Best Practices for Post-Approval Changes: Modernizing PAC

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Why PAC Modernization Matters

The opportunity is to preserve the practical strengths of SUPAC while improving predictability for today's products, technologies, and global supply networks.

Legacy Framework

Dosage-form-specific change levels
Testing and documentation recommendations
Useful risk-based foundation

Current State

Guidance gaps for complex products
Unclear evidence expectations for selected changes
Conservative filing strategies and variable global outcomes

Modernized State

Risk-proportionate CMC and BE evidence
Prospective pathways using Comparability Protocols and PACMPs
Greater reliance on product knowledge and PQS



Preserve what works

Close guidance gaps

Enable Agility

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A Modern PAC Operating Model

1

UNDERSTAND

Product, process, device, and patient-use risks

2

STRATIFY

Change significance, uncertainty and residual risk

3

DEMONSTRATE

Proportionate CMC and BE comparability evidence

4

ALIGN

Proposed reporting pathway and acceptance criteria

5

IMPLEMENT

PQS controls, verification and knowledge capture

The proposed reporting category and supporting evidence package should reflect the potential impact of the change, strength of the control strategy, and the uncertainty remaining after controls and comparability evidence are considered.

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ICH Q12: A Science- and Risk-Based Lifecycle Management Toolbox

Established Conditions

Identify the approved elements of control strategy and define associated reporting categories when changed.

PACMP / U.S. Comparability Protocol

Prospectively define the change, scientific rationale, studies, acceptance criteria and proposed reporting category.

PLCM Document

Maintain application-level visibility of approved conditions, protocols, commitments and implemented lifecycle changes.

Pharmaceutical Quality System

Assess, control, implement, verify, and document changes using a robust knowledge management and change management system.

Q8 Product knowledge + Q9 Risk management + Q10 PQS + Q11 Drug-substance understanding

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Modernizing PAC Classification

A modern framework would connect the potential impact of the change with product knowledge, control capability and comparability evidence.

LOWER RESIDUAL RISK

Well understood change
Strong controls and prior knowledge
Comparability readily demonstrated

May support Annual Report reporting

MODERATE RESIDUAL RISK

Some uncertainty remains
Focused studies and defined criteria
Manageable implementation controls

May support a CBE-0 or CBE-30 pathway

HIGHER RESIDUAL RISK

Potential significant quality or performance impact
Material uncertainty or novel evidence needs
FDA review before implementation

May require PAS review

Conceptual Industry Model for discussion. The applicable reporting category is governed by regulations, FDA guidance, approved application conditions, product-specific considerations, and FDA agreement.

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RECOMMENDATIONS

Modern PAC Framework

1	**Modernize and consolidate SUPAC guidance**	Retain useful dosage-form principles while removing overlap and outdated assumptions.
2	**Clarify change classifications and evidence expectations**	Link filing category and CMC/BE package to potential impact and residual uncertainty.
3	**Expand product-specific PAC guidance**	Prioritize Transdermal systems, MDIs, DPIs, and other complex product categories.
4	**Expand appropriate use of prospective protocols**	Use comparability protocols and PACMPs for suitable repeatable, well-characterized and planned site, scale, equipment or process transitions.
5	**Advance global convergence**	Advance convergence through ICH Q12 concepts, aligned terminology, and greater acceptance of common data packages.

The objective: Implement well-understood, lower-risk changes more predictively while focusing regulatory and Industry resources on changes with greatest potential impact.

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Thank you

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