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The Role of Biostatistics in Pharmaceutical Quality Control and Process Validation

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ABSTRACT

Background: Pharmaceutical quality control and process validation are fundamentally problems of inference under variation. Specifications define acceptable product attributes, but they do not by themselves establish process stability, capability, reproducibility, analytical reliability or the probability of future conformance. Contemporary lifecycle frameworks therefore require statistical evidence across process design, process performance qualification (PPQ), continued process verification (CPV) and analytical procedure management. The extent to which the published pharmaceutical-quality literature integrates these distinct biostatistical functions has not been quantified systematically.

Methods: An original quantitative evidence-mapping study was performed using 42 peer-reviewed, method-focused publications issued from 2006 through 10 December 2025, supplemented by current FDA, ICH, EMA, EU GMP and compendial guidance. Publications were classified into seven lifecycle focus groups and coded against nine prespecified statistical-method families: design of experiments (DoE), regression/ANOVA/general modelling, risk-based sampling and interval estimation, statistical process control (SPC), process capability, multivariate analysis/chemometrics, Bayesian methods, measurement uncertainty/decision risk, and artificial intelligence or machine learning (AI/ML). A Statistical Integration Score (SIS; 0–9) captured the number of method families represented per publication. Older (2006–2019) and recent (2020–2025) publications were compared using Fisher exact tests with Benjamini–Hochberg false-discovery-rate correction and a two-sided Mann–Whitney U test with tie correction.

Results: General statistical modelling was represented in 40/42 publications (95.2%), multivariate analysis in 29/42 (69.0%), SPC in 20/42 (47.6%), DoE in 17/42 (40.5%), measurement uncertainty/decision-risk methods in 14/42 (33.3%), sampling/interval methods in 13/42 (31.0%), capability indices in 12/42 (28.6%), and Bayesian and AI/ML methods in 4/42 each (9.5%). Recent publications integrated more method families than older publications (median SIS 4 [IQR 4–4] versus 3 [IQR 3–4]; U=307, P=0.0227; rank-biserial effect=0.39). Multivariate analysis and measurement-uncertainty methods showed nominal era associations, but no individual method-family trend remained significant after false-discovery-rate adjustment. The evidence map revealed strong lifecycle specialization: PPQ literature concentrated on sampling and assurance; CPV literature on SPC and capability; PAT/continuous-manufacturing literature on multivariate monitoring; and analytical-validation literature on DoE, interval estimation and measurement uncertainty.

Conclusions: Biostatistics functions as the quantitative control architecture of pharmaceutical quality rather than as a narrow support activity. The strongest validation strategy links experimental design, risk-based sampling, estimation, SPC, capability analysis, multivariate monitoring and analytical uncertainty to the specific decision being made at each lifecycle stage. A proposed Biostatistical Validation Architecture translates this evidence into a practical workflow for process design, PPQ, CPV and analytical procedure lifecycle management, while highlighting common errors such as treating specification limits as control limits, calculating capability before demonstrating statistical stability, and deploying high-dimensional AI models without model-lifecycle governance.

Keywords: biostatistics; pharmaceutical quality control; process validation; process performance qualification; continued process verification; statistical process control; process capability; design of experiments; analytical procedure validation; measurement uncertainty; process analytical technology; quality by design

1. INTRODUCTION

Pharmaceutical manufacturing is an exercise in controlling variation. Every batch, analytical measurement and unit operation contains variation arising from raw materials, equipment, operators, environmental conditions, sampling, analytical procedures and the underlying stochastic behavior of the process itself. Good manufacturing practice establishes requirements for control, documentation and conformance, but the scientific interpretation of variation requires statistical reasoning. Biostatistics provides the tools for separating common-cause variability from signals of change, estimating uncertainty, designing informative experiments, quantifying process performance, and making decisions with explicit control of producer and patient risk [1–15].

The modern regulatory view of process validation is explicitly lifecycle-based. FDA's 2011 process-validation guidance organizes validation around process design, process qualification and continued process verification, replacing the historical idea that validation can be completed by producing a fixed number of apparently successful commercial-scale batches [1]. ICH Q8(R2) similarly describes enhanced pharmaceutical development through multivariate experimentation, process understanding, statistical process control and lifecycle verification [3]. ICH Q9(R1) places risk-based decision making at the center of pharmaceutical quality [4], while ICH Q10 integrates monitoring, knowledge management, change management and continual improvement across the product lifecycle [5]. ICH Q13 extends those principles to continuous manufacturing, where high-frequency and serially correlated data make statistical architecture even more important [6].

Biostatistics has an equally important role in laboratory quality control. A numerical assay result is not a direct observation of an unknowable "true" product value; it is an estimate subject to sampling variability, analytical repeatability, intermediate precision, calibration, model assumptions and sometimes multivariate signal processing. The revised ICH Q2(R2) and ICH

Q14 guidelines strengthen the lifecycle treatment of analytical procedures, including scientifically justified validation designs, confidence intervals, prior knowledge, multivariate procedures, robustness studies, parameter ranges and change management [7,8]. These developments move analytical validation away from a checklist mentality toward a quantitative demonstration that an analytical procedure is suitable for its intended decision.

Despite this convergence, statistical practice in pharmaceutical quality remains fragmented. Development scientists may use DoE and response-surface models; validation teams may focus on PPQ sample size and tolerance intervals; manufacturing teams may emphasize control charts and Cpk/Ppk; PAT groups may use principal-component analysis (PCA), partial least squares (PLS) and multivariate statistical process control; and laboratory statisticians may focus on measurement uncertainty and decision risk. Each toolkit is legitimate, but quality failures can emerge at the boundaries. Capability analysis can be misleading when a process is not stable; control charts can be over-sensitive when high-frequency observations are autocorrelated; PPQ sample sizes can be ritualized rather than risk-based; and specification compliance can be mistaken for evidence of control [13,23–31].

The distinction between specification limits and control limits is particularly consequential. Specifications reflect requirements for product acceptance. Control limits are empirically estimated boundaries for process behavior under a defined state of statistical control. A process can produce all observations within specification and still exhibit a non-random drift that requires investigation; conversely, a statistically stable process can be incapable of meeting tight specifications. Capability metrics such as Cpk and Ppk are useful only when their assumptions, time horizon, distributional form, measurement system and state of control are understood [13,29,30]. Biostatistics therefore does not merely summarize data; it protects the logic connecting data to quality decisions.

The growth of continuous manufacturing, multivariate sensing and AI-enabled monitoring creates a second challenge. Traditional Shewhart charts remain powerful for many well-behaved univariate signals, but data-rich pharmaceutical processes may violate independence, stationarity and linearity assumptions. Multivariate statistical process monitoring can detect coordinated changes across process variables that are invisible in separate univariate charts, while machine-learning models can support prediction and fault detection. Yet greater model complexity also creates risks of overfitting, opaque decision rules, data leakage, model drift and false confidence. Modern biostatistics must therefore include model validation and lifecycle governance, not simply algorithm selection [32–44].

This study addresses two questions. First, which statistical methods are most visibly represented across the published pharmaceutical quality-control and validation literature, and how does this pattern differ by lifecycle focus and publication era? Second, how can the resulting evidence be translated into a practical, stage-specific architecture for quality decisions? We answer these questions using an original quantitative evidence map of method-focused publications and a separate regulatory-content analysis. The purpose is not to estimate the prevalence of methods across the entire pharmaceutical industry; rather, it is to characterize how major statistical functions are represented in a reproducible purposive corpus and to derive practical recommendations for integrated validation practice.

2. MATERIALS AND METHODS

2.1 Study design

We conducted a quantitative evidence-mapping and regulatory-content study. The peer-reviewed evidence map was intentionally purposive and method-focused rather than an exhaustive systematic review. This design was selected because the research objective was to compare the statistical architecture represented across distinct quality domains—pharmaceutical development, PPQ, CPV, PAT/continuous manufacturing and analytical validation—rather than to estimate an industry-wide utilization rate. Regulatory and compendial sources were analyzed separately to prevent guidance requirements from being counted as if they were empirical publications.

2.2 Evidence identification and eligibility

Candidate publications were identified using combinations of the terms pharmaceutical, quality by design, process validation, process performance qualification, continued process verification, statistical process control, process capability, sampling, Bayesian, measurement uncertainty, analytical procedure validation, analytical quality by design, process analytical technology, multivariate, chemometrics, continuous manufacturing, machine learning and artificial intelligence. Priority was given to peer-reviewed publications with an explicit statistical or validation methodology and sufficient detail to determine which method families were central to the work. The final corpus included 42 publications from 2006 through 10 December 2025 [16–57].

Publications were eligible when they addressed at least one of the following: statistical design of pharmaceutical development studies; quantitative PPQ/validation strategy; CPV or process-performance monitoring; PAT or continuous-manufacturing data analysis; pharmaceutical process capability; or statistical development/validation of quality-control analytical procedures. Papers whose primary purpose was clinical biostatistics, pharmacometrics, epidemiology or efficacy analysis were excluded because their inferential targets differ from manufacturing quality. General narrative reviews were included only when they provided a clearly defined methodological framework relevant to the coding scheme.

2.3 Regulatory and standards layer

The regulatory-content layer included FDA Process Validation: General Principles and Practices, FDA PAT guidance, ICH Q8(R2), Q9(R1), Q10, Q13, Q2(R2) and Q14, EU GMP Annex 15, 21 CFR Part 211 and relevant USP lifecycle/statistical chapters [1–12]. These sources were used to identify the decision context for statistical methods rather than to generate quantitative prevalence estimates. Regulatory documents were checked against current agency or ICH pages available through 10 December 2025; in particular, Q2(R2) and Q14 were treated as final guidelines effective in the EU from June 2024, and Q13 as the established continuous-manufacturing guideline [6–8].

2.4 Coding framework

Each publication was coded using a prespecified binary codebook for nine method families. “Present” required the method to be part of the substantive analytical framework, not merely named in background text. Coding was first performed at the title/abstract/method level and then re-audited against the available full text or detailed indexed abstract. No independent second coder was used; this limitation is acknowledged explicitly. The nine method families and their intended interpretation are shown in Table 1.

2.5 Lifecycle focus classification

Publications were assigned to one dominant focus: Framework (cross-lifecycle QbD/statistical architecture), Development, PPQ, CPV, QC/CPV, PAT/continuous manufacturing (PAT/CM), or Analytical. Assignment reflected the primary decision problem rather than the product modality. The final distribution was: Analytical, 13 publications; PAT/CM, 9; CPV, 7; Framework, 5; PPQ, 4; Development, 2; and QC/CPV, 2.

2.6 Statistical Integration Score

For each publication, we calculated an unweighted Statistical Integration Score (SIS) equal to the number of coded method families present (range 0–9). The SIS was designed as a breadth indicator, not a measure of methodological quality. A paper using one carefully justified method can be scientifically stronger than a paper mentioning several techniques. The score therefore supports descriptive comparison of integration only and should not be interpreted as a quality ranking.

2.7 Statistical analysis

Method-family prevalence was summarized as n (%). Publications were divided a priori into an older era (2006–2019) and a recent era

(2020–2025), yielding 21 publications in each group. Era-specific differences in binary method-family presence were assessed using two-sided Fisher exact tests. To control multiplicity across the nine family-level comparisons, P values were adjusted using the Benjamini–Hochberg procedure with a false-discovery-rate threshold of $q<0.05$. SIS distributions were compared using a two-sided Mann–Whitney U test with tie correction; rank-biserial correlation was reported as an effect-size measure. Association between publication year and SIS was explored using Spearman rank correlation. Analyses were performed in Python using pandas and SciPy. All computations were deterministic, and the coded corpus is reproduced in Appendix A.

2.8 Ethical considerations and reproducibility

The study used public documents and published literature and involved no human participants, patient data, proprietary manufacturing data or animal experimentation; institutional ethics review was therefore not applicable. No laboratory or manufacturing observations were fabricated. Quantitative results derive solely from the reproduced evidence-map coding matrix. Because the corpus is purposive, inferential P values are interpreted as within-corpus pattern tests and not as population estimates of pharmaceutical-industry practice.

3. RESULTS

3.1 Corpus characteristics

The final evidence map contained 42 publications spanning 2006–10 December 2025. The temporal distribution was intentionally broad enough to capture the transition from early PAT/QbD and lifecycle-validation concepts to contemporary analytical-lifecycle and AI/ML work. Exactly half of the publications were from 2006–2019 and half from 2020–2025. Analytical-validation/AQbD papers formed the largest focus group (31.0%), followed by PAT/continuous manufacturing (21.4%) and CPV (16.7%).

3.2 Prevalence of statistical method families

General statistical modelling was nearly universal (40/42; 95.2%), reflecting the centrality of regression, ANOVA, variance modelling or related estimation across quality questions. Multivariate analysis was the second most frequent family (29/42; 69.0%), driven by PAT/continuous-manufacturing and analytical-QbD literature. SPC was represented in 20/42 publications (47.6%), DoE in 17/42 (40.5%), measurement uncertainty/decision-risk methods in 14/42 (33.3%), risk-based sampling or interval methods in 13/42 (31.0%), and process capability in 12/42 (28.6%). Bayesian methods and explicit AI/ML were each represented in 4/42 publications (9.5%).

The low overall prevalence of Bayesian and AI/ML methods should not be interpreted as evidence that they are unimportant. Both were concentrated in narrower decision contexts: Bayesian approaches were mainly used for PPQ/sample-size or analytical-validation problems, whereas all four AI/ML publications were recent CPV studies. The pattern is therefore one of specialization rather than simple adoption frequency.

3.3 Lifecycle specialization of statistical methods

Method use differed sharply by lifecycle focus. All four PPQ papers used sampling or assurance methods, while half used Bayesian approaches. CPV papers universally used statistical modelling and SPC, with 71.4% using multivariate methods and 57.1% using AI/ML. All PAT/CM publications used statistical modelling and multivariate analysis, and 77.8% incorporated SPC. Analytical publications showed a different profile: 100% used modelling and measurement-uncertainty/decision-risk concepts, 76.9% used DoE, 69.2% used multivariate methods and 46.2% used sampling or interval-estimation methods. This pattern supports the interpretation that “biostatistics in validation” is not one technique but a set of stage-specific inferential tools.

3.4 Change in statistical integration over time

Recent publications used a broader combination of method families. The 2020–2025 group had a median SIS of 4 (IQR 4–4) compared with 3 (IQR 3–4) in 2006–2019. The two-sided Mann–Whitney test gave $U=307$, $P=0.0227$, with a rank-biserial effect of 0.39. Publication year showed a positive but non-significant monotonic association with SIS (Spearman $\rho=0.27$, $P=0.0858$). The latter result indicates that integration increased unevenly rather than following a simple linear time trend.

3.5 Era-specific method-family signals and multiplicity control

At the individual method-family level, several descriptive shifts were apparent. Multivariate analysis appeared in 18/21 recent publications versus 11/21 older publications (odds ratio [OR] 5.45; nominal $P=0.0431$), while measurement-uncertainty/decision-risk methods appeared in 11/21 versus 3/21 (OR 6.60; nominal $P=0.0203$). DoE also increased from 5/21 to 12/21 publications (OR 4.27; $P=0.0578$). In contrast, conventional capability indices appeared less often in the recent group (3/21 versus 9/21; OR 0.22; $P=0.0855$), consistent with a shift toward broader lifecycle and multivariate approaches in the selected literature. AI/ML was absent from the older group and present in 4/21 recent publications, but the small count produced substantial uncertainty ($P=0.1069$).

Importantly, none of the nine family-level comparisons remained significant after Benjamini–Hochberg correction (all $q\geq0.17$). We therefore interpret these as nominal pattern signals rather than definitive temporal effects. The more robust corpus-level result is the broader SIS distribution in recent work, which aggregates method integration rather than testing many individual method families.

3.6 Regulatory crosswalk

The regulatory-content analysis showed that no single guideline prescribes one universal statistical algorithm. Instead, regulators consistently expect scientific justification matched to the lifecycle question. FDA’s process-validation guidance emphasizes collection and evaluation of data from process design through commercial production [1]. ICH Q8(R2) explicitly connects enhanced development to multivariate experiments, continuous process verification and statistical process control [3]. Q9(R1) requires risk-based decision making [4], while Q10 embeds monitoring and continual improvement in the pharmaceutical quality system [5]. Q13 adds lifecycle and control considerations specific to continuous manufacturing [6]. Q2(R2) and Q14 extend the same logic into the analytical-procedure lifecycle and explicitly accommodate confidence intervals, prior knowledge, multivariate procedures, robustness studies and enhanced development approaches [7,8].

4. DISCUSSION

4.1 Principal findings

This evidence map supports a simple but consequential conclusion: biostatistics is the connective tissue of pharmaceutical quality control and process validation. Statistical modelling was represented in almost every publication, but the informative result was the distribution of specialized methods across lifecycle stages. Development literature emphasized designed experimentation; PPQ literature emphasized evidence strength, sample size and assurance; CPV literature emphasized control charts, capability and multivariate monitoring; PAT/continuous-manufacturing work was predominantly multivariate; and analytical-validation work increasingly combined DoE, interval estimation, uncertainty and multivariate approaches. The significant increase in SIS in 2020–2025 suggests that contemporary publications more often integrate several of these functions within one lifecycle argument.

The result should not be misread as a claim that “more methods are always better.” Statistical complexity is not a surrogate for scientific rigor. A stable, low-dimensional process may be controlled effectively with a well-designed sampling plan and a simple Individuals/Moving Range chart. Conversely, a high-frequency continuous process may require multivariate latent-variable models and explicit autocorrelation handling. The essential principle is alignment among the quality question, data-generating process, statistical assumptions and decision consequence.

4.2 Biostatistics in Stage 1: converting development data into process knowledge

Stage 1 process design is where biostatistics can prevent expensive

downstream uncertainty. One-factor-at-a-time experimentation is inefficient for multivariable processes because it does not estimate interactions reliably and can produce false confidence about robustness. Factorial and response-surface DoE allow simultaneous estimation of main effects, interactions and curvature, while randomization, blocking and replication protect the interpretation of effects against nuisance variation [14,16–22]. In pharmaceutical QbD, the statistical model is not the design space itself; it is one source of evidence linking critical material attributes and critical process parameters to CQAs. Mechanistic understanding and engineering judgment remain essential.

Variance components deserve equal attention. Replicate measurements can be nested within locations, time points, containers, batches and campaigns. Treating all observations as independent can produce pseudoreplication and artificially narrow standard errors. Mixed-effects models can separate within-batch, between-batch and measurement variability, directly informing sampling plans and the expected behavior of future batches. This is particularly important for blend uniformity, fill-weight control, content uniformity, biologic upstream/downstream processes and analytical transfer, where multiple levels of variation coexist.

The literature also supports early use of multivariate methods when process variables are correlated. PCA can summarize covariance structure and reveal clusters, leverage points or atypical trajectories; PLS can relate correlated process variables to CQAs; and multivariate design-space models can identify combinations of settings that are not apparent from isolated one-variable limits [36–44]. These methods are most valuable when combined with domain knowledge and prospective experimental design rather than applied retrospectively as pattern-finding tools.

4.3 Stage 2 PPQ: replacing batch-count ritual with quantified evidence

PPQ asks whether the commercial process, operated by trained personnel using qualified facilities and equipment, can reproducibly manufacture acceptable product. A common statistical failure is to reduce that question to a predetermined number of successful batches. FDA's lifecycle guidance does not establish a universal three-batch rule; the amount of PPQ evidence should be scientifically justified using process knowledge, risk and the ability of the sampling plan to detect meaningful variation [1,23–28].

The PPQ literature illustrates several complementary approaches. Pazhayattil and colleagues proposed using prior process knowledge to inform the number of PPQ batches [25]. Faya et al. formalized Bayesian assurance and sample-size logic across the validation lifecycle [26]. Charoo et al. showed how sample sizes for dosage-unit uniformity can be linked to risk and reliability goals rather than chosen by convention [28]. These methods make the decision criterion explicit: what defect rate, variability shift or unacceptable condition should the study be able to detect, with what probability?

A robust PPQ sampling plan should distinguish coverage from replication. Taking many units from one moment in a batch may provide precise information about local measurement variability but weak evidence about temporal or spatial heterogeneity. Stratification across the beginning, middle and end of a process, across equipment positions, filling heads or relevant hold times can be more informative. For hierarchical data, mixed models or variance-component methods allow the plan to quantify both within- and between-stratum variability. Tolerance intervals can address the expected proportion of future units meeting a criterion, whereas confidence intervals address uncertainty in estimated parameters. Confusing these two interval types can lead to underpowered qualification strategies.

4.4 Stage 3 CPV: distinguishing control, capability and conformance

Continued process verification is the statistical surveillance phase of the lifecycle. The first question is not whether the current batch passed release specifications; it is whether the process behavior remains consistent with the validated state. Control charts are designed for this purpose. Rational subgrouping, chart selection and pre-specified escalation rules matter more than the aesthetic appearance of a dashboard. For low-frequency batch data, Individuals/Moving Range charts may be appropriate; for subgrouped continuous measurements, X-bar/R or X-bar/S approaches may be useful; attribute outcomes may require p, np, c or u charts. When data are autocorrelated, standard Shewhart limits can produce excessive false alarms and should be replaced or supplemented with time-series or model-based residual monitoring [13,23,24,29–35].

Capability analysis answers a different question: whether the process distribution, over a stated time horizon, is sufficiently narrow and centered relative to specification limits. Cpk is a short-term within-process index under specific assumptions; Ppk reflects overall observed performance. Neither index proves statistical control, and neither should be interpreted without checking distributional behavior, subgrouping, sample size, censoring and the adequacy of the measurement system. Calculating a high Cpk from a drifting process can create false assurance because the metric summarizes dispersion around a moving target.

Gunter et al. highlighted another practical issue: pharmaceutical data are often skewed or otherwise poorly summarized by normal-theory assumptions, motivating quantile-based performance measures and graphical drill-down [30]. This is consistent with a broader principle: transformation, nonparametric quantiles, generalized models or distribution-specific capability methods may be preferable to forcing every CQA into a normal model. Statistical methods should describe the process that generated the data, not force the process to resemble a preferred textbook distribution.

4.5 Analytical quality control: validation as quantified decision performance

The analytical laboratory is itself a measurement process and must be validated with the same discipline used for manufacturing. ICH Q2(R2) and Q14 make this explicit by connecting analytical development, validation, robustness, parameter ranges, lifecycle knowledge and change management [7,8]. A strong analytical validation plan therefore begins with the intended use of the procedure and the consequence of measurement error. Repeatability, intermediate precision, accuracy, range, specificity and other performance characteristics should be analyzed using models that match the study design rather than summarized as disconnected percentages.

Recent work demonstrates the increasing statistical maturity of analytical validation. Rozet et al. connected validation to a QbD paradigm [46]. Chiang and Hsiao examined tolerance-interval approaches for simultaneous accuracy and precision assessment [47]. Faya, Wolfe and Rauk provided confidence-interval examples directly responsive to the revised Q2(R2) expectation that interval limits for validation performance characteristics be compatible with acceptance criteria unless otherwise justified [48]. Analytical QbD studies increasingly use DoE to establish method-operable design regions, quantify robustness and justify control strategies [49–57].

Measurement uncertainty deserves particular emphasis because release decisions occur near specification boundaries. Separovic and Lourenço showed how analytical uncertainty can translate into false-conformity decisions in liquid chromatography [45]. A result numerically inside specification does not eliminate decision risk when uncertainty is large. Guard bands, uncertainty budgets or decision rules may be appropriate where the clinical or quality consequence of a false accept is material. At the same time, uncertainty approaches should not be used mechanically; the required framework depends on the regulatory setting, assay type and established procedure.

4.6 PAT, continuous manufacturing and multivariate statistical control

PAT and continuous manufacturing increase both the opportunity and the statistical complexity of quality control. Spectroscopic and process sensors can produce hundreds or thousands of correlated observations per batch or campaign. Separate univariate control charts for each sensor can generate a large multiplicity burden and numerous false alarms. PCA-based monitoring compresses correlated variables into latent dimensions; Hotelling T^2 and residual statistics can identify observations that depart from the multivariate process model; PLS can link process spectra or

settings to product attributes; and multivariate statistical process control can monitor trajectories through complex unit operations [36–44].

The selected PAT/CM literature was uniformly multivariate, which reflects the structure of the underlying data rather than a fashionable preference. Tavares da Silva et al. applied multivariate SPC to continuous twin-screw granulation and fluid-bed drying [36], Silva et al. extended multivariate monitoring to continuous-manufacturing data [37], and commercial/case-study literature demonstrates the integration of PAT models with real-time process understanding [38–41]. ICH Q13 provides a regulatory framework for lifecycle management of continuous manufacturing, but it does not remove the need to validate sensor models, define data treatment, handle residence-time effects and verify model performance after process or raw-material changes [6].

4.7 AI/ML: extension of statistical thinking, not replacement for it

AI/ML appeared only in recent CPV publications in the coded corpus, consistent with its relatively new role in regulated manufacturing. Ondracka et al. evaluated AI-powered CPV for bioreactor processes [33]; Stassen et al. developed practical recommendations for AI use in CPV [34]; Jesubalan et al. combined machine learning, statistical trending and capability assessment in a UF/DF CPV framework [32]; and a 2025 paper examined how artificial intelligence can extend process analytical technology and continued process verification in data-rich biopharmaceutical manufacturing [35].

These developments do not make classical biostatistics obsolete. Model performance must still be quantified using appropriate training/validation partitions, calibration, discrimination or prediction-error metrics; the data-generating process must be understood; and false-positive/false-negative consequences must be specified. Time-ordered manufacturing data also make random train/test splitting potentially misleading because it can leak future information into model development. Prospective or temporally separated validation is generally more defensible. Model drift should be monitored just as process drift is monitored, and retraining should occur under pre-specified governance rather than as an informal response to deteriorating performance.

Interpretability requirements depend on the decision. A model that provides advisory anomaly detection may tolerate more algorithmic complexity than a model that directly triggers batch diversion or release. The statistical plan should therefore define model role, training domain, performance criteria, uncertainty, drift detection, change control and human oversight. The key point is that AI is a model class within the quality system—not an exemption from statistical validation.

4.8 Common statistical failure modes in pharmaceutical validation

4.9 A practical stage-specific biostatistical toolkit

4.10 Proposed Biostatistical Validation Architecture

Based on the quantitative evidence map and regulatory synthesis, we propose a seven-step Biostatistical Validation Architecture. Step 1 is decision definition: state exactly what conclusion is required and what error would matter. Step 2 is variance mapping: identify independent and nested sources of manufacturing, sampling and analytical variability. Step 3 is design: use prospective experiments or sampling structures that make the desired effects estimable. Step 4 is estimation: report effect sizes, variance components and uncertainty rather than relying on P values alone. Step 5 is qualification: define PPQ evidence requirements using risk, interval width, assurance or defect-detection probability. Step 6 is monitoring: use control charts, multivariate methods or time-series models to detect departure from the validated state. Step 7 is lifecycle updating: revise models, sampling plans and control limits through formal change management as knowledge accumulates.

This architecture clarifies where statistical methods should not be substituted for one another. DoE estimates causal factor effects under a designed experiment; control charts monitor temporal stability; tolerance intervals address future population coverage; capability indices compare a stable process distribution with specification limits; Bayesian methods combine prior and current evidence; and measurement-uncertainty analysis describes confidence in an analytical decision. Using one tool to answer a different question—such as treating Cpk as proof of control—is a category error rather than a minor technical preference.

4.11 Future directions

Several directions are likely to define the next phase of pharmaceutical biostatistics. First, hierarchical and Bayesian models can formalize the use of prior process knowledge while preserving uncertainty, particularly when commercial batches are expensive and data are naturally nested. Second, adaptive sampling may allow CPV resources to be concentrated on high-risk strata while maintaining pre-specified statistical operating characteristics. Third, model-based CPV will increasingly integrate process, laboratory, deviation, maintenance and raw-material data, creating a need for reproducible data pipelines and explicit missing-data strategies. Fourth, measurement uncertainty will become more tightly integrated with analytical lifecycle management as Q2(R2)/Q14 implementation matures. Finally, AI/ML governance is likely to converge with established validation concepts: intended use, validated domain, performance criteria, independent verification, drift monitoring and controlled change.

The statistical profession also has an organizational role. Biostatisticians should be involved before data are generated, not only after validation runs are complete. Early involvement can convert vague statements such as “demonstrate consistency” into estimable quantities and acceptance logic. It can also prevent avoidable problems such as inadequate replication, uncontrolled multiplicity, confounded sampling, unrepresentative validation ranges and dashboards that generate alarms without decision rules. In this sense, biostatistics is a design discipline as much as an analysis discipline.

4.12 Limitations

The study has several limitations. The evidence corpus was purposive and method-focused rather than exhaustively systematic; prevalence percentages therefore describe the selected 42-publication map and should not be generalized to all pharmaceutical companies or published work. Coding reduced complex papers to binary method-family indicators and did not score methodological rigor, implementation success or regulatory acceptance. Focus assignment forced each publication into one dominant category even when it crossed lifecycle stages. The single-coder design introduces classification uncertainty, although the codebook and full coded matrix are reproduced to make judgments auditable. The era comparison is also susceptible to changes in publication mix; for example, the recent group contains more analytical-QbD papers, which can increase apparent DoE and uncertainty-method prevalence. For these reasons, method-family P values were multiplicity-adjusted and interpreted conservatively.

A second limitation is the separation between the public literature and proprietary manufacturing practice. Mature pharmaceutical companies may use sophisticated statistical methods without publishing them, and published case studies may overrepresent innovative methods. The analysis therefore describes visible scientific discourse rather than confidential operational prevalence. Nevertheless, the regulatory crosswalk and consistent lifecycle specialization across the evidence map provide a useful foundation for a practical validation framework.

5. CONCLUSIONS

Biostatistics is central to pharmaceutical quality control and process validation because pharmaceutical quality decisions are decisions under variation and uncertainty. The original evidence map showed that contemporary literature increasingly integrates multiple statistical functions, with a significant increase in method breadth in 2020–2025. Yet the more important finding is specialization: DoE and modelling dominate development, sampling and assurance dominate PPQ, SPC and capability dominate CPV, multivariate analysis dominates PAT/continuous

manufacturing, and uncertainty-aware modelling is increasingly prominent in analytical validation.

The practical implication is that organizations should build a lifecycle statistical architecture rather than a collection of isolated statistical tests. Specifications should remain distinct from control limits; capability should follow evidence of stability; PPQ sample sizes should follow explicit risk and evidence targets rather than ritual batch counts; analytical uncertainty should be considered when decisions approach acceptance boundaries; and AI/ML should be governed as a validated model throughout its lifecycle. When these principles are integrated, biostatistics becomes a mechanism for process knowledge, early detection, defensible validation and continual improvement—not merely a calculation performed after manufacturing data have already been collected.

DECLARATIONS

Ethics approval

Not applicable; this study analyzed publicly available publications and regulatory documents and used no human-participant or patient-level data.

Consent for publication

Not applicable.

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Author contributions

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Data availability

The coded evidence-map matrix used for the analyses is reproduced in Appendix A. A machine-readable CSV can be generated directly from the prespecified coding table.

Use of artificial intelligence

[Authors should complete this statement according to the target journal's policy, describing any permitted language or technical assistance and confirming author verification of the scientific content].

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APPENDIX A. REPRODUCIBLE CODED EVIDENCE MAP

The table below reproduces the complete publication-level coding in compact form. “Method families present” lists every method family coded 1 under the prespecified codebook; omitted families were coded 0. SIS is the unweighted count of listed families. The accompanying machine-readable CSV generated with this manuscript contains the full binary matrix used in the analyses. The corpus was purposive and is not intended to estimate industry-wide method prevalence.

APPENDIX B. IMPLEMENTATION CHECKLIST FOR A VALIDATION STATISTICIAN

1. Define the decision before selecting the statistical method: estimation, equivalence, detection of drift, population coverage, capability, prediction or classification.

2. Draw the data hierarchy: material lot → batch/campaign → time/position → sample → preparation → replicate measurement. Identify which units are independent.

3. Separate specification limits, alert/action limits and statistical control limits in protocols and dashboards.

4. Pre-specify handling of missing data, below-quantitation results, outliers, transformations and repeated measurements before reviewing validation outcomes.

5. For PPQ, justify batch count and within-batch sampling using risk, prior knowledge and an explicit precision/assurance/detection objective.

6. For capability analysis, demonstrate a defensible state of control and check distributional assumptions or use a non-normal/quantile alternative.

7. For CPV, define rational subgrouping, chart type, run rules, review frequency, escalation criteria and the statistical response to sustained shifts.

8. For multivariate/PAT models, preserve an independent or temporally separated validation set and define the model’s applicability domain.

9. For analytical validation, model accuracy and precision using the study design; report confidence or tolerance intervals where they answer the intended question.

10. Quantify measurement uncertainty or decision risk when results near acceptance boundaries can materially alter release decisions.

11. Correct for multiplicity when many attributes, models or rule tests are evaluated simultaneously, or explicitly control the monitoring false-alarm strategy.

12. Treat AI/ML as a validated lifecycle model: document training data, preprocessing, performance, uncertainty, drift monitoring, retraining and change control.

13. Preserve code, analysis datasets and versioned outputs so that validation conclusions are reproducible and auditable.

14. Report effect sizes and uncertainty alongside P values; statistical significance alone is not a pharmaceutical-quality criterion.

15. Reassess the statistical strategy after significant process, site, scale, analytical-procedure, formulation or raw-material changes.

Table 1. Prespecified statistical-method coding framework.

Family	Operational definition	Primary pharmaceutical-quality role
DoE	Factorial, response-surface, mixture or other designed experiments	Identify factor effects, interactions and robust operating regions during development/analytical development
Model	Regression, ANOVA, variance models or general statistical modelling	Estimate effects, variance components, predictions and relationships among process/material variables and CQAs
Sampling	Risk-based sample size, confidence/tolerance/prediction intervals or assurance	Quantify evidence strength in PPQ, QC and analytical validation; control probability of missed defects or uncertain conclusions
SPC	Control charts, run rules, trend or change monitoring	Distinguish common-cause from special-cause variation during routine manufacture/CPV
Capability	Cpk, Ppk, sigma level or related performance indices	Relate process distribution to specification limits after appropriate stability/assumption checks
MVA	PCA, PLS, chemometrics or multivariate statistical process monitoring	Analyze correlated high-dimensional PAT/process data and detect coordinated departures
Bayes	Bayesian assurance, updating or prior-informed inference	Combine prior/process knowledge with new data; support sample-size or lifecycle decisions
MU	Measurement uncertainty, conformity risk or error-budget analysis	Quantify uncertainty in analytical decisions and false-accept/false-reject risk
AI	Machine learning/deep learning or adaptive algorithmic monitoring	Prediction, fault detection and pattern recognition in data-rich manufacturing with model governance

Table 2. Characteristics of the 42-publication evidence corpus by primary focus.

Focus	n	%	Median SIS	Mean SIS	Year range
Analytical	13	31.0%	4.0	4.08	2015–2025
PAT/CM	9	21.4%	3.0	2.89	2006–2022
CPV	7	16.7%	4.0	4.29	2016–2025
Framework	5	11.9%	5.0	4.20	2008–2021
PPQ	4	9.5%	3.5	3.25	2013–2017
Development	2	4.8%	2.5	2.50	2017–2024
QC/CPV	2	4.8%	2.5	2.50	2012–2018

Table 3. Prevalence of statistical-method families in the evidence corpus.

Method family	n (N=42)	%
Model	40	95.2%
MVA	29	69.0%
SPC	20	47.6%
DOE	17	40.5%
MU	14	33.3%
Sampling	13	31.0%
Capability	12	28.6%
Bayes	4	9.5%
AI	4	9.5%

Table 4. Era comparison of statistical-method families with false-discovery-rate correction.

Family	2006–2019	2020–2025	OR recent vs older	P	BH-FDR q
DOE	5/21	12/21	4.27	0.0578	0.1735
Model	19/21	21/21	∞	0.4878	0.5687
Sampling	8/21	5/21	0.51	0.5055	0.5687
SPC	12/21	8/21	0.46	0.3543	0.5314
Capability	9/21	3/21	0.22	0.0855	0.1924
MVA	11/21	18/21	5.45	0.0431	0.1735
Bayes	3/21	1/21	0.30	0.6060	0.6060
MU	3/21	11/21	6.60	0.0203	0.1735
AI	0/21	4/21	∞	0.1069	0.1925

Table 5. Regulatory crosswalk: lifecycle expectations and corresponding biostatistical functions.

Source	Primary scope	Biostatistical implications	Operational interpretation
FDA Process Validation (2011)	Process design → PPQ → CPV	DoE/model building; risk-based PPQ evidence; ongoing statistical monitoring	Validation is a lifecycle evidence program, not a fixed three-batch ritual
FDA PAT (2004)	Real-time process understanding and control	Multivariate calibration, chemometrics, model verification, feedback/feed-forward control	Measurement strategy and model performance become part of control strategy
ICH Q8(R2)	Pharmaceutical development/QbD	Multivariate experiments, design space, SPC, trend analysis	Quantifies material/process relationships to CQAs
ICH Q9(R1)	Quality risk management	Risk-informed sampling, decision thresholds, uncertainty-aware escalation	Statistical effort should be proportionate to risk and knowledge
ICH Q10	Pharmaceutical quality system	Performance indicators, monitoring, knowledge management and improvement	Statistical monitoring supports management review and lifecycle learning
ICH Q13	Continuous manufacturing	Time-series/multivariate monitoring, residence-time and diversion logic, model lifecycle	Serial correlation and high-frequency data require appropriate statistical structure
ICH Q2(R2)	Analytical procedure validation	Accuracy/precision modelling, confidence intervals, range, robustness, prior knowledge	Validation quantifies whether performance supports intended use
ICH Q14	Analytical procedure development	DoE, MODR, multivariate procedures, ATP/control strategy, lifecycle management	Development and validation are linked rather than isolated
EU GMP Annex 15	Qualification and validation	Risk-based sampling and scientifically justified acceptance strategy	Statistical rationale supports qualification/validation evidence

Table 6. Common statistical failure modes and practical remedies.

Failure mode	Why it is statistically invalid/weak	Quality consequence	Practical remedy
Treating specification limits as control limits	Specification limits represent product requirements; control limits estimate process behavior	False reassurance about drift or excessive alarms	Use statistically derived control limits and maintain separate specification overlays
Calculating Cpk/Ppk before demonstrating stability	Capability assumes a meaningful distribution over the chosen time horizon	High capability can coexist with non-random drift	Establish control/stationarity first; then assess capability with appropriate distribution
Fixed “three PPQ batches” without power/assurance rationale	Batch count alone does not quantify evidence strength	Important variability may be missed	Use risk, prior knowledge, stratified sampling and explicit probability/precision targets
Pseudoreplication	Multiple units within a batch are not equivalent to independent batches	Standard errors become artificially small	Use hierarchical models and distinguish within-/between-batch variation
Excessive univariate alarms in correlated data	Multiple correlated charts inflate alert burden	Alarm fatigue and low diagnostic value	Use MVA/MSPC or multiplicity-aware strategy where appropriate
Ignoring analytical uncertainty	Measured value is treated as truth	False accept/reject near specification boundary	Quantify precision/uncertainty and define decision rule proportionate to risk
Using normal theory by default	Many CQAs are skewed, bounded or censored	Misleading limits and capability estimates	Check distribution; use transformation, quantile or suitable generalized models
Retrospective DoE logic	Observational correlations are interpreted as causal factor effects	Confounding and fragile design space	Use prospective randomization/blocking where feasible
Black-box AI without lifecycle controls	Model judged only by development-set accuracy	Overfitting, drift, data leakage and opaque decisions	Validate temporally; monitor drift; govern retraining and change control

Table 7. Stage-specific biostatistical toolkit for pharmaceutical quality and validation.

Lifecycle context	Primary statistical question	Recommended toolkit	Decision output
Stage 1 – Process design	Which factors and interactions drive CQAs?	Factorial/RSM DoE; regression/ANOVA; variance components; MVA	Effect sizes with uncertainty; design-space evidence; robust ranges
Analytical development	Can the procedure reliably measure the intended attribute across operating conditions?	DoE; calibration models; variance models; robustness analysis; ATP/MODR concepts	Procedure control strategy and risk-based robustness evidence
Stage 2 – PPQ	How much commercial-scale evidence is enough?	Risk-based sample size; confidence/tolerance intervals; Bayesian assurance; hierarchical models	Quantified probability/precision supporting reproducibility conclusion
Release QC	Does the measured lot meet requirements with acceptable decision risk?	Validated estimation; uncertainty analysis; OOS/OOT rules; trend review	Conformance decision with understood analytical error
Stage 3 – CPV	Has the process changed from its validated behavior?	SPC; EWMA/CUSUM where appropriate; change detection; variance monitoring	Early signal of special-cause variation
Capability review	Can the stable process reliably meet specifications?	Cpk/Ppk or non-normal/quantile alternatives; interval estimates	Process-performance assessment with uncertainty
PAT/continuous manufacturing	Are correlated, high-frequency process trajectories in control?	PCA/PLS; MSPC; time-series/residual monitoring; model validation	Real-time/near-real-time state assessment and fault diagnosis
AI-enabled monitoring	Can an algorithm add prediction or anomaly-detection value safely?	Cross-validation plus temporal holdout; calibration; uncertainty; drift monitoring	Governed model performance with defined retraining/change-control rules

Appendix Table A1. Publication-level coding map.

Year	Focus	Publication (short title)	Method families present	SIS
2006	PAT/CM	PAT initiative and multivariate process analysis, monitoring and control	Model, SPC, MVA	3
2008	Framework	Quality by design: concepts for ANDAs	DOE, Model, SPC, Capability, MVA	5
2012	QC/CPV	SPC for determining process capability and sigma level	SPC, Capability	2
2013	PAT/CM	Chemometrics and multivariate measurements in solid dosage manufacturing	Model, SPC, MVA	3
2013	PPQ	Risk-based methodology for validation of pharmaceutical batch processes	Model, Sampling, SPC, Capability	4
2014	Framework	Understanding pharmaceutical quality by design	DOE, Model, SPC, Capability, MVA	5
2015	Analytical	Analytical procedure validation and the QbD paradigm	DOE, Model, Sampling, Bayes, MU	5
2015	PAT/CM	Multivariate analysis in pharmaceutical industry	Model, SPC, MVA	3
2016	CPV	A roadmap for implementation of continued process verification	Model, Sampling, SPC, Capability, MVA	5
2016	PPQ	Stage 2 PPQ: scientific approach to determine number of PPQ batches	Model, Sampling, Capability	3
2017	CPV	Assessment methodology for process validation lifecycle Stage 3A	Model, Sampling, SPC, Capability	4
2017	Development	Design of experiments (DoE) in pharmaceutical development	DOE, Model	2
2017	Framework	Application of quality by design in current drug development	DOE, Model, MVA	3
2017	PAT/CM	MSPC of continuous twin-screw granulation and fluid-bed drying	Model, SPC, MVA	3
2017	PPQ	Bayesian assurance and sample size determination in process validation	Model, Sampling, Capability, Bayes	4
2017	PPQ	Sample size for tablet compression and capsule filling during process validation	Sampling, Bayes	2
2018	PAT/CM	PAT in continuous manufacturing of a commercial product	Model, MVA, MU	3
2018	QC/CPV	Risk index and data display for process performance	Model, SPC, Capability	3
2019	Analytical	Measurement uncertainty and risk of false conformity in LC procedures	Model, Sampling, MU	3
2019	PAT/CM	In-depth evaluation of continuous manufacturing data using MSPM	Model, SPC, MVA	3
2019	PAT/CM	PAT for continuous manufacturing tableting: case study	Model, MVA	2
2020	Framework	Quality by design in pharmaceutical manufacturing: systematic review	DOE, Model, SPC, Capability, MVA	5
2021	Analytical	Tolerance interval testing for accuracy and precision	Model, Sampling, MU	3
2021	Framework	Quality-by-design in pharmaceutical development	DOE, Model, MVA	3
2021	PAT/CM	PAT tools for monitoring pharmaceutical unit operations	Model, SPC, MVA	3
2022	PAT/CM	PAT implementation for advanced process control in solid dosage manufacturing	Model, SPC, MVA	3
2023	Analytical	AQbD tools to support switching of QC method	DOE, Model, MVA, MU	4
2023	CPV	CPV of the future: AI-powered CPV for bioreactor processes	Model, SPC, MVA, AI	4
2024	Analytical	DoE and data treatment in AQbD chromatographic development	DOE, Model, MVA, MU	4
2024	Analytical	DoE-QSRR model for virtual MODR assessment	DOE, Model, MVA, MU	4
2024	Analytical	Drilling into QbD approach for analytical methods	DOE, Model, MVA, MU	4
2024	Analytical	ICH Q14-inspired SFC purity method for carbamazepine	DOE, Model, MVA, MU	4
2024	Analytical	Q14 case study of mass spectrometry NDSRI procedure	DOE, Model, Sampling, MVA, MU	5
2025	Analytical	Modern framework for analytical procedure development under Q14	DOE, Model, Sampling, MVA, MU	5
2025	Analytical	Practical ICH Q14 implementation in capillary electrophoresis	DOE, Model, MVA, MU	4
2025	CPV	Recommendations for AI application in CPV	Model, SPC, MVA, AI	4
2025	Analytical	Confidence intervals for validation under ICH Q2(R2)	Model, Sampling, Bayes, MU	4
2024	Analytical	Recent applications of AQbD methodology for chromatographic analysis	DOE, Model, MVA, MU	4
2025	CPV	AI-enhanced CPV for ultrafiltration/diafiltration	Model, SPC, Capability, MVA, AI	5
2025	CPV	AI empowering PAT and continued process verification	Model, SPC, MVA, AI	4
2021	CPV	Lyophilization validation: process qualification and continued process verification	Model, Sampling, SPC, Capability	4
2024	Development	Design of experiments for pharmaceutical analysis using HPLC	DOE, Model, MVA	3

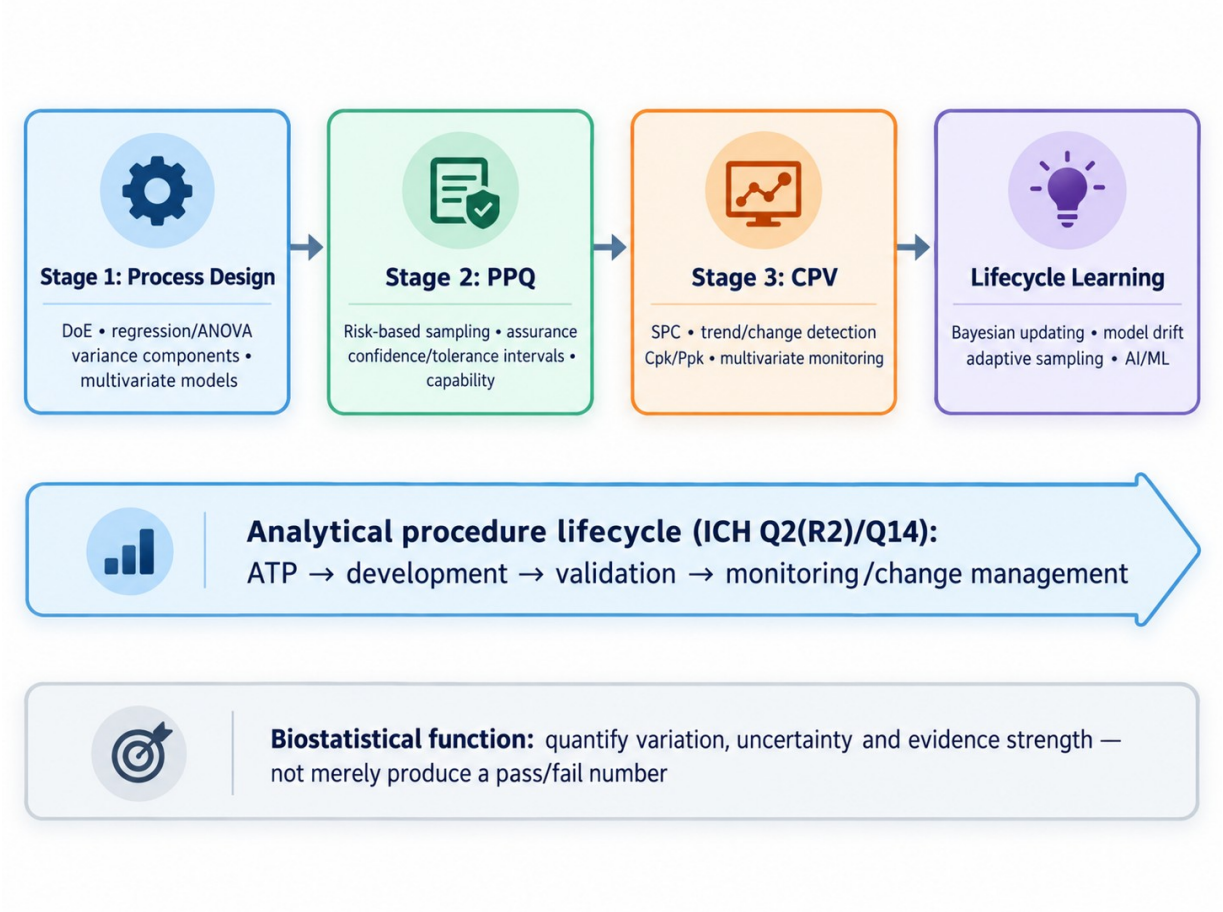

Figure 1. Biostatistical Validation Architecture across the pharmaceutical process and analytical-procedure lifecycles. The framework separates the statistical question at each stage while preserving feedback of knowledge into later monitoring and change management.

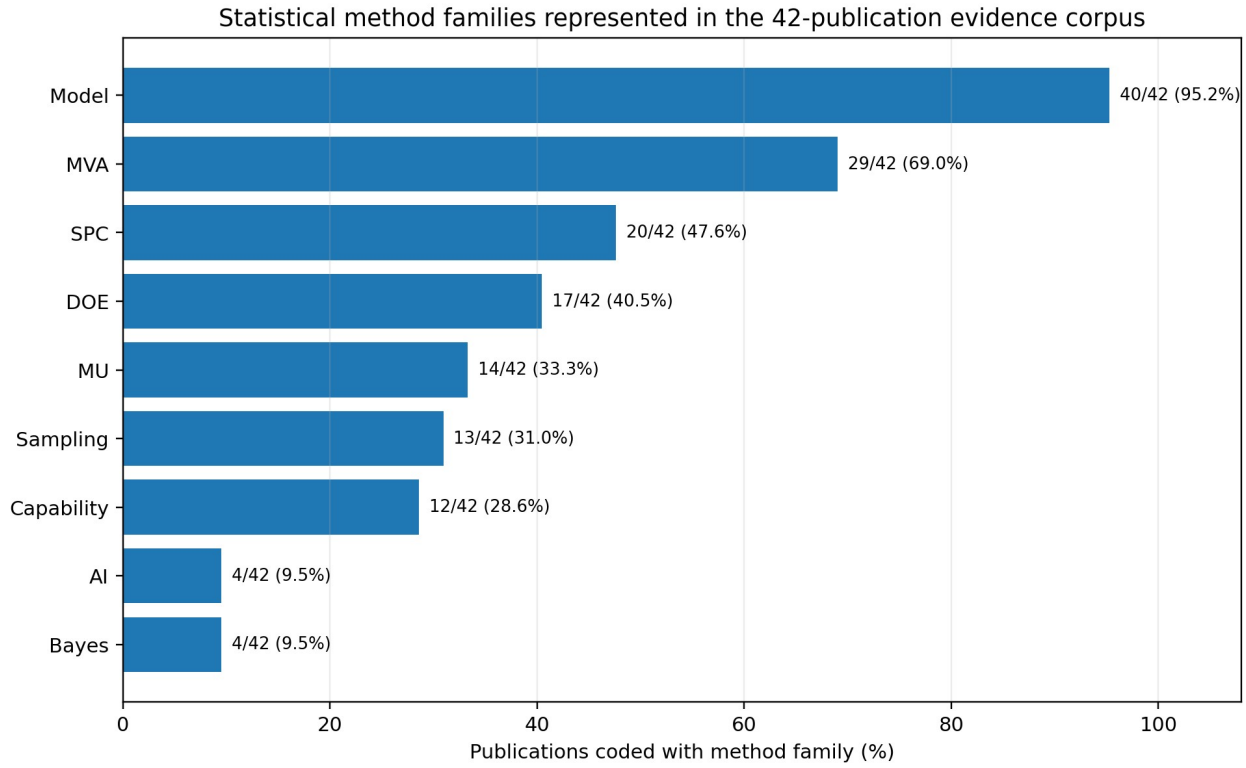

Figure 2. Prevalence of statistical-method families in the 42-publication method-focused corpus. Percentages describe this purposive evidence map and are not estimates of industry-wide utilization.

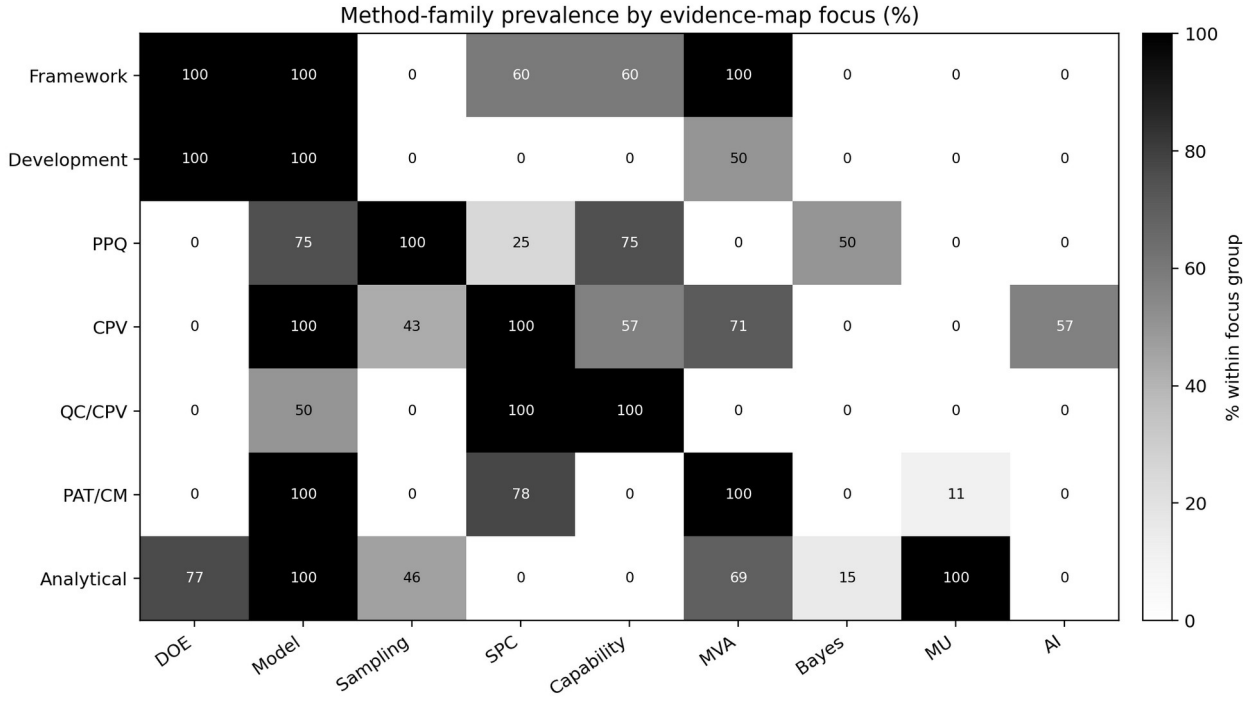

Figure 3. Heatmap of method-family prevalence by evidence-map focus. Values are percentages within each focus group; zeros indicate that the method family was not a substantive component of the coded publications in that group.

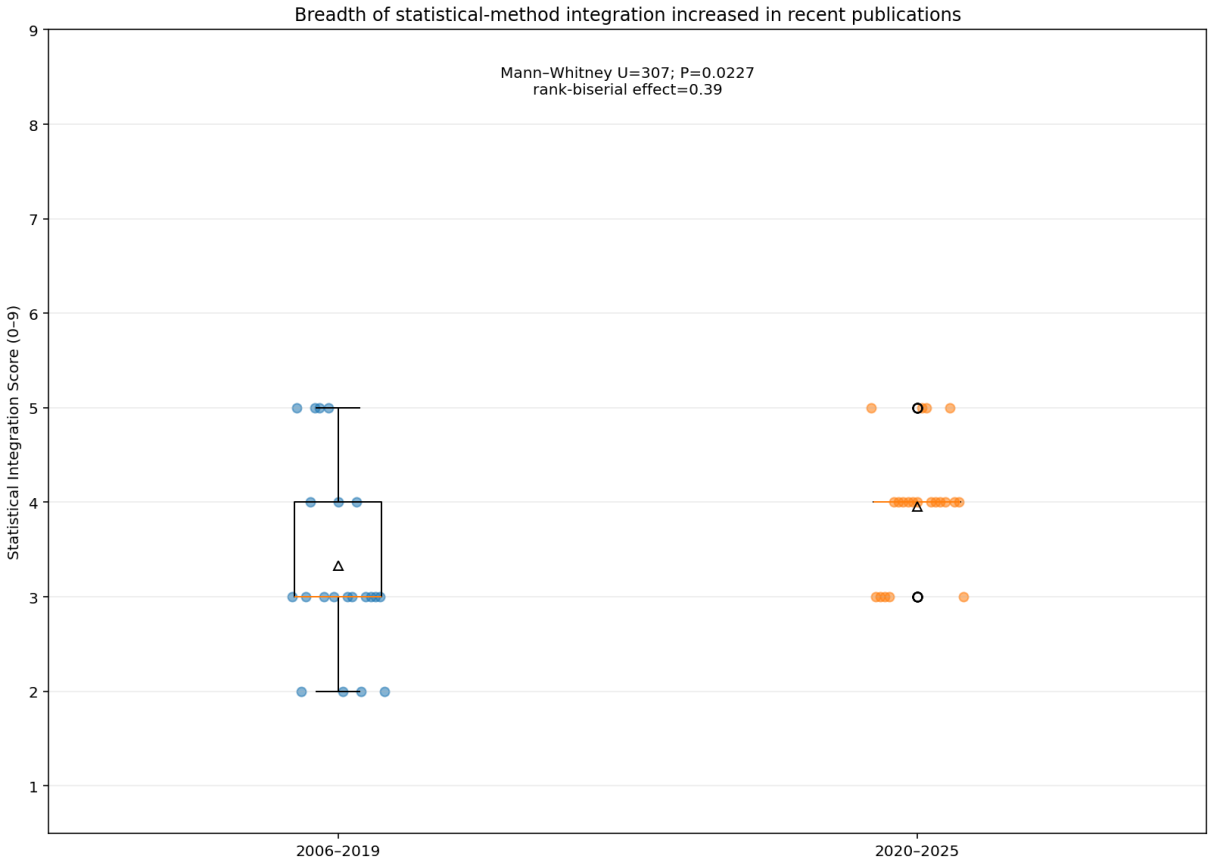

Figure 4. Statistical Integration Score by publication era. Dots represent individual publications; boxes show medians and interquartile ranges. The score counts represented method families and is not a methodological-quality rating.

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