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Review Article

DATA INTEGRITY IN PHARMACEUTICAL QUALITY SYSTEM: A REVIEW

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Data Integrity, which is data deemed Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available (ALCOA-plus), has been the focus of the pharmaceutical industry in recent years. With the growing use of computerized systems and rising prevalence of outsourcing manufacturing processes, ensuring data integrity is becoming more challenging in an increasingly complex pharmaceutical manufacturing industry. To address this issue, multiple legislation and guidance documents such as 'Data Integrity and Compliance with CGMP Guidance for Industry' from the US Food and Drug Administration (FDA), 'GxP' Data Integrity Guidance and Definitions from the UK Medicines & Healthcare products Regulatory Agency (MHRA), and 'Guidance on Good Data and Record Management Practices' from the World Health Organization (WHO), have been published in recent years. However, with rising data integrity issues observed by FDA, WHO, MHRA and other pharmaceutical inspectors even after these guidance documents have been published, their overall effectiveness is yet to be determined. It appears that these legislation and guidance are insufficient in maintaining data integrity in the industry when used alone. Last, but not least, this paper also reviews other solutions, such as the need for a company culture of integrity, to aid in maintaining data integrity in the manufacturing industry.

KEYWORD: Data integrity, ALCOA, Data, Good documentation practices (GDPs), Regulatory Body, Risk Management.

INTRODUCTION

Once a pharmaceutical product receives marketing authorization, it does not remain static for the rest of its commercial life. Manufacturers routinely need to increase batch size to meet market demand, move production between facilities, replace or upgrade equipment, adjust a formulation for supply or cost reasons, refine an analytical method, or change a container-closure system. Each of these adjustments is a post-approval change, and each carries the possibility, however small, of altering the identity, strength, quality, purity,

or potency of the product as it relates to its safety and effectiveness. Regulatory systems therefore require that such changes be evaluated, justified, and, depending on their risk, reported to or approved by the competent authority before or after implementation.[1]

Scale-up refers specifically to the deliberate increase of batch size relative to the batch used to generate the pivotal bioavailability, bioequivalence, or clinical data that supported approval. Because many pharmaceutical unit operations, such as blending, granulation, drying, compression, and coating, are sensitive



to equipment geometry, mixing intensity, and residence time, an increase in batch size can change the way a process behaves even when the qualitative and quantitative formula remains identical. Scale-up is consequently treated as a distinct, well-studied category of post-approval change with its own body of guidance, most notably the United States Food and Drug Administration's SUPAC series of documents.[2]

Scope and Regulatory Significance of Post-Approval Changes

The regulatory significance of post-approval changes lies in the principle that approval is granted for a specific, defined manufacturing process and control strategy, not merely for a chemical entity. Any deviation from what was approved is, by definition, a change to the approved application, and its potential impact on product performance must be assessed before the change can be relied upon for commercial supply. Regulatory agencies have therefore developed tiered systems that classify changes according to their likelihood of affecting product quality, and that specify the testing, documentation, and reporting mechanism appropriate to each tier. Protects patients by ensuring that manufacturing flexibility does not compromise the quality attributes established during development and confirmed at approval. Provides manufacturers with predictable, risk-proportionate pathways

for implementing necessary changes without unnecessary delay.[3]

Creates a documented history of a product's manufacturing evolution that supports inspection readiness and lifecycle knowledge management.

Enables regulators to focus review resources on changes that carry meaningful risk while allowing low-risk changes to be implemented with lighter-touch notification.

Supports global supply chains by offering a common vocabulary, even though implementation details differ by region.[4]

Relationship Between Scale-Up and Change Management

Scale-up and post-approval change management are best understood as overlapping rather than separate disciplines. A scale-up decision is rarely limited to batch size alone; it frequently triggers parallel changes in equipment, in-process controls, and sometimes site, all of which must be evaluated together. Guidance documents such as SUPAC therefore treat batch size as one of several interrelated change categories, alongside components and composition, manufacturing site, and manufacturing process or equipment, because a realistic scale-up project usually touches more than one of these categories at the same time.[5]

Regulatory Frameworks Governing Post-Approval Changes



Several regulatory systems address post-approval changes, and although their underlying risk-based philosophy is similar, their categories, terminology, and procedural timelines differ. A manufacturer supplying multiple markets must therefore map a single technical change against several parallel classification systems.

Despite these differences, every major framework asks the same underlying questions: what is changing, how likely is the change to affect a quality attribute linked to safety or effectiveness, what evidence is needed to demonstrate that the change does not compromise that attribute, and who must review that evidence before the change can be relied upon for commercial supply. Understanding this shared logic makes it easier to interpret an unfamiliar regional guideline, because the specific terminology and thresholds are, in effect, a local implementation of the same risk-based reasoning.[6]

United States Framework: 21 CFR 314.70 and the SUPAC Guidances

In the United States, changes to an approved new drug application or abbreviated new drug application are governed by 21 CFR 314.70, which establishes three broad reporting categories based on the potential of the change to have an adverse effect on product identity, strength, quality, purity, or potency: changes requiring a prior approval supplement, changes

that may be made and reported through a changes-being-effected supplement, and changes that may be reported in the next annual report. The SUPAC series of guidances, beginning with SUPAC-IR for immediate-release solid oral dosage forms and later extended to SUPAC-MR for modified-release forms and SUPAC-SS for non-sterile semisolids, translates this general framework into specific, dosage-form-appropriate level definitions covering components and composition, site, batch size, and manufacturing process or equipment changes.[7]

European Union Variation Classification

The European Union classifies post-authorization changes as variations under a dedicated variations regulation and accompanying classification guideline. Variations are grouped into minor Type IA variations, including an immediate-notification subtype, minor Type IB variations, and major Type II variations, with the classification driven by an annex of predefined change types and their associated conditions and documentation. Changes that fall outside the scope of a variation, such as a new indication requiring substantial new clinical data, may instead require an extension application treated similarly to a new marketing authorization.[8]

World Health Organization Guidance

The World Health Organization provides



guidance for manufacturers of multisource (generic) products, particularly those supplying prequalified products or products intended for procurement by international agencies. WHO guidance on variations groups changes in a manner broadly comparable to the SUPAC and EU systems, distinguishing minor variations that can be notified, from major variations that require prior assessment, while placing strong emphasis on risk justification, comparative dissolution or bioequivalence data, and stability commitments appropriate to the change.[9]

ICH Q12 Framework

The International Council for Harmonisation's ICH Q12 guideline, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, was developed to bring greater consistency and predictability to post-approval change management across regions. It introduces the concepts of established conditions, which are the legally binding elements of an approved application necessary to ensure product quality, and post-approval change management protocols, which allow a company to agree in advance with a regulator on the testing and evidence needed to implement a specific future change, often permitting a reduced reporting category when the protocol is executed as agreed. [10]

Definition and Rationale for Scale-Up

Scale-up is the process of increasing batch size from the scale used during formulation

development, pilot manufacture, or the pivotal bioequivalence or clinical batch, to a larger, commercially viable batch size. The rationale is primarily economic and logistical: commercial batches must be large enough to supply the market efficiently, but the equipment and processing conditions used to achieve this larger scale are not always a simple linear extension of small-scale operations. A central premise of scale-up science is that a formulation which performed acceptably at pilot scale will not automatically perform identically at commercial scale unless the process has been designed, or subsequently adjusted, to preserve the critical material attributes and critical quality attributes that were established at the smaller scale.[11]

Scale-Up Factor and Batch-Size Relationships

The scale-up factor is commonly expressed as the ratio of the proposed commercial batch size to the size of the biobatch, pilot batch, or the smallest batch used to support the original approval. Regulatory level definitions for batch-size changes are typically tied to this ratio: a modest increase, generally up to a defined multiple of the reference batch and manufactured with the same equipment and qualitative and quantitative formula, is treated as lower risk, whereas an increase beyond that multiple, or one involving a change in the type of equipment, is treated as carrying a greater



potential to affect product performance and therefore requires more extensive supporting data.[11]

Scale-Dependent and Scale-Independent Parameters

Scale-up planning benefits from distinguishing parameters that are intrinsically scale-dependent from those that are largely scale-independent. Scale-dependent parameters include mixing time and shear, granulation endpoint, drying rate, blend uniformity, compression dwell time, and coating spray and drying kinetics, all of which are governed by equipment geometry, impeller or bed design, and energy input that change with batch size. Scale-independent parameters, such as the qualitative composition of the formula or the chemistry of a coating polymer, are less likely to change with batch size but may still be affected indirectly if a scale-dependent parameter drifts outside its intended range. Identifying which parameters in a specific process are scale-dependent is a key input to deciding what data are needed to support a proposed scale-up.

A practical approach used by many formulation and process-development teams is to build a scale-up risk map early in development, listing each unit operation, the equipment attribute that could plausibly change at larger scale, and the material or in-process attribute that each equipment attribute is expected to influence.

This map, revisited and refined as pilot- and demonstration-scale data become available, provides a structured starting point for the risk assessment that will later support a specific scale-up submission, and it helps ensure that engineering or demonstration batches are designed to generate the comparative data that regulators are most likely to expect.[12]

SUPAC-IR: Immediate-Release Solid Oral Dosage Forms

SUPAC-IR was the first guidance in the SUPAC series and established the analytical framework later extended to other dosage forms. It addresses four principal change categories for immediate-release solid oral products: components and composition, manufacturing site, manufacturing process and equipment, and batch size, and defines three levels of change within each category based on the likelihood of a detectable effect on formulation performance.[13]

Components and Composition Changes

Changes to excipients are classified according to the percentage change in the excipient relative to the approved target, the function of the excipient (for example, filler, disintegrant, binder, or lubricant), and whether the change is within or outside the range validated during development. A small percentage change in a non-functional filler is generally treated as lower risk than an equivalent percentage change in a disintegrant or a coating that



governs drug release, reflecting the different sensitivity of dissolution and bioavailability to each excipient's function.[14]

Manufacturing Site Changes

Site-change levels depend on whether the new site is part of the same physical campus or a genuinely different location, whether the equipment, standard operating procedures, and environmental controls are equivalent, and whether the change also involves a process or equipment change. A move within the same campus, using the same equipment and personnel familiar with the process, generally poses lower risk than a transfer to an unrelated facility with different equipment and a new operating team.[14]

Manufacturing Process and Equipment Changes

Process and equipment changes are evaluated according to whether the fundamental processing principle remains the same, for example whether wet granulation is replaced by direct compression, and whether the new equipment operates on the same underlying mechanism as the original. A change in operating parameters within the equipment's established range is generally lower risk than a change in the type or design of equipment, and a change in the fundamental process technology is treated as the highest risk category because it can alter the mechanism by which the dosage form is formed.[15]

Batch-Size (Scale-Up/Scale-Down) Changes

Batch-size changes are assessed relative to the pilot or biobatch size, using the same equipment class and qualitative and quantitative formula. Increases within a defined, modest multiple of the reference batch, produced using equipment of the same design and operating principle, are treated as posing a lower risk of altering product performance. Larger increases, or any increase accompanied by a change in equipment type, require additional evidence, which typically includes updated batch records, in-process controls, and comparative dissolution testing, to demonstrate that the scaled-up product remains equivalent to the original.[15]

Reporting Categories and Supporting Documentation

Across all four SUPAC-IR change categories, the reporting mechanism, whether an annual report, a changes-being-effected supplement, or a prior approval supplement, and the chemistry, manufacturing, and controls documentation and in vitro or in vivo testing expected, increase with the assigned level. Typical supporting evidence includes updated batch production records, in-process control data, comparative dissolution profiles, and, for the highest-risk changes, in vivo bioequivalence data.[15]

Illustrative Scale-Up Assessment

Consider a manufacturer seeking to increase

the commercial batch size of an immediate-release tablet well beyond the size of the original biobatch, while continuing to use granulation and coating equipment of the same design and operating principle. The assessment would begin by confirming that the qualitative and quantitative formula, and the fundamental process sequence, remain unchanged. It would then examine whether the scale-up factor falls within or beyond the threshold associated with a lower-risk level, and would generate comparative in-process data, such as blend uniformity, granule particle size distribution, and tablet hardness and friability, alongside dissolution profiles from the proposed commercial-scale batches compared with the original biobatch or a representative production batch. If the comparative data demonstrate equivalence and the scale-up factor and equipment class fall within the lower-

risk thresholds, the change is typically reportable at a lower category; if the factor is exceeded, or if equivalence is not clearly demonstrated, the manufacturer should expect to generate additional data, potentially including an in vivo bioequivalence study, and to file at a higher reporting category. This example illustrates why scale-up decisions should be planned jointly by formulation, manufacturing, analytical, and regulatory functions rather than treated as a purely operational batch-size adjustment.[15]

SUPAC-MR and SUPAC-SS: Modified-Release and Semisolid Dosage Forms: SUPAC-MR Considerations

Modified-release products depend on a rate-controlling mechanism, such as a polymeric matrix, a functional coating, or an osmotic system, to achieve their intended release profile. SUPAC-MR therefore applies the same

Table 1: Risk-Based Post Approval Change Level

Change Level	Typical Risk Interpretation	Illustrative Reporting Route
Level 1	Minimal or no observable effect on formulation quality or performance	Annual report
Level 2	Some potential for a detectable effect on formulation quality or performance	Changes-being-effected supplement, with dissolution or other confirmatory data
Level 3	Significant potential for a change in formulation quality or performance	Prior approval supplement, often with in vivo bioequivalence data



four change categories used in SUPAC-IR but sets generally more conservative thresholds, because even small changes to a rate-controlling excipient, coating weight gain, or processing condition can meaningfully shift the release profile. Comparative dissolution testing across multiple time points and multiple dissolution media is emphasized more heavily than for immediate-release products, and a change that alters the release mechanism itself is treated as high risk regardless of the magnitude of the individual formulation adjustment.[16]

SUPAC-SS Considerations

SUPAC-SS addresses non-sterile semisolid dosage forms such as creams, ointments, gels, and lotions. In addition to components and composition, site, batch size, and process or equipment changes, SUPAC-SS explicitly addresses container-closure system changes, because packaging can influence moisture loss, microbial quality, and physical stability of a semisolid product. Physicochemical and, where relevant, in vitro release testing, along with rheological characterization, are used to demonstrate that a scaled-up or otherwise changed semisolid product remains comparable to the originally approved formulation.[17]

Comparing SUPAC-IR, SUPAC-MR, and SUPAC-SS

Although the three SUPAC guidances share a www.pharmaerudition.org Aug 2026, 16(2), 21-42

common risk-based structure, the specific attributes considered most sensitive differ by dosage form. For immediate-release solids, attention centers on dissolution rate and content uniformity. For modified-release products, the release-controlling mechanism itself, and the full dissolution profile across the release period, take priority. For semisolids, physicochemical characteristics such as viscosity, particle size in suspensions, globule size in emulsions, and in vitro release rate are typically the most informative indicators of whether a change has altered product performance. Recognizing which dosage-form-specific attributes are most sensitive helps a development or regulatory team select the right comparative testing strategy for a given change.[18]

Classification of Post-Approval Changes In the United States

Under 21 CFR 314.70, every post-approval manufacturing change is placed into one of three reporting categories, and the SUPAC level assigned to a specific change generally maps to one of these categories.

Major Changes: Prior Approval Supplement

A major change has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to safety or effectiveness. Such changes require FDA approval of a prior approval supplement before the product



manufactured using the change may be distributed. Examples include a change in the qualitative formulation, a change to a different manufacturing site with a different process, or a change involving a new synthetic route for the drug substance.

Moderate Changes: CBE-30

A moderate change with a moderate potential for an adverse effect may be implemented through a changes-being-effected supplement submitted at least thirty days before distribution, allowing the agency to review the submission and object if necessary before commercial batches reach the market. This category is often used for scale-up changes and process modifications that fall short of a major change but still warrant premarket regulatory review.

Moderate Changes: CBE-0

A defined subset of moderate changes, specified in regulation and guidance, may be implemented immediately upon submission of a changes-being-effected supplement without waiting thirty days, because the risk is well

characterized and adequately mitigated by the documentation submitted. Certain established, low-risk site changes and specific editorial or administrative corrections often fall into this category.

Minor Changes: Annual Report

A minor change has minimal potential to have an adverse effect on product quality and may simply be described in the product's next annual report, without requiring premarket notification or approval. Most Level 1 changes under SUPAC fall into this category, reflecting their low inherent risk.[19]

European Union Variation: Classification

Type IA and IA(IN) Minor Variations

Type IA variations have a minimal impact, or no impact at all, on the quality, safety, or efficacy of the medicinal product, and can generally be notified to the authority within a set period after implementation, sometimes described as a 'do and tell' mechanism. A subset, Type IA(IN), requires immediate notification, typically within a short number of days, because although the impact is still minor, the authority needs to be

Table:2 FDA Post-Approval Changes Reporting Categories

Reporting Category	Risk Level	Timing of Implementation
Prior Approval Supplement (PAS)	Substantial potential for adverse effect	Only after FDA approval
CBE-30	Moderate potential for adverse effect	30 days after submission, absent FDA objection
CBE-0	Moderate, but well-characterized and mitigated risk	Immediately upon submission
Annual Report	Minimal potential for adverse effect	May be implemented and reported later



informed promptly.

Type IB Minor Variations

Type IB variations are minor variations that do not meet the specific conditions for a Type IA classification and are not explicitly classified elsewhere. They require notification before implementation, with the authority given a short period to review and raise objections; if no objection is raised within that period, the applicant may proceed.[20]

Type II Major Variations

Type II variations may have a significant impact on the quality, safety, or efficacy of the product and require formal assessment and approval by the competent authority before implementation. Examples include significant manufacturing process changes, changes to specifications outside previously approved limits, and new manufacturing sites for biological products.[20]

Extensions of Marketing Authorisation

Certain changes are considered substantial enough that they cannot be handled as variations at all and instead require an extension application, which is assessed largely as if it were a new marketing authorization. Typical examples include a new pharmaceutical form, a new strength, or a change in the route of administration.[20]

Categories Of Changes By Subject Area

Beyond the region-specific classification systems, it is useful to organize post-approval

changes by the subject-matter area they affect, since each area carries its own typical risk drivers and evidentiary expectations.

Composition and Formulation Changes

Changes to the qualitative or quantitative composition of a drug product, including excipient grade, supplier, or concentration, require an assessment of the excipient's functional role, its interaction with the active ingredient, and its influence on critical quality attributes such as dissolution, content uniformity, and stability.[21]

Manufacturing Site Changes

A site change requires confirmation that the receiving facility has equivalent or scientifically justified equipment, environmental controls, utilities, and a qualified workforce capable of reproducing the approved process, supported by comparative batch data and, where the process itself has also changed, additional validation evidence.

Manufacturing Process and Equipment Changes

Process and equipment changes are assessed against whether the underlying processing principle is preserved and whether operating parameters remain within, or are scientifically justified outside, previously validated ranges, with process validation or verification batches used to confirm continued performance.[21]

Batch-Size and Scale-Up Changes

As discussed in the SUPAC framework above,

batch-size changes are evaluated against a defined scale-up factor and the equipment used, with escalating documentation requirements, including comparative dissolution and, in higher-risk cases, in vivo bioequivalence data, as the scale-up factor increases.[21]

Specification and Analytical Method Changes

Tightening a specification generally poses lower risk than widening it, and a change to a validated analytical method requires demonstration that the new method is at least as capable as the original of detecting out-of-specification material, often supported by a side-by-side method comparison or a full method validation package.[21]

Container-Closure System Changes

Container-closure changes are evaluated for their effect on product protection from moisture, oxygen, and light, for compatibility and potential extractables or leachables, and, for semisolid, liquid, and inhalation products in particular, for their effect on dose delivery and physical stability.[21]

Labeling and Packaging Changes

Labeling changes range from purely administrative corrections to changes in dosing instructions or safety information that may require prior regulatory review; packaging changes that do not alter the container-closure system itself, such as carton artwork, are typically classified as low risk.[21]

Table:3 Risk Based Classification Of Post Approval Changes

Subject Area	Common Low-Risk Example	Common High-Risk Example
Composition	Minor adjustment to a non-functional filler within a validated range	Change to a functional excipient controlling drug release
Site	Relocation within the same campus using identical equipment	Transfer to an unrelated facility with different equipment and personnel
Process/Equipment	Operating-parameter adjustment within a validated range	Change in fundamental processing technology or mechanism
Batch size	Modest increase within the defined scale-up factor using equivalent equipment	Increase beyond the defined factor or with a change in equipment class
Analytical method	Minor procedural clarification with no change to acceptance criteria	Replacement of a compendial or validated method with a different technology
Container-closure	Change in secondary packaging artwork only	Change in primary container material affecting product protection



Stability Requirements For Post-Approval Changes

Stability data provide ongoing assurance that a changed product will maintain its quality throughout the labeled shelf life. The extent of stability data required scales with the risk level of the change: low-risk changes may require only a commitment to place batches on long-term stability with periodic reporting, while higher-risk changes typically require accelerated and, in some cases, a minimum amount of long-term stability data available at the time of submission, together with a protocol for continued monitoring after approval.[22]

Stability Protocol Design for Changed Batches

A stability protocol supporting a post-approval change should specify the number of batches placed on study, the storage conditions and testing intervals, the analytical methods and acceptance criteria, and, where relevant, comparison against historical data for batches manufactured before the change. For a scale-

up or site change, it is common practice to place the first several commercial-scale or newly sited batches on formal stability, in addition to the routine ongoing stability program, so that any divergence from the established stability profile is detected promptly. Where a product is sensitive to moisture, oxidation, or photodegradation, the protocol should also confirm that the container-closure system used for the changed batches provides equivalent protection to that used for the batches on which the original shelf life was established.[23]

Bioequivalence, Dissolution Testing, And Bcs-Based Biowaivers

For oral solid dosage forms, in vitro dissolution testing is the primary tool used to demonstrate that a post-approval change has not altered the rate or extent of drug release. Comparative dissolution profiles, evaluated using a model-independent similarity factor or an appropriate statistical comparison, are generally sufficient evidence for low- and moderate-risk changes.

Table 3: Stability Protocol Design for Changed Batches

Change Risk Level	Typical Stability Expectation
Low	Ongoing stability commitment and inclusion in the annual stability program
Moderate	Accelerated stability data at submission plus a long-term stability commitment
High	Accelerated and available long-term stability data at submission, with continued monitoring through expiry



For higher-risk changes, particularly those involving narrow therapeutic index drugs, low aqueous solubility, or a change in release mechanism, in vivo bioequivalence studies may be required.

The Biopharmaceutics Classification System (BCS) provides a scientific basis for waiving in vivo bioequivalence studies for certain highly soluble, highly permeable (BCS Class I) and, under defined conditions, highly soluble but poorly permeable (BCS Class III) drug products, provided that the formulation meets rapid or very rapid dissolution criteria and other qualifying conditions. Where applicable, a BCS-based biowaiver can substantially reduce the burden associated with demonstrating that a post-approval change has not affected bioavailability, while still requiring robust in vitro comparability data.

Certain product categories warrant particular caution regardless of the nominal SUPAC level assigned to a change. Narrow therapeutic index drugs, where small differences in systemic exposure can produce a clinically meaningful effect, are generally held to tighter bioequivalence acceptance criteria and, in some regulatory systems, to different study designs than typical products. Locally acting products, such as topical, inhaled, and ophthalmic formulations, often cannot rely on systemic bioequivalence measures at all and instead depend on a combination of in vitro

release testing, physicochemical characterization, and, where necessary, comparative clinical or pharmacodynamic endpoints. Extended-release and complex dosage forms, including multiparticulate and osmotic systems, may also require dissolution testing under multiple conditions to adequately probe the release mechanism across the physiologically relevant range.[24]

ICH Q12: Established Conditions And Lifecycle Management

Established Conditions

Established conditions are the elements of an approved application, such as specific process parameters, in-process controls, and specifications, that are considered necessary to assure product quality and that therefore require a regulatory submission if they are to be changed. ICH Q12 encourages applicants to identify established conditions explicitly, supported by a science- and risk-based justification, so that parameters outside this defined set can be managed within the firm's pharmaceutical quality system without a separate regulatory filing, provided the change does not affect the established conditions themselves.[25]

Post-Approval Change Management Protocols

A post-approval change management protocol, referred to in the United States as a comparability protocol, is a detailed,



prospective plan submitted to and agreed with a regulatory authority that describes the specific change intended in the future, the tests and acceptance criteria that will be used to demonstrate that the change does not adversely affect product quality, and the reporting category that will apply once the protocol has been successfully executed. Because the scientific justification and testing strategy are agreed in advance, execution of the protocol often allows the change to be reported at a reduced category, improving predictability for both the manufacturer and the regulator.[25]

Product Lifecycle Management Document

ICH Q12 also introduces the concept of a product lifecycle management document, a regulatory tool intended to consolidate a summary of established conditions and planned or foreseeable post-approval changes in a single, updatable location, supporting a more structured and transparent conversation between the manufacturer and regulators over the life of the product.

Pharmaceutical Quality System Change Categorization

ICH Q12 also describes a category of changes that can be managed entirely within a firm's pharmaceutical quality system, without any regulatory submission, where the change does not affect an established condition and is adequately controlled by the firm's own

change-management procedures under ICH Q10. Encouraging appropriate use of this category, supported by a mature quality system and robust internal change control, is intended to free regulatory review capacity for changes that carry genuine potential to affect patients, while still requiring the firm to maintain full documentation of the change for inspection purposes.[26]

Comparability Protocols and Risk-Based Change Management

The Comparability Protocol Concept

A comparability protocol allows a manufacturer to define, in advance, the analytical and, where relevant, in vivo testing that will be used to show that a product manufactured after a specified future change remains comparable to the product manufactured before the change. Once the protocol itself has been reviewed and accepted by the regulator, subsequent execution of the described change, if the predefined acceptance criteria are met, can often be reported through a lower-tier mechanism than would otherwise apply, because the uncertainty about the adequacy of the testing strategy has already been resolved.

Application of Quality Risk Management

The quality risk management principles described in ICH Q9 are directly applicable to scale-up and post-approval change decisions. A structured risk assessment, considering the severity of potential harm, the probability that a



given change will produce an adverse effect, and the ability of existing controls to detect a problem before it reaches the patient, provides an objective basis for assigning a change to an appropriate reporting category and for deciding what additional testing, if any, is warranted beyond regulatory minimums.[27]

Role Of Quality By Design In Managing Scale-Up And Changes

Quality by Design principles, applied during development, generate the process understanding that later makes scale-up and post-approval change management more predictable. When critical quality attributes and critical process parameters have been identified, and a design space describing the multidimensional combination of parameters known to assure quality has been established and included in the approved application, a manufacturer may be able to move within that design space, including to a different scale or piece of equipment performing the same function, without triggering a new regulatory filing. Even where a formal design space has not been submitted, a strong internal understanding of which parameters genuinely influence product performance allows a company to prioritize testing resources efficiently when planning a scale-up or other change.[27]

Documentation, Change Control, and Regulatory Submission

A documented change-control system is the operational backbone of post-approval change management. Every proposed change should be raised formally, assessed for its technical and regulatory impact, reviewed and approved by the quality unit, implemented according to an approved plan, and closed out with documented evidence that the predefined acceptance criteria were met.

A clear description of the proposed change and the reason it is being made.

An impact assessment covering product quality, other approved products sharing the same process or site, validation status, and regulatory filings in every market where the product is registered.

A defined testing and data-generation plan appropriate to the assessed risk level.

Identification of the applicable reporting category in each relevant regulatory region.

Quality unit review and approval before implementation, or before submission where prior approval is required.

Update of master batch records, specifications, validation documents, and stability protocols as applicable.

A closure record summarizing the outcome, including any deviations encountered during implementation.[28]

Regulatory Submission Content

A regulatory submission supporting a post-approval change should allow an independent



reviewer to understand exactly what is changing, why it is being made, what evidence supports the conclusion that quality is unaffected, and how the change will be monitored going forward, typically including updated chemistry, manufacturing, and controls sections, comparative data, and, where applicable, updated stability protocols and commitments.[28]

Electronic Change-Control Systems

Electronic quality management systems increasingly support change control through structured workflows that route a proposed change to the correct reviewers, enforce completion of an impact assessment before approval, link the change record to affected documents such as batch records and specifications, and maintain an auditable history of every decision and approval. Such systems reduce the risk that a change is implemented without the required cross-functional review, and they make it easier to

demonstrate during a regulatory inspection that the firm's change-control process was followed consistently.[28]

Organizational Roles and Responsibilities in Change Management

Effective management of scale-up and post-approval changes depends on clearly defined cross-functional responsibilities, since no single department holds all the information needed to assess a proposed change

Change-Control Boards and Governance

Many organizations route significant post-approval changes through a cross-functional change-control board that meets regularly to review proposed changes, confirm that impact assessments are complete, resolve conflicting priorities between sites or product lines, and track open changes through to closure. A well-run change-control board provides visibility across the organization, preventing a change approved for one purpose, such as a supplier substitution, from being implemented without

Table4: Cross-Functional Change Control Responsibility

Function	Typical Responsibility
Regulatory Affairs	Determines applicable reporting category in each market and prepares submissions
Quality Assurance	Owns the change-control system, approves risk assessments, and authorizes implementation
Manufacturing/Engineering	Executes the change, generates process and equipment comparability data
Quality Control/Analytical	Performs comparative testing, method verification, and stability testing
Validation	Coordinates qualification and process validation or verification activities
Supply Chain	Manages transition planning, inventory, and continuity of supply during the change



recognition of its knock-on effect on a different approved product or market that shares the same material or process step.[28]

Training and Competency

Personnel involved in assessing, approving, or executing post-approval changes should be trained not only in the applicable standard operating procedures but also in the underlying regulatory framework, so that risk assessments reflect a genuine understanding of why a given classification threshold exists rather than a mechanical checklist exercise. Periodic refresher training, informed by lessons learned from previous changes and by evolving regulatory guidance, helps sustain this competency over time.[28]

Global Harmonization And Regional Differences

Although the SUPAC, EU variation, WHO, and ICH Q12 frameworks share a common risk-based philosophy, they differ in terminology, thresholds, and procedural timelines. A change classified as low risk in one region may not automatically qualify for the equivalent classification elsewhere, because regional guidance reflects different legal structures and historical development.

Regulatory Intelligence and Submission Sequencing

Global manufacturers typically maintain a regulatory intelligence function that tracks the classification of a given change in every market

where the product is registered, identifies the market with the longest review timeline or the most conservative classification, and sequences submissions so that this market does not become the bottleneck for worldwide implementation. This function also monitors updates to national and regional guidance, since classification thresholds and documentation expectations are periodically revised.[29]

Convergence Initiatives

ICH Q12 is intended to narrow regional differences over time by encouraging convergence on the concepts of established conditions and prospective change-management protocols, and regional authorities have progressively incorporated its principles into local guidance. Mutual recognition and reliance arrangements between regulators, along with international initiatives that share assessment outcomes for selected products, further reduce duplication of review effort. Nevertheless, full alignment across regions has not yet been achieved, and region-specific analysis, supported by qualified local regulatory expertise, remains necessary for the foreseeable future when planning any multi-market post-approval change.[29]

Common Challenges and Risk Areas

Misclassification of Change Risk

Underestimating the risk of a change, for example by treating an equipment change as a



simple like-for-like replacement when it in fact alters a scale-dependent processing parameter, can result in an inadequately supported filing or, worse, implementation through too low a reporting category.

Inadequate Comparative Data

Comparative testing that does not use a sufficiently discriminating method, or that compares too few batches, may fail to detect a real difference introduced by the change, creating a false sense of assurance.

Fragmented Documentation

When development knowledge, validation data, and change history are scattered across different systems or departments, it becomes difficult to assemble a complete and internally consistent impact assessment for a new change.[29]

Multi-Market Coordination

Coordinating a single manufacturing change across many national approvals, each with its own classification and timeline, is logistically demanding and can create periods where different markets are supplied by product manufactured under different approved conditions.

Underuse of Prospective Regulatory Tools

Comparability protocols and post-approval change management protocols remain underutilized relative to their potential benefit, in part because developing a robust prospective protocol requires early investment

of technical effort that some organizations are reluctant to commit before the need for the change is imminent.[21,29]

Legacy Products with Limited Development Data

Products approved many years ago, sometimes before contemporary process-development and quality-risk-management expectations were established, may have thin or poorly organized development records. When such a product requires a scale-up or site transfer, the absence of a documented rationale for original process parameters can make it difficult to judge which aspects of the process are truly critical, often requiring supplementary characterization work before a change can be confidently classified and justified.[28,20]

Equipment Obsolescence and Like-for-Like Assumptions

As legacy equipment is retired, replacement models are not always identical in design, and a change that is informally treated as a routine like-for-like replacement can in practice alter mixing intensity, heat transfer, or spray characteristics. Verifying genuine equivalence, rather than assuming it from superficially similar specifications, is an area where insufficient diligence has historically contributed to unexpected post-implementation deviations. scale-up is attempted. Best Practices, Performance Indicators, And Future



Perspectives Build process understanding during development so that scale-dependent parameters are identified before commercial

Classify every proposed change against a documented, risk-based procedure rather than informal precedent. Use comparative dissolution, analytical, and where necessary in vivo data that are sufficiently discriminating to detect a meaningful difference.

Maintain a single, accessible change-history record for each product and manufacturing site. Coordinate multi-market submissions early, sequencing filings around the most conservative regional requirement. Consider comparability protocols or post-approval change management protocols for changes that are foreseeable well in advance of the need to implement them. Keep established conditions and supporting rationale current as process understanding matures over the product lifecycle. Involve quality, regulatory,

manufacturing, and analytical functions from the earliest planning stage of any proposed change.[29] Future Perspectives

The trajectory of scale-up and post-approval change management is toward greater use of established conditions, wider adoption of post-approval change management protocols, and continued convergence between regional frameworks under the influence of ICH Q12. Advances in process analytical technology and digital process models are expected to strengthen the scientific basis for predicting the effect of a proposed change before it is implemented, potentially allowing a larger share of routine, well-understood changes to be managed within the pharmaceutical quality system with reduced reliance on prior regulatory approval, while changes with genuine potential to affect patient safety continue to receive the level of regulatory scrutiny they warrant.[29]

Table:5 Suggest Change-Management Performance Indicator

Indicator	Purpose
Change classification accuracy	Measures whether risk assessments correctly predict regulatory category
Time from change proposal to implementation	Measures efficiency of the change-control process
Rate of post-implementation deviations	Indicates whether the change was adequately assessed
Comparative testing pass rate	Reflects the robustness of the underlying process and formulation
Number of markets pending approval for an implemented change	Highlights multi-market coordination risk
Use of prospective protocols	Tracks adoption of PACMP/comparability protocol tools



Illustrative Timeline Considerations

Realistic project timelines should account for the reporting category expected for each affected market. A change reportable only in an annual report can often be implemented as soon as internal testing and quality-unit approval are complete, whereas a change requiring a prior approval supplement or a Type II variation cannot be relied upon for commercial supply until formal regulatory approval has been received, which may take several months depending on the region and the complexity of the submission. Planning should also allow contingency time for the possibility that a regulator requests additional information, since this is common for higher-risk changes and can extend the review period beyond the standard target timeline.[30]

CONCLUSION

Scale-up and post-approval changes are essential for capacity expansion, cost reduction, supply-chain needs, and continuous improvement in pharmaceutical manufacturing. Regulatory systems such as **FDA, EU, WHO, and ICH** follow a risk-based approach, requiring stronger evidence for changes that may affect product quality. Effective management depends on **process understanding, risk assessment, change control, comparative testing, stability studies, and proper documentation**. Tools such as established conditions and post-

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approval change management protocols improve regulatory predictability. Overall, a **scientific, risk-based, and well-documented approach** ensures manufacturing flexibility while maintaining the **quality, safety, efficacy, and consistency** of pharmaceutical products.

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Conflict of Interest

The authors declare that they have no conflict of interest
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