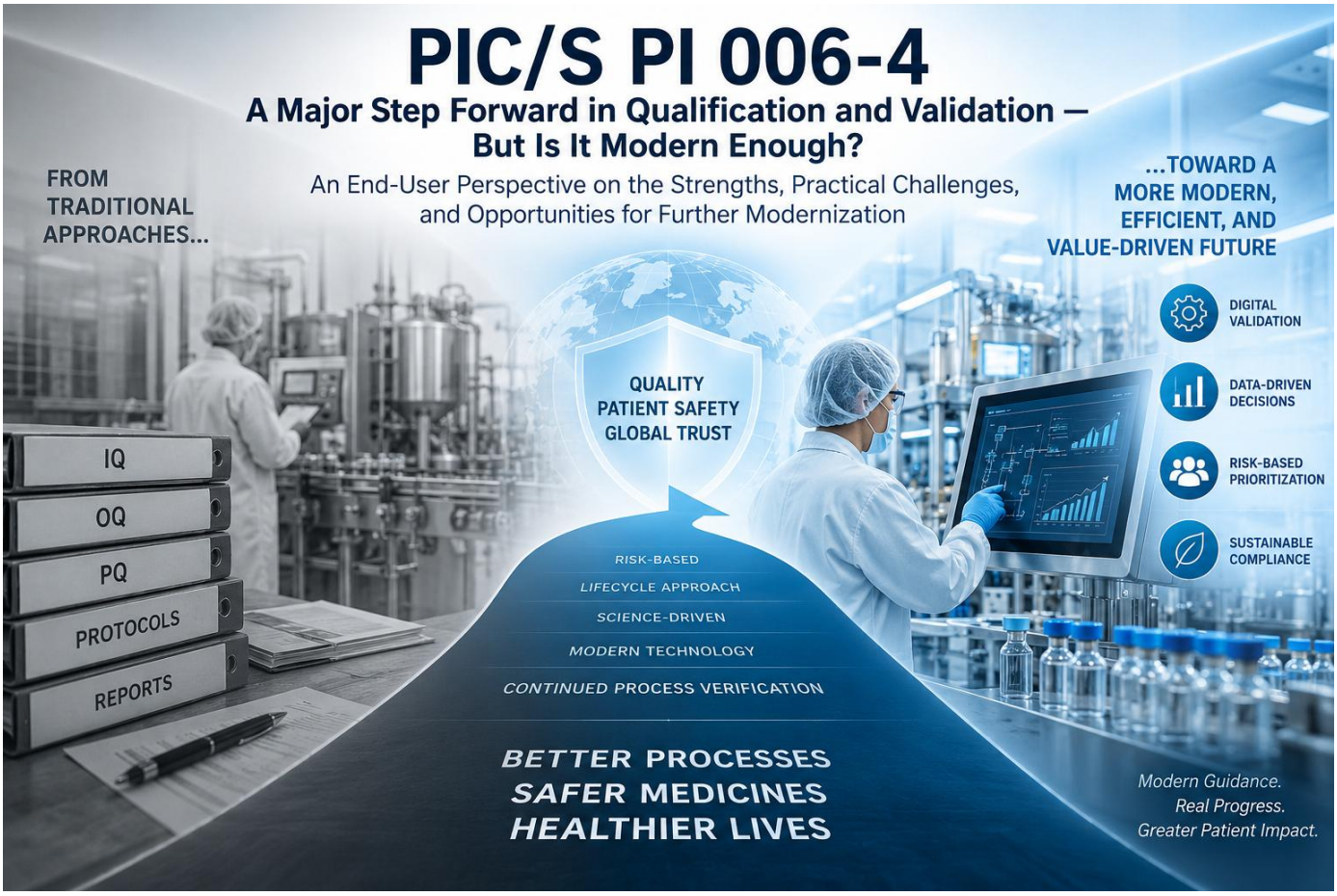

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The publication of PIC/S PI 006-4, *Recommendations on Qualification and Validation*, represents one of the most significant updates to PIC/S validation guidance in nearly two decades. The previous PI 006-3 became effective in September 2007; PI 006-4 becomes effective on October 1, 2026. [1]

That time gap alone makes this revision important.

Pharmaceutical manufacturing has changed dramatically since 2007. Manufacturing systems have become more automated and data-rich. Digital validation platforms have increasingly replaced paper protocols. Process analytical technology, advanced statistics, continuous manufacturing, single-use technologies, electronic records, and science- and risk-based commissioning and qualification have become increasingly common.

From the perspective of an end user, someone responsible for designing, executing, defending, and maintaining qualification and validation programs, the new PI 006-4 contains a great deal to support.

At the same time, the document illustrates an ongoing tension within pharmaceutical validation: **How do we preserve the regulatory rigor that protects patients while eliminating qualification activities and documentation that add little scientific or quality value?**

PI 006-4 moves the industry substantially in the right direction. But there remain areas where future guidance could go further.

One of the Strongest Improvements: Qualification Is Finally Presented as a Lifecycle

One of the most important principles in PI 006-4 appears early in the document. PIC/S states that qualification and validation should be conducted using a **lifecycle approach**, with the methodology, documentation and effort appropriate to the lifecycle stage. [1]

That sounds straightforward, but its practical importance should not be underestimated.

For many years, organizations treated qualification as a project rather than a lifecycle. Equipment was installed, IQ/OQ/PQ protocols were executed, reports were approved, and the qualification package was archived.

The system was then considered "validated."

PI 006-4 reinforces a different philosophy: qualification and validation establish a state of control that must subsequently be maintained.

This concept is especially strong in process validation. PIC/S states that process validation is **not a one-time activity** and requires monitoring throughout the lifecycle to detect process changes, variability and deterioration in performance.

For end users, this is an important advancement because it shifts attention from the question:

> ***"Did we successfully execute the validation protocol?"***

to the much more meaningful question:

> ***"Do the accumulated data continue to demonstrate that the process is in control?"***

That is where modern validation should be heading.

Quality Risk Management Is No Longer an Add-On

Another major strength is integrating **Quality Risk Management (QRM)** throughout qualification and validation.[1,5]

PI 006-4 states that decisions about the scope and extent of qualification and validation should be based on justified, documented risk assessments. Importantly, it connects those decisions specifically to **product quality and patient health**. [1,5]

That principle has substantial practical value.

A pharmaceutical facility can contain thousands of components. They are not equally important to product quality, and they should not receive equal qualification effort.

A temperature control loop affecting a critical process parameter should not necessarily receive the same level of verification as a non-product-impact utility or non-critical ancillary component.

PI 006-4 recognizes this.

The document even provides a simple but useful example: the qualification effort associated with an autoclave would likely be greater than that required for a packaging leaflet insertion machine.

That is exactly the type of proportionality the industry needs.

However, successful implementation will depend on whether organizations actually use QRM to **reduce unnecessary qualification**, rather than simply creating another risk-assessment document and then performing essentially the same testing as before.

That distinction matters.

> ***Risk assessment should determine the validation strategy—not merely justify it after the strategy has already been selected.***

Recognition of ASTM E2500 Is a Major Step Forward

Perhaps the most important modernization in the qualification section is the explicit recognition of **ASTM E2500**.[1,4]

PI 006-4 acknowledges that while the traditional qualification approach has been established and proven, alternative approaches grounded in sound scientific and engineering practices, including ASTM E2500, may be appropriate. The stated objective is ultimately the same: demonstrating that facilities, utilities, equipment, and systems are fit for their intended purpose. [1,4]

The document goes even further by reproducing the ASTM E2500-25 specification, design, and verification model.[1,4]

This is significant.

For years, many organizations have struggled with the perceived regulatory expectation that the traditional sequence of:

URS → DQ → IQ → OQ → PQ

must always be followed as a rigid documentation structure.

ASTM E2500 instead places greater emphasis on:

Requirements → Design → Critical Aspects → Risk Management → Verification → Acceptance and Release → Continued Improvement

This can eliminate significant duplication.

A properly documented engineering test should not need to be repeated merely because the original test was called FAT rather than OQ.

PI 006-4 reinforces this concept by explicitly allowing appropriately justified **FAT and SAT testing to reduce the scope of IQ and OQ testing.** [1]

From an end-user perspective, this is one of the strongest elements of the entire revision.

The pharmaceutical industry has spent enormous resources repeating technically sound engineering testing, simply to place the results in a different validation document.

That practice does not inherently improve product quality.

Good evidence should be usable evidence, regardless of which project phase generated it, provided its quality, traceability, and applicability can be demonstrated.

Where PIC/S Could Have Gone Further: Moving Beyond IQ/OQ/PQ

This is also where PI 006-4 reveals one of its principal limitations.

Although the document recognizes ASTM E2500, much of the qualification section continues to be organized around the conventional **IQ/OQ/PQ model**.[1,4]

For example, PIC/S states that IQ, OQ, and PQ should be linked to the URS and DQ, describes their individual purposes, and establishes progression between qualification stages.

There is nothing inherently wrong with IQ/OQ/PQ.

The problem arises when organizations interpret those terms as requiring separate documents and repetitive testing rather than as verification concepts.

A more modern approach would emphasize **verification of critical requirements and risks**, allowing the evidence to originate from engineering, supplier testing, commissioning, automation testing, FAT, SAT or formal qualification.

The question should not be:

"Where is the OQ test?"

The better question is:

"Where is the objective evidence demonstrating that this critical requirement has been verified?"

That subtle change in philosophy can remove hundreds or even thousands of hours from large capital projects without reducing assurance of product quality.

Future PIC/S guidance could make that distinction considerably stronger.

Process Validation Moves Much Closer to Modern Science

The process-validation section is another substantial improvement.

PI 006-4 explicitly permits **traditional, Continuous Process Verification (CPV), and hybrid validation approaches**. [1]

More importantly, PIC/S moves away from treating a predetermined number of batches as validation by itself.

The document states that the number of consecutive validation batches should be **scientifically justified**, considering risk, process understanding, and intra- and inter-batch variability. Greater

process understanding may support flexible approaches, potentially including fewer replicate batches.

PIC/S even acknowledges that this advances the application of science and QRM beyond the familiar Annex 15 expectation that three consecutive batches will generally be acceptable. [1,3]

That is an important philosophical change.

Three successful batches do not automatically prove process control.

Conversely, three batches should not automatically be required when extensive development, characterization, process understanding, and statistically meaningful data already demonstrate control.

The amount of validation should be driven by knowledge and uncertainty, not tradition.

Statistics Finally Receive the Attention They Deserve

Another strong aspect of PI 006-4 is how it treats statistical methods.[1]

PIC/S discusses process capability and performance indices such as **Cpk and Ppk**, multivariate statistical process control, trend analysis, intra- and inter-batch variability, scientifically justified sampling strategies, and predefined statistical approaches.

It also makes an important point: sophisticated statistical tools require appropriate expertise, and statistical evaluation should involve both subject-matter experts and statisticians.

This is an area where industry practice still varies considerably.

Validation has historically relied heavily on binary acceptance:

Pass / Fail

Modern process understanding requires more:

What is the distribution?
What is the variability?
Is the process stable?
What is its capability?
Is performance drifting?
What does the accumulated data tell us about future performance?

PI 006-4 clearly pushes the industry toward this more mature view.

Ongoing Process Verification May Be More Important Than the Initial Validation

One of the document's strongest statements is that **Ongoing Process Verification (OPV) should continue for every manufacturing process throughout the product lifecycle**.

PIC/S further states that OPV has effectively replaced periodic revalidation as the mechanism for demonstrating continued process control.

This makes scientific sense.

Three PPQ batches represent a very small sample of a commercial process's lifecycle.

Imagine instead having:

100 batches,
500 batches, or
1,000 batches

of manufacturing data.

That information can tell us far more about process capability and variability than the original qualification campaign.

The future of validation should therefore increasingly involve **continuous evaluation of manufacturing data**, with automated trending that can identify emerging deterioration before specifications are exceeded.

PI 006-4 establishes much of the conceptual foundation for that transition.

Cleaning Validation Is Significantly Stronger

The cleaning-validation section is another major improvement.

PI 006-4 places toxicological risk assessment and **Health-Based Exposure Limits (HBELs)** at the center of determining the extent of cleaning controls. It recognizes that the most difficult-to-clean product is not necessarily the highest-risk product and allows scientifically justified worst-case grouping. [1]

That is a meaningful advancement over simplistic historical approaches based primarily on potency, batch size, or arbitrary residue limits.

The document also distinguishes cleaning validation from cleaning verification and explicitly describes cleaning as a lifecycle consisting of development, validation, and ongoing evaluation.

The emphasis on manual-cleaning variability is particularly appropriate. PIC/S expects increased personnel qualification and oversight when manual cleaning introduces greater variability.

Its treatment of visual inspection is also appropriately nuanced. Visual cleanliness remains the minimum expectation, but PIC/S recognizes that visual inspection alone may not be appropriate where HBEL-based limits approach or fall below the visible residue threshold.

These are practical improvements that should strengthen cleaning programs.

The Major Missed Opportunity: Digital Validation

Where PI 006-4 feels noticeably less modern is **digital qualification and validation**.[1]

The document appropriately addresses data governance and data integrity. It states that data governance should be considered throughout qualification and validation and that project personnel should understand their data integrity responsibilities.

It also expects the VMP to define data-integrity requirements.

Those requirements are necessary.

But data integrity is not the same thing as **digital validation transformation**.

Modern validation programs increasingly use electronic protocols, electronic approvals, automated test execution, electronic requirements traceability, direct acquisition of instrument data, automated exception reporting, and integrated lifecycle platforms.

Future guidance should address how these technologies can fundamentally change the validation model.

For example, a digital requirements-management system can potentially maintain continuous traceability between:

URS → Risk → Design → Verification → Deviation → Change → Continued Verification

rather than recreating that traceability manually in separate Word documents and spreadsheets.

That represents far more than replacing a paper signature with an electronic signature.

It changes the architecture of validation itself.

Documentation Should Become Evidence-Centric Rather Than Document-Centric

PI 006-4 appropriately emphasizes documentation. Pharmaceutical companies must be able to demonstrate what was tested, why it was tested, who performed the work, what the results were and how deviations were resolved.[1]

But there is an opportunity to modernize the philosophy.

Historically, validation has often become **document-centric**.

The deliverable becomes the protocol.

The protocol becomes the evidence.

That thinking should be reversed.

Objective evidence is the deliverable. The document is simply the mechanism used to organize, review, and approve that evidence.

This distinction becomes increasingly important as manufacturing and validation become digital.

The future regulatory model should permit companies to demonstrate assurance through connected data and controlled digital records without forcing those records to imitate the structure of a paper validation binder.

Another Area for Modernization: Supplier and Engineering Data

PI 006-4 deserves credit for allowing FAT and SAT results to reduce IQ/OQ testing. [1]

Future revisions could take this concept considerably further.

Modern pharmaceutical equipment suppliers frequently conduct extensive testing before delivery. Automation vendors perform software testing. Engineering firms conduct commissioning. Instrument suppliers perform calibration and functional checks.

The industry should increasingly adopt the principle of:

Test once, verify the quality of the evidence, and use it wherever scientifically appropriate.

The pharmaceutical manufacturer remains accountable for determining whether supplier evidence is adequate.

But accountability should not automatically mean repetition.

A mature supplier-quality and engineering-assurance program should let companies leverage reliable evidence rather than reproduce it solely because the equipment has moved from an engineering project to a validation project.

The Overall Assessment

From an end-user perspective, **PI 006-4 is a strong and necessary modernization of PIC/S qualification and validation expectations.**[1]

Its strongest features are the integration of lifecycle thinking and QRM; explicit recognition of ASTM E2500; ability to leverage FAT/SAT; science-based determination of validation batch numbers; greater use of statistics; recognition of CPV and hybrid approaches; lifecycle OPV; and a substantially strengthened, HBEL-driven cleaning-validation framework.[1,4,5]

The document itself makes an important statement that should guide how industry interprets the entire revision: qualification and validation approaches should be **continually reassessed and updated to incorporate modern concepts, technological advances, and greater use of statistical tools.**

That may ultimately be one of the most important statements in PI 006-4.

However, the industry should not interpret the new guidance simply as an instruction to add more requirements to existing validation procedures.

Doing so would miss the opportunity.

The real value of PI 006-4 is the opportunity to **remove low-value activities while strengthening high-value assurance**.

The next stage in qualification and validation should move even further away from document volume as a measure of compliance and toward demonstrable knowledge of critical aspects, scientifically justified risk management, reliable engineering evidence, connected digital traceability, statistical process understanding and continuous verification of the state of control.

The objective should never be to produce the largest qualification package.

The objective is to produce the strongest evidence that the facility, system, equipment or process is fit for its intended use and remains in a state of control.

On that journey, **PI 006-4 represents an important step forward—but not the final destination.**

How Does the New PIC/S Approach Compare With FDA and EU Expectations?

An important way to evaluate PI 006-4 is to compare it with the two regulatory frameworks that most multinational pharmaceutical manufacturers routinely work under: the **U.S. FDA process-validation lifecycle model** and **EU GMP Annex 15**.[1,2,3]

The three approaches converge considerably. FDA has promoted lifecycle process validation since its 2011 guidance, organized around **Process Design, Process Qualification, and Continued Process Verification**. EU Annex 15 similarly requires managing qualification and validation throughout the lifecycle, using QRM to determine the scope and extent of activities. [2,3]

PIC/S PI 006-4 now brings these principles together in a more detailed implementation-oriented document. It explicitly calls for lifecycle qualification and validation, QRM, scientifically justified validation effort, ongoing verification, and recognition of alternative approaches such as ASTM E2500. [1,4,5]

Table 1. High-Level Comparison of FDA, EU and New PIC/S Validation Expectations

Validation Element	U.S. FDA	EU GMP Annex 15	PIC/S PI 006-4	End-User Perspective
Overall philosophy	Lifecycle validation based on scientific evidence and process understanding	Lifecycle qualification and validation	Explicit lifecycle approach to qualification and validation	Strong alignment across regulators
Process lifecycle structure	Very clear three-stage model: Stage 1 Process Design, Stage 2 Process Qualification, Stage 3 Continued Process Verification	Traditional, continuous and hybrid approaches within lifecycle framework	Prospective, CPV/hybrid and OPV lifecycle concepts	FDA remains especially clear conceptually
Quality Risk Management	Science- and risk-based approach encouraged; ICH Q9 supports implementation	Explicit requirement to use QRM throughout lifecycle	QRM explicitly determines scope and extent of qualification and validation	Strong PIC/S advancement
Qualification terminology	Does not mandate a rigid IQ/OQ/PQ documentation sequence; focuses on suitability, installation and operation	URS/DQ/FAT/SAT/IQ/OQ/PQ structure explicitly described	Retains URS/DQ/FAT/SAT/IQ/OQ/PQ while also recognizing ASTM E2500	PIC/S could go further toward verification-based terminology
ASTM E2500 / alternative CQV	FDA guidance is compatible with science- and risk-based engineering approaches	Annex 15 permits justified use of external/vendor data	Explicitly references ASTM E2500-25 as an acceptable	One of PI 006-4's strongest modernization steps

Validation Element	U.S. FDA	EU GMP Annex 15	PIC/S PI 006-4	End-User Perspective
	but does not structure its process-validation guidance around ASTM E2500	and combining qualification documents	alternative qualification approach	
FAT/SAT leverage	Engineering and qualification evidence may support demonstration of equipment suitability	FAT testing need not be repeated during IQ/OQ where justified	Explicitly permits FAT/SAT to reduce IQ/OQ scope	Strong opportunity to eliminate duplicate testing
Number of PPQ/validation batches	No predetermined minimum; manufacturer provides scientifically sound rationale	Three consecutive batches are generally acceptable, but another number may be scientifically justified	Number should be scientifically justified based on risk, variability and process understanding	PIC/S moves closer to FDA's science-based model
Continuous Process Verification	Core part of FDA lifecycle philosophy	Explicitly permitted as alternative to traditional validation	Explicit CPV and hybrid approaches	Strong regulatory convergence
Ongoing/continued verification	Stage 3 Continued Process Verification is fundamental	Ongoing Process Verification maintains validated state	OPV required across the product lifecycle	Very strong alignment
Statistics	Quantitative and statistical methods encouraged, including evaluation of intra- and inter-batch variability	Statistical tools expected where appropriate for process capability and variability	Stronger discussion of Cpk, Ppk, MSPC and statistical sampling	PI 006-4 adds useful implementation detail
Retrospective validation	Lifecycle approach effectively replaces historical retrospective validation concepts for current process validation	Explicitly no longer acceptable	Explicitly no longer acceptable	Fully aligned
Cleaning validation	Requirements arise from CGMP expectations and FDA guidance/inspection expectations; no single FDA equivalent as comprehensive as Annex 15/PI 006-4	Dedicated Annex 15 section with toxicological limits and cleaning validation expectations	Expanded detailed cleaning-validation section including HBEL, visual inspection, microbiological aspects and ongoing verification	PIC/S provides particularly useful operational detail
Digital validation	FDA framework can support electronic/digital systems under	Annex 11 covers computerized systems separately	PI 006-4 addresses data governance but does not deeply address digital CQV execution	Major opportunity for future modernization

Validation Element	U.S. FDA	EU GMP Annex 15	PIC/S PI 006-4	End-User Perspective
	CGMP/data-integrity requirements, but 2011 process guidance predates today's digital-validation environment			

Note: *FDA defines process validation as activities occurring throughout the product and process lifecycle and specifically separates this into Process Design, Process Qualification and Continued Process Verification. EU Annex 15 likewise requires lifecycle qualification and validation and explicitly permits the use of justified FAT evidence to eliminate unnecessary repetition during IQ/OQ.* [2,3]

Where FDA Is More Flexible Than the Traditional European Model

One particularly interesting difference concerns the number of process-validation batches.

FDA deliberately does **not specify a minimum number of PPQ batches**. FDA states that the manufacturer should provide a sound scientific rationale for the number selected rather than simply relying on a predetermined number. [2]

EU Annex 15 takes a somewhat different position. It states that the number of batches should be determined and justified using QRM, but also notes that **three consecutive batches under routine conditions are generally considered acceptable**. An alternative number may be justified. [3]

PI 006-4 takes an important step toward resolving this difference. The new recommendation states that the number of consecutive validation batches should be **scientifically justified** based on process understanding, risk, and variability, and specifically notes that this advances science- and QRM-based thinking beyond the historical three-batch convention. [1]

Table 2. The "Three-Batch Rule": FDA vs. EU vs. PIC/S

Question	FDA	EU Annex 15	PIC/S PI 006-4
Is three batches mandatory?	**No**	**No**, but three consecutive batches are generally considered acceptable	**No**
What determines the number?	Process understanding, variability, risk and sufficient objective evidence	QRM, process knowledge and sufficient data; three remains a recognized conventional starting point	Science, QRM, process understanding and intra-/inter-batch variability
Can fewer batches be justified?	Yes	Potentially, with justification	Explicitly recognized where extensive process knowledge supports it

Question	FDA	EU Annex 15	PIC/S PI 006-4
Can more batches be required?	Yes	Yes	Yes
Main philosophy	Evidence determines the number	Risk-based but retains three-batch convention	Moves toward fully science-based determination

From an end-user perspective, this distinction is important.

Three batches should not be treated as a scientific constant.

For a highly characterized platform process with substantial development and commercial-history data, three additional batches may provide relatively little new information. Conversely, a highly variable or poorly understood process may require far more than three batches before a manufacturer can credibly claim that it understands and controls the variability.

Equipment Qualification: An Area Where FDA Can Be Read as Less Prescriptive

Another important difference is how qualification is described.

FDA's 2011 process-validation guidance does not prescribe the classic IQ/OQ/PQ sequence as a mandatory documentation architecture. Instead, during Stage 2 FDA expects manufacturers to demonstrate that facilities, utilities, and equipment are appropriately designed, installed and operate according to process requirements across their anticipated operating ranges. [2]

EU Annex 15 describes the more familiar:[3]

URS → DQ → FAT/SAT → IQ → OQ → PQ

sequence, although it permits stages to be combined and allows FAT information to eliminate repeat testing when scientifically justified.

PI 006-4 retains this familiar structure, but importantly acknowledges alternative science- and engineering-based approaches such as ASTM E2500. [1,4]

Table 3. Equipment Qualification Philosophy

Topic	FDA	EU Annex 15	PIC/S PI 006-4
URS	Expected through appropriate requirements/design definition, but terminology is less prescriptive	Explicit expectation	Explicit expectation
DQ	Design suitability expected; DQ terminology not central to FDA lifecycle guidance	Explicit DQ stage	Explicit DQ/DS

Topic	FDA	EU Annex 15	PIC/S PI 006-4
FAT/SAT	Can form part of engineering/qualification evidence	Explicitly recognized	Explicitly recognized
IQ	Installation suitability must be demonstrated; FDA does not require a particular document title	Explicit stage	Explicit stage
OQ	Operation throughout anticipated ranges must be demonstrated	Explicit stage	Explicit stage
PQ	FDA distinguishes equipment qualification from process PPQ; terminology can therefore differ from EU practice	Explicit equipment PQ	Explicit equipment PQ
Combined protocols	Permissible through risk/science-based approach	IQ/OQ may be combined	Alternative approaches allowed
Alternative verification approach	Broadly compatible with risk-based engineering	Possible, although conventional structure remains prominent	ASTM E2500 explicitly identified
Primary regulatory question	Does the system reliably perform its intended function and support a controlled process?	Has lifecycle qualification been appropriately performed and documented?	Is the system fit for intended use and maintained in a state of control?

This comparison highlights an important issue for multinational companies.

Organizations frequently create separate "FDA qualification" and "EU qualification" interpretations, even when the underlying scientific requirements are essentially identical.

In reality, all three frameworks converge on the same fundamental expectation:

Define what the system needs to do, understand what can affect product quality, verify the critical requirements, document credible objective evidence, manage changes, and maintain the system in a state of control.

> ***Terminology should not become more important than science.***

Continued Process Verification: Perhaps the Greatest Area of Regulatory Convergence

The strongest agreement among FDA, EU and PIC/S is arguably the expectation that validation continues after initial qualification.[1,2,3]

FDA's **Stage 3 Continued Process Verification** requires ongoing assurance, during routine manufacturing, that the process remains under control. FDA encourages quantitative and statistical methods, as well as monitoring of intra- and inter-batch variability. [2]

EU Annex 15 similarly requires Ongoing Process Verification throughout the product lifecycle and specifically states that statistical tools should be used where appropriate to evaluate process variability and capability. [3]

PI 006-4 goes further in operational detail, stating that OPV should begin for every manufacturing process after initial validation and continue until manufacturing is discontinued. [1]

Table 4. Continued Verification Expectations

Lifecycle Activity	FDA	EU	PIC/S PI 006-4
Continuous monitoring after PPQ	Yes	Yes	Yes
Detect process trends	Yes	Yes	Yes
Assess variability	Explicit	Explicit	Explicit
Use statistical methods	Recommended	Expected where appropriate	Strongly supported
Adjust monitoring based on knowledge	Yes	Yes	Yes
Incorporate deviations/complaints/quality-system data	Expected through pharmaceutical quality system	Lifecycle/PQR linkage	Explicit linkage encouraged
Periodic revalidation as sole lifecycle mechanism	Not the modern model	Replaced/supplemented by ongoing verification	OPV explicitly takes the place of routine periodic process revalidation

Note: This is where industry practices now need to catch up with regulatory philosophy.

Many companies still devote substantially more resources to executing the original PPQ than to interrogating the hundreds of commercial batches generated afterward.

Scientifically, that priority should increasingly be reversed.

What the Comparison Tells Us

The FDA, EU and PIC/S approaches are much closer than they sometimes appear.

FDA led the industry toward an explicit process-validation lifecycle model in 2011. EU Annex 15 subsequently embedded lifecycle validation, QRM, continuous verification and flexible qualification concepts into the European GMP framework. The new PI 006-4 expands those concepts with additional practical guidance, particularly on risk assessment, statistics, cleaning validation, supplier testing, and ASTM E2500. FDA describes its process-validation framework as lifecycle-based and makes Continued Process Verification a distinct third stage, while Annex 15

requires lifecycle qualification and validation and allows traditional, continuous, and hybrid process-validation approaches. [1,2,3,4,5]

The remaining differences increasingly concern how validation is organized and documented, rather than disagreement about its scientific objective.

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