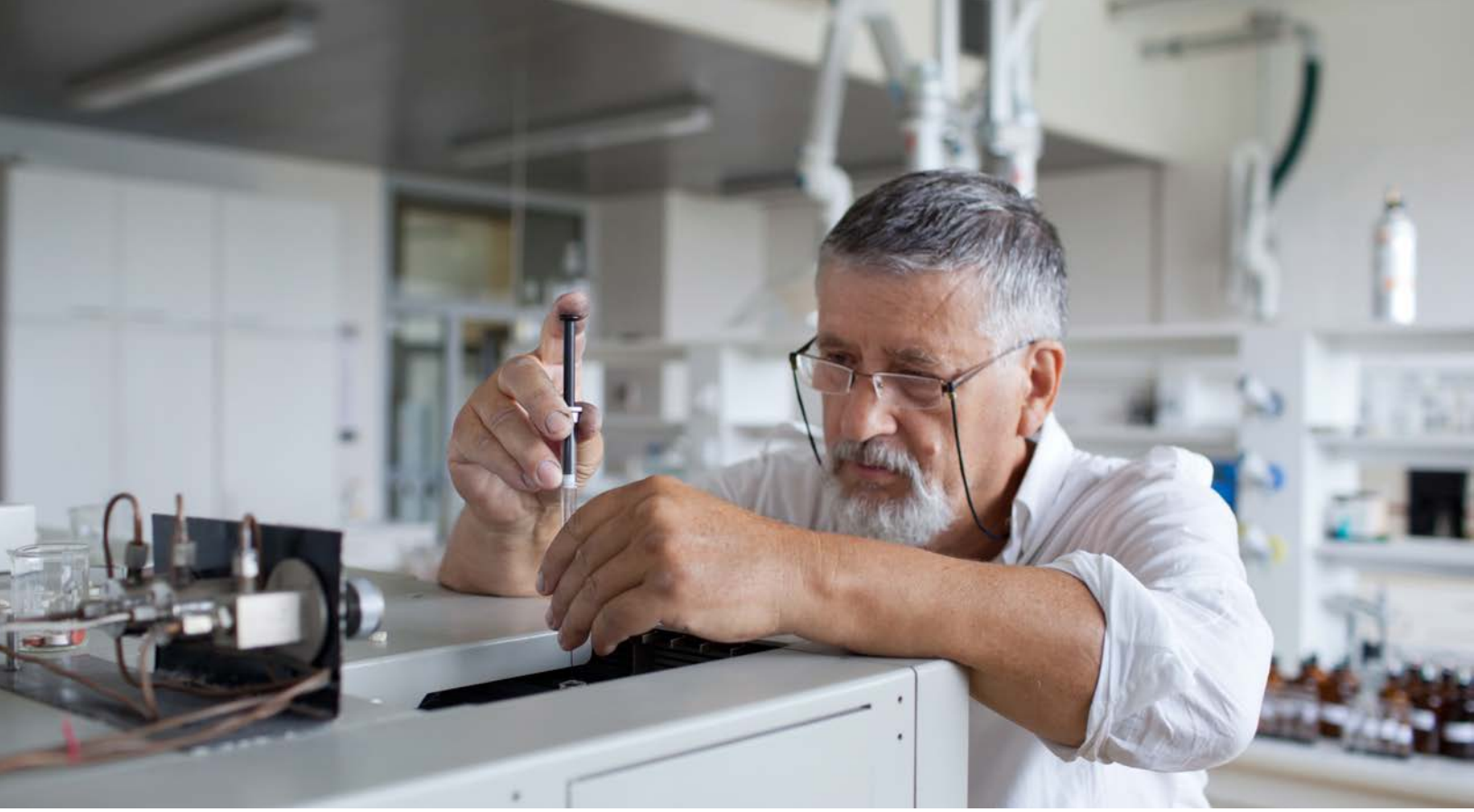
Pharmaceutical firms may lack a formal Design Review process or may simply fail to follow their formal process due to competing priorities and constraints, and a lack of understanding of the value of Design Review. When Design Review is performed, roles and responsibilities are often unclear, the appropriate SMEs may not be involved, and everyone assumes others are performing needed reviews.

Data from CAI C&Q benchmarking reveals that most firms do not perform Design Review. Those that do perform Design Review typically have Design Review required per SOP; however, in practice, it tends to be a checkbox activity required by Validation (i.e. as Design Qualification "light") and not seen as adding value. The same perception generally holds true for DQ, with most firms performing DQ as part of Design Review activity, or as EDR that is used as an exercise to meet EU Annex 1 requirements.

Opportunity Cost of Failure to Perform Design Review

So, what happens as a result?

Critical design features fail to meet specification. Product-contact materials of construction are designed incorrectly or with incorrect surface finishes. Components are sized incorrectly. Instrument ranges or accuracy are designed incorrectly. Hygienic piping (dead legs, slope, drainage, etc.) is designed incorrectly.



Systems are designed with operability, physical, mechanical, or automation integration issues. These issues lead to system implementation and commissioning failures that directly impact risk to product quality, resulting in often extensive and time-consuming re-design and re-implementation. Verification costs and schedule increase. Quality oversight increases.

Important maintenance, environmental, safety, and ergonomic features fail to meet specifications, because they were not considered adequately during Design Review. These issues lead to implementation changes or remediation.

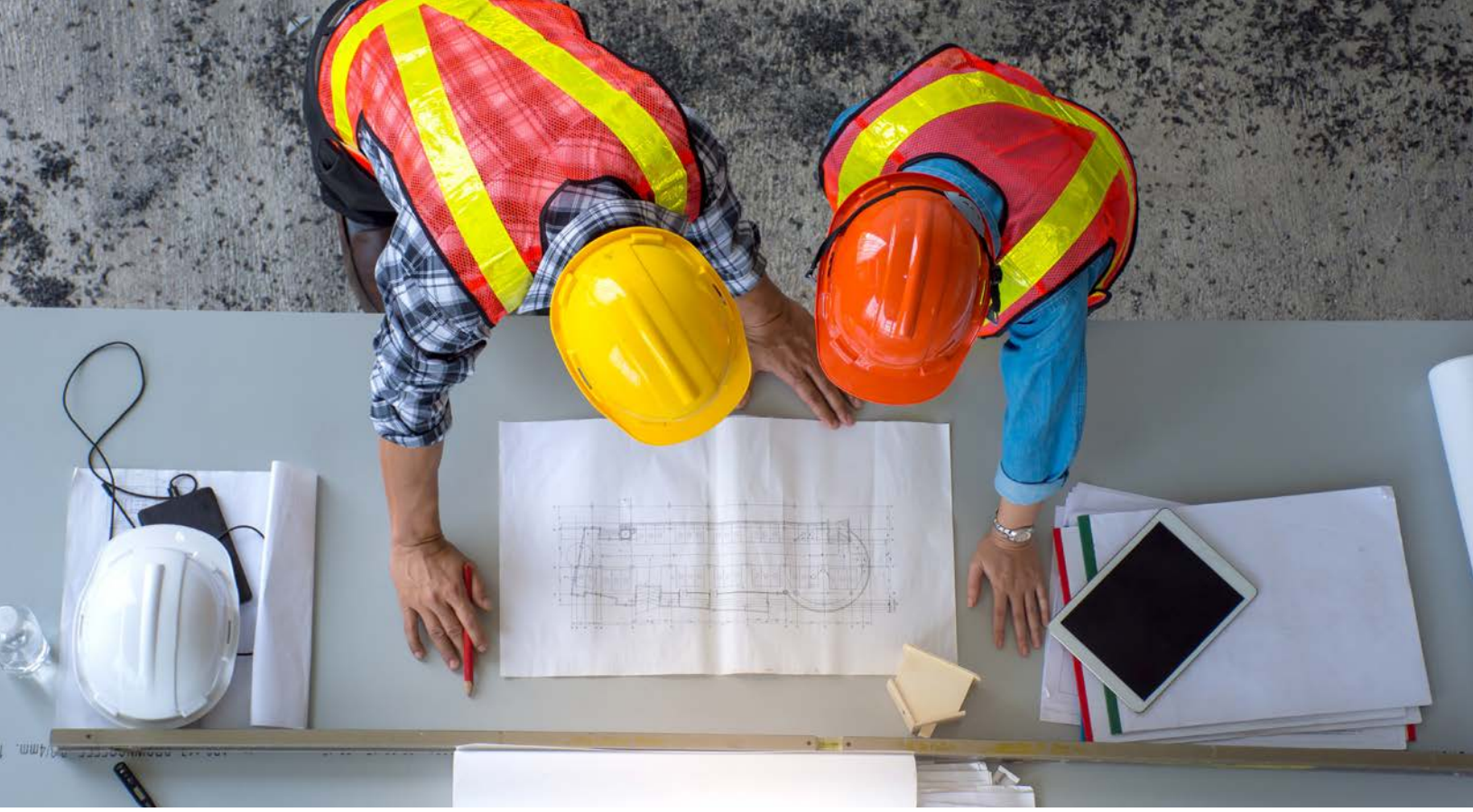
Issues that would otherwise be simple are missed, such as incorrect P&ID component or instrument tags. Such issues may lead to multiple drawings and documents that require revision post-implementation, resulting in considerable issue management and document control overhead.

All of these outcomes adversely impact overall project cost and schedule, causing costly delays that were entirely preventable and implementation changes that are far more expensive than if they had been resolved during the Design phase.

Design Review and Project Time and Cost Savings

A review of PCI working group change management case studies from 2014-2015 demonstrates the project time and cost savings of Design Review:

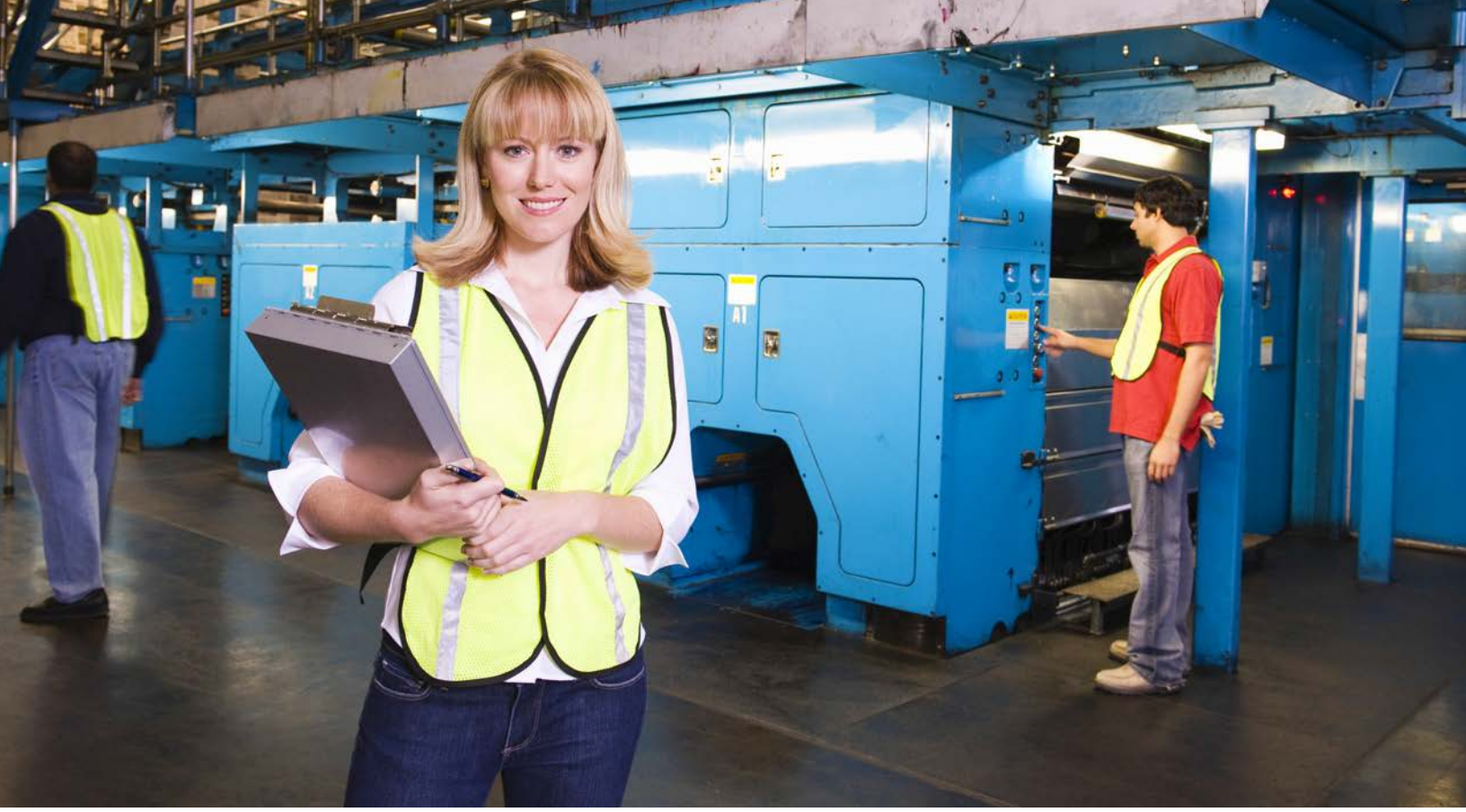
- Case Study #1: a project to expand an existing fill-finish facility resulted in 357 change controls, of which 35% were deemed to be items that were missed during Design Review.
- Case Study #2: a project to build a greenfield Biotech Mab facility resulted in 2,319 issues, of which 1,674 resulted in Engineering Changes subsequent to Mechanical Completion (MC), 41% of which were determined to be items that were missed during Design Review.



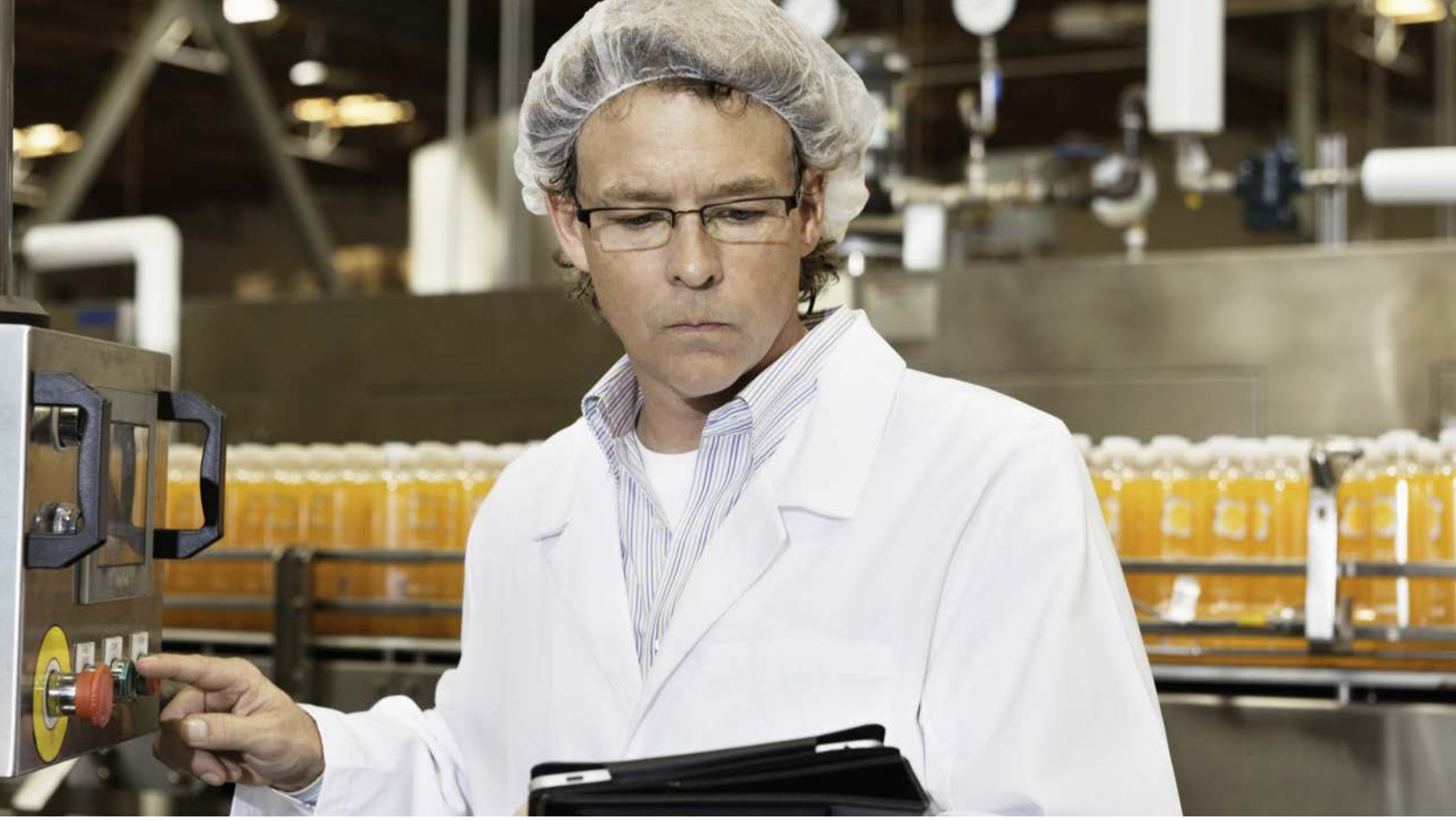
- Case Study #3: a project to expand an existing medical device facility and install a new generation of equipment resulted in 1,241 Project Change Notices, 398 of which were post-MC Engineering Changes. Of those, 19% were determined to be items that should have been detected as part of Design Review.
- A review of the types of issues determined to be missed during Design Review include incorrect component or instrument tags (one P&ID instrument tag error propagated to nine total documents that required revision), incorrect material of construction, incorrect surface finish of components, incorrect component sizing, incorrect instrument range and accuracy, automation/physical/mechanical integration issues, piping issues (slope, dead legs, drainage, 3D layout clashes), ergonomics (filter locations, sample points, hose connections), and operability issues.

Several CAI projects demonstrate similar results:

- On a project in which CAI was engaged for CQV services, the client did not perform Design Review for custom-built warehouse stability chambers, including a custom-designed PLC control circuit in which the two temperature control probes were additive. As a result, a critical failure mode, in which one temperature probe fails, causing the PLC to incorrectly read the chamber temperature low, was missed. Upon failure of a temperature probe, the PLC set the chamber temperature to double its setpoint, resulting in 155°F temperatures which set off the chamber sprinkler system and the fire alarm and site fire pumps. The chamber flooded with three feet of water, which subsequently flooded the warehouse when the fire department opened the chamber door, causing considerable damage to equipment and facility. The incident resulted in time and cost for cleanup and repair of the facility, control circuit redesign, and contributed significantly to nine months of schedule loss and hundreds of thousands of dollars in unplanned costs for the stability chambers.



- Design Review for three jacketed vessels being incorporated into a platform to fit a specific footprint revealed that the diameter needed to be decreased for two of the vessels. However, following the subsequent change order, adequate Design Review was not performed on the redesigned vessels and failed to identify that the working volume line was not moved as a result of the diameter change. Verification activities observed that the working volume of the vessels submerged the J-tubes and spray balls inside the vessels. As a result, the vessels could not be released, were replaced entirely under change control, and requalified.
- Design Review for process equipment included a full review of impact to surrounding systems. Design Review revealed undersized planned utilities, the discovery of which allowed for changes to the planned water generation system URS and procurement of the required capacity. In another scenario, it was determined that the existing utilities would be undersized for the planned new equipment, and the process design was altered to facilitate current capacity. Without Design Review, the incorrect equipment would have been ordered, and the design intent would not have been met, with discovery very late in the project, possibly as late as engineering runs.
- In multiple instances, a cross-functional team of stakeholders performed Design Review for equipment layout and general requirements and determined that maintenance would be extremely difficult or impossible. The inclusion of maintenance stakeholders allowed for resolutions including an orientation change, addition of a mezzanine, or wall alteration/relocation. These design changes had significant impact to post turnover operability.
- Design Review revealed that different Variable Frequency Drive (VFD) makes were being specified in the design. The Design Review team recommended using the same manufacturer for all VFDs, which saved on short- and long-term training requirements, maintenance, and spare parts requirements.



- Design Review revealed that emergency power was not being provided to equipment identified for emergency power in Basis of Design. Failure to discover this issue during Design Review would have resulted in unplanned outage and downtime, possible loss of critical process data, and potential impact to emergency power design and capability, resulting in costly rework or additional equipment.

How CAI Can Help

How significant is it to your success to deliver a large project two months earlier?

CAI had four authors on the original ASTM E2500 standard, published in 2007, and CAI has two authors on ISPE Baseline Guide Volume 5 2nd Edition, expected to be released later this year. CAI has executed multiple projects using a QRM-based integrated C&Q approach per the principles defined in ASTM E2500, ICH Q9, and the upcoming ISPE Baseline Guide Volume 5, 2nd Edition. Leverage our experience to optimize your C&Q program and deliver your projects more quickly with increased compliance and reduced costs. Design Review is an essential GEP and an enabling process for QRM-based integrated C&Q. CAI can help you develop your GEPs and a QRM-based integrated C&Q approach using the latest industry practices.

Regulatory Guidance Regarding Design Review

Design of facilities and equipment is within the scope of GMP. 21 CFR 211, Subpart C (Buildings and Facilities), Section 211.42, Design and construction features, states:

> *(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.*

> *(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.*

ICH Q8, Pharmaceutical Development, first published in 2004 and revised in 2008, introduced the principles of Quality by Design (QbD), as applied both to pharmaceutical products and the manufacturing processes that produce them.

In 2004, the FDA published *Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach*, Final Report, which adopted the QbD principles defined in ICH Q8 and quoted the ICH Q8 working group in describing the "desired state" for the pharmaceutical industry in the 21st century as, *"[p]roduct quality and performance achieved and assured by design of effective and efficient manufacturing processes."* Further, this report references the final Guidance for Industry – *Sterile Drug Products Produced by Aseptic Manufacturing – Current Good Manufacturing Practice* and states as one of its central themes to *"[e]nsure robust product protection through adequate design and control of equipment and Facilities."*

ICH Q9, Quality Risk Management (2005), includes QRM principles as applied to design of facilities and equipment within its scope.

In 2011, the FDA published Guidance for Industry – *Process Validation: General Principles and Practices, which states:*

> *Proper design of a manufacturing facility is required under part 211, subpart C, of the CGMP regulations on Buildings and Facilities. It is essential that activities performed to assure proper facility design and commissioning precede PPQ.*

Similarly, EU Annex 15 (2015), states:

> *The next element in the qualification of equipment, facilities, utilities, or systems is [Design Qualification] DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.*

References:

FDA 21 CFR 211.42: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.42

FDA Pharmaceutical cGMPs for the 21st Century: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmpfordrugs/ucm176374.pdf

ICH Q8: http://www.ich.org/products/guidelines/quality/quality-single/article/pharmaceutical-development.html

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FDA Guidance for Industry – Process Validation (2011): https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

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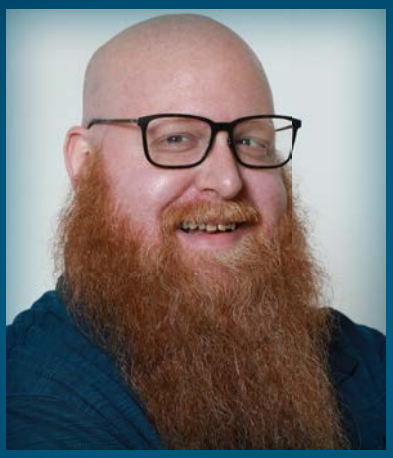
ISPE Baseline Guide Volume 5: https://ispe.org/publications/guidance-documents/baseline-guide-volume-5-commissioning-qualification



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Chip, a PMI® Certified Project Management Professional (PMP), is a Project Manager and Senior Validation Engineer with 18 years of experience in the pharmaceutical and regulated non-pharmaceutical industries with expertise in risk-based verification, quality systems, and owner project management. Chip is a CAI Subject Matter Expert in Commissioning and Qualification as well as CQV Program Development. He has achieved internal Tier III qualification in Owner Project Management (OPM), Quality Risk Management (QRM), and Aseptic Manufacturing.

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