Post-Approval Changes: Navigating Complexity, Delivering Solutions

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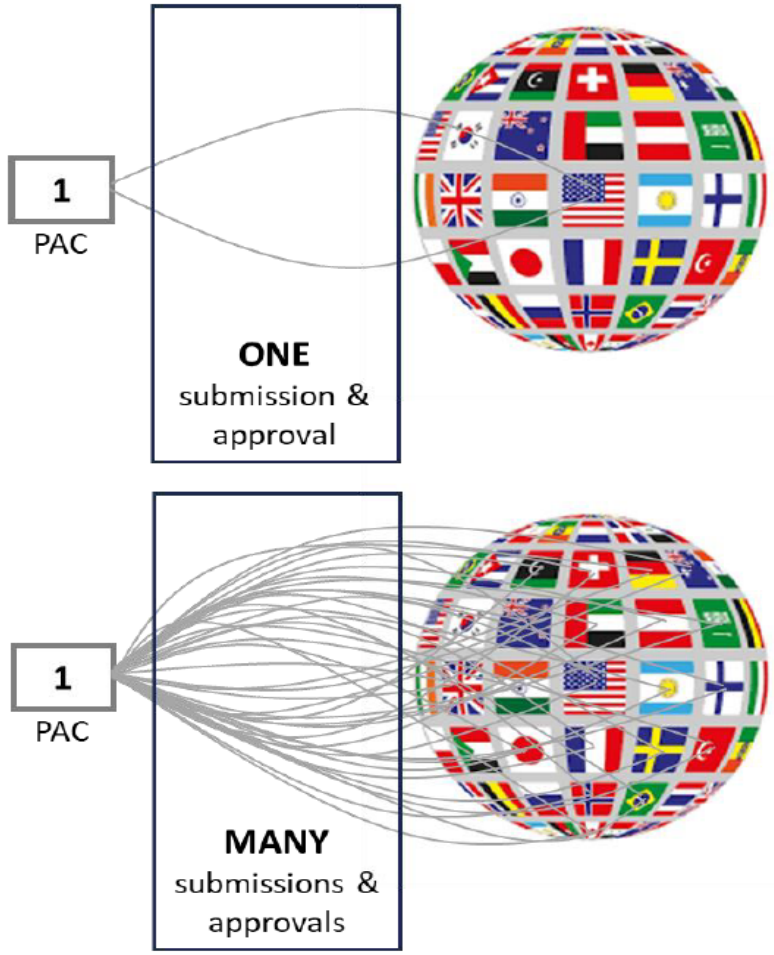
Increasing Domestic Manufacturing Requires a Flexible Regulatory Framework for PACs Including Site Transfers

- All biologics are treated as though they have the same level of risk(s) under the current framework
- Unintended constraints exist for timely implementation of manufacturing changes, such as the approval of a site transfer or new or expanded facilities.
- New or expanded manufacturing lines can be 'production ready' for up to one year before gaining FDA approval while data are being reviewed and inspections occur

Occurs even when a well-established process, with substantial prior knowledge, is moved from one site to another with negligible changes in processes or differences in equipment

Complexity of Global Post-Approval Changes Continues to Increase Causing Delays in Continuous Improvement and Supply Chain Management Challenges Which Could Lead to Drug Shortages



Current PAC Management is driven by **national frameworks not globally**

One PAC requires prior approval by multiple countries that have

- ***different*** reporting thresholds
- ***different*** requirements
- ***different*** timelines

First to last country approval can be often 3-5 years or more

Reference: EMA Interested Parties Briefing Session March 2 2026, E. Ramnarine and A. Vinther

ICH Q12 is Implemented in the U.S., But Global Uptake is Slow

Table 1a. ICH Q12 Implementation Landscape[a]

Country	Comments
United States	Implemented
Japan	Implemented
Canada	ISPE Training[b]; In the process of implementation
Brazil	ISPE Training[b]; In the process of implementation
China	Implemented
European Union	In the process of implementation[2]
United Kingdom	ISPE Training[b]; In the process of implementation
Singapore	ISPE Training[d]; In the process of implementation
Republic of Korea	In the process of implementation
Switzerland	In the process of implementation
Chinese Taipei	In the process of implementation
Mexico	In the process of implementation
Jordan	ISPE Training; not yet implemented

Table 1b. PACMPs are Becoming More Global[a]

Country	Year PACMP Introduced
United States	2003 (Comparability Protocol)
European Union	2013
Switzerland	2019
Japan	Piloted
China	2025
Canada	Piloted; 2025 (Biologics)[e]
Brazil	Currently being piloted[f]

[a]ICH Quality Guidelines Website
[b]Training provided by ISPE ICH Q12 Team

Reference: Industry Survey Results on Barriers to ICH Q12 Implementation and Control Strategy Harmonization, T. Graul, J. Lo Surdo Pinder, N. Cauchon, A. Chang, C. Langer, A. Nissar, submitted to Pharmaceutical Engineering, March 2026

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PACMP is a Useful Tool But Sometimes Feedback is Inconsistent

Obstacles to the utilization of PACMPs include:

- Two submissions with the risk that no agreement on downgrade of reporting category for the second submission will be obtained
  - Some examples seen of PACMPs being submitted even with no downgrade
- Requests for burdensome amounts of data in the first (prior approval) submission for the PACMP can cause delays
- Rigid interpretation of consequential changes
- Concern that inclusion of minor corrections/updates could conflict with PACMP implementation plan requirements, resulting in a loss of reporting agreements
- Evolution of business decisions over time that could make the PACMP obsolete
- Regional requirements/review complicate use of PACMPs. e.g. if company agrees to regulatory request for revision/modifications in one jurisdiction it complicates global implementation

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Experience with PACMP Submissions

Example 1: Batch size increase for mature well-characterized product

- A comparability protocol was submitted to FDA to 1) downgrade batch size increase reporting to CBE-30 2) allow for faster implementation and 3) to exclude stability data in filing thereby enabling faster submission.
- This batch size increase should be considered a low to moderate risk change - low if in the existing validated aseptic processing time. The risk that a batch size increase is going to impact the stability of the product is low, and a commitment to put the lot on stability and monitor in the PQS should be sufficient
- 2 rounds of RTQs; 2 months stability data was negotiated to be included at the time of submission and 6 months comparative degradation data was required to be provided within 4 months of variation submission.
- Overall, submission of the CP did not improve implementation timing significantly
  - Implementation was only a month faster than if the CP had not been filed, and had instead filed one PAS with no stability data in submission (provided during review period upon request)

Example 2: Introduction of external process challenge devices for external sterilization

- A PAMCP was submitted and approved by EU, CH, UK, CA, AU and US
- Successfully used to reduce submission category for US, EU, UK, and CH. Protocol approved for AU and CA

Experience with PACMP Submissions (cont'd)

Example 3: Transfer of non-platform drug substance process from a CMO (considered to be a high-risk change)

- Process developed in early 2000 with limited process characterization and support from the transfer site
- Multiple changes implemented with the transfer to bring product as close as possible to existing platform
  - Removal of animal derived materials and equipment and process changes
  - Process parameters adapted to reflect platform product approach
  - Control strategy changes (IPCs for intermediates, attributes removed from specification)
- Business risk mitigation included:
  - Additional process characterization and at scale manufacturing prior to validation critical to ensure success
  - Planning additional validation runs (i.e., more than 3) essential to dealt with potential process-extrinsic run failures
- Consideration was given to not implementing some changes at first to increase the probability of getting a reduction in filing category. Ultimately, a PACMP was not filed
- There are cases such as this one where a PACMP may not provide increased confidence of approvability and acceleration, but sometimes there is little benefit even for changes where the level of risk is substantially lower, as per example 1.

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Experience with PACMP Submissions (cont'd)

Example 4: Initial registration of a secondary drug substance site did NOT include a PACMP

- The site was essentially identical (e.g. same footprint, facility design, environmental controls, same equipment)
- A PAS was filed for a secondary DS manufacturing site for a mature well-characterized product
- There were no major changes in manufacturing process, internal control strategy (IPC's), raw materials, test methods or acceptance criteria
- However, as a brand new facility there was expectation of GMP inspections and a reduction in filing category was unlikely
- No PACMP was submitted
- For this type of transfer, other tools are needed to accelerate approvals

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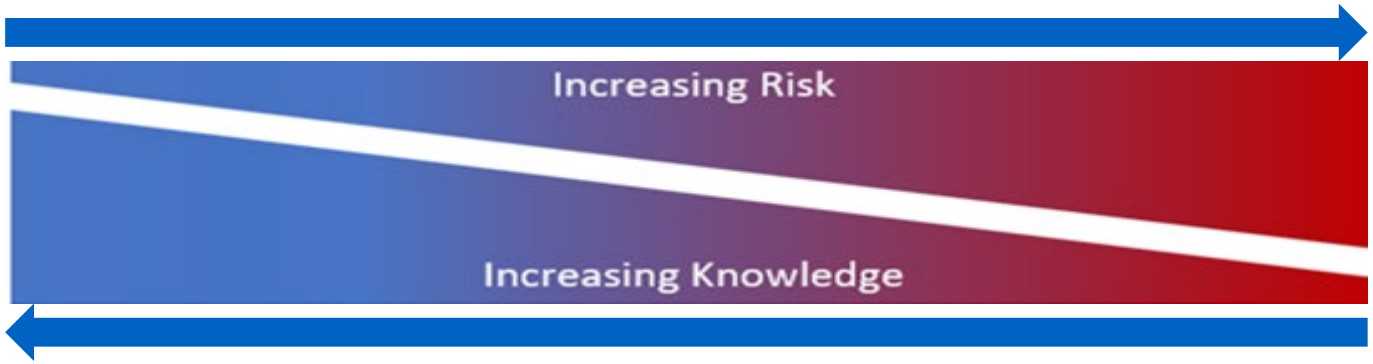
Continuum of Risk: Leveraging Product, Process, and Site Knowledge to Manage Risk

Low Risk
High Knowledge
Less data needed in submission



High Risk
Low Knowledge
More data needed in submission

Tech transfer for a mature well-characterized product

Multiple prior transfers

Established site under same PQS, equipment

Very limited process changes ("facility fit")

Extensive existing analytical and stability data on historical batches

Tech transfer for a well-characterized product

Established site under same PQS

Process changes with known impact and/or scale change

Extensive analytical and stability data on historical batches

Tech transfer for a novel modality

New site

Process changes with unknown impact

Analytical and stability data on limited number of batches

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Low Risk Change Example: Scale Up of DP Aseptic Process in Same Facility Without Changes in Equipment

- For DP aseptic processes, some scale ups can be achieved without significant changes in equipment and process, and therefore could be classified as low risk with minor potential to impact product quality
  - e.g., increase in scale with low risk changes to equipment (such as hold tanks), process parameters and filter area, with extended fill duration covered by existing media fill challenges
- An approach using a CBE-30 would align with FDA's current expectations and enables better life-cycle management; in actuality this type of change is typically prior approval globally but should be considered a low to moderate risk change
  - For example, risk of differing stability profile is very low, so stability data should not be needed at the time of submission
- Recent expectations have been more conservative and may require higher reporting categories
- Approaches to reduce reporting categories and data requirements include meetings with FDA and other health authorities

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Low Risk Change Example: New Line for Device Assembly in an Approved Facility

- Current Guidance[1,2] classifies "Site change for labeling or secondary packaging" as a change with minor impact to product quality
  - The level of risk is considered independent of the of the type of drug product dosage form or specific type of operation being performed
  - However, they are silent with respect to site change for combination product device assembly
- As device assembly may impact functionality, the level of risk may be assessed as higher than a labeling and secondary packaging site change, depending on the type of device; but typically is lower than the risk associated with the transfer of an aseptic fill drug product to a new facility.
- Initial transfers of device assembly to a new site (requiring site inspection), or an approved site without prior experience with assembly of device delivery systems such as autoinjectors or on-body injectors would be expected to fall in the major to moderate filing category
- Once a site obtains approval of the first product for the specific device assembly operation, introduction of the same device into additional lines/buildings, for same or different products, can be justified to pose minor potential to impact product quality
- The lack of guidance drives the need for potential interactions with FDA

[1] Guidance for Industry - CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports (2021)
[2] Guidance for Industry – Changes to an Approved NDA or ANDA – "For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product is considered to be independent of the type of drug product dosage form or specific type of operation being performed.

Note also: ICH Q12 Training Module 8 (starting page 45)

Legacy FDA Post-Approval Change Guidance Documents are Being Reassessed to Align with Science and Risk-based Lifecycle Management

FDA is explicitly asking industry and other stakeholders which SUPAC recommendations still work, which ones are difficult to interpret or apply, and what new content should be added

FDA says SUPAC's risk-based foundation remains relevant, but acknowledges that later frameworks, including ICH Q12 and ICH Q9(R1), may supersede or conflict with parts of the current framework

The push to update SUPAC is tied not only to regulatory modernization, but also to broader U.S. policy goals around **domestic pharmaceutical manufacturing**, including FDA's PreCheck initiative and the wider onshoring agenda

A central industry complaint is that the current post-approval change system is not flexible enough, especially for **site transfers or adding manufacturing sites**, which often require a PAS and can slow operations

In the future, a holistic reassessment of all post-approval change guidance documents may provide opportunities to allow superior risk management for well-characterized biologics, for hybrid modalities, and for 'sister site' transfers

Suggested PreCheck Enhancements to Accelerate Site Transfers

PreCheck enhancements could reduce site-transfer and new-facility approvals by at least 12 months and improve timeline predictability

- Expand use of prior knowledge for well-characterized biologics
  - Apply prior knowledge across products and sites
  - Allow streamlined validation when comparable experience exists at another site
  - Equipment equivalency/functional equivalency principles can be used to establish that a new manufacturing train is comparable or equivalent
- Take facility evaluations off the critical path
  - For compliant, previously inspected facilities, use pre-submission or remote reviews and avoid requiring commercial manufacture before inspection
  - Flexible inspection scheduling is key

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Streamlined CMC Data and Review Model for PAC Regulatory Submissions

- Use protocol-based CMC submissions for marketed biologics
  - Approve based on agreed protocols, with stability, PPQ, and comparability data submitted during review or post-approval (e.g. Annual Report)
- Apply risk-based data expectations for low-risk changes
  - Leverage existing stability data, allow concurrent validation, and focus comparability testing only on attributes affected by the transfer
  - Risk management should be adequately communicated to ensure understanding
- Shorten review timelines and modernize FDA-sponsor communication by reducing reviews from about 4 months to about 1 month when facility issues are addressed pre-filing and using real-time, cloud-based exchanges

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For Well-Characterized Biologics, the Enhanced Levels of Product and Process Understanding Support Risk-based Approaches

The following characteristics are well-understood and prior knowledge exists

- Criticality/impact of quality attributes
- Product and process impurities
- Quality attribute impact on biological activity (potency)
- Risk of immunogenicity for each attribute
- Degradation profile and knowledge of pathways
- Stability profile for all critical, stability-indicating attributes at recommended and accelerated storage conditions
- Analytical methods are validated and those monitoring attributes with potential to change are stability-indicating

Generation of PPQ and stability data is typically rate-limiting

Adaptation of shelf-life from previous manufacturing sites is done by leveraging stability data

- Some agencies prefer that shelf-life is based on real-time data at the long-term conditions
- Not all potentially stability-indicating attributes may be easily modelled; prior or platform knowledge should be acceptable
- ICH Q1 revision adoption target date is end of 2026

Analytical comparability can utilize knowledge obtained from prior site transfers

- Risk assessment of site differences concluding low risk of impact to product

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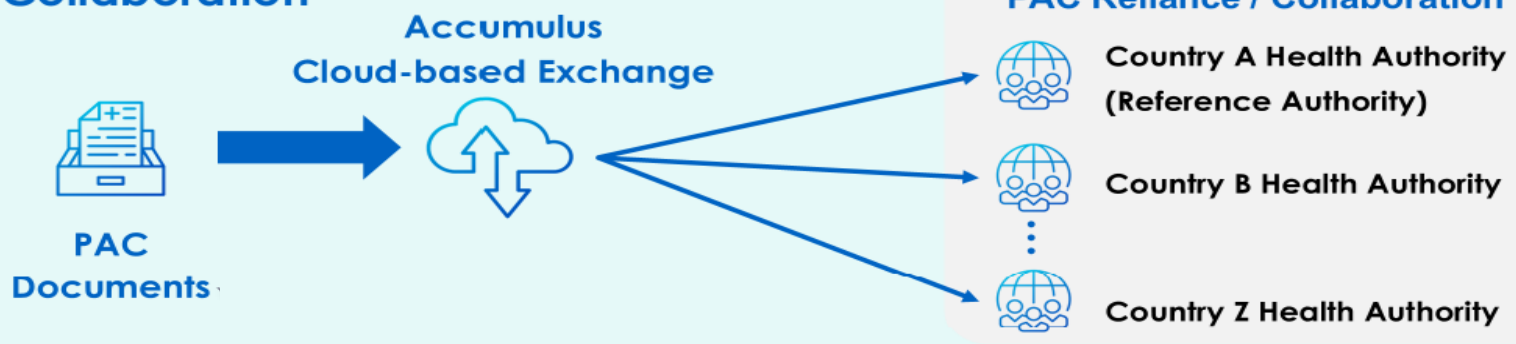
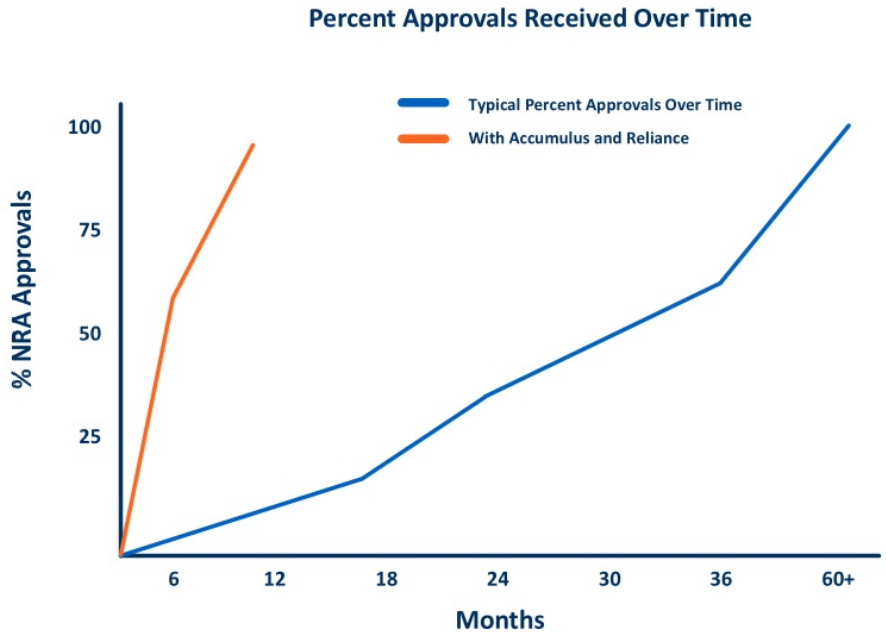
Streamlining Global PAC Approval Timelines Through Collaboration

Parallel 'Real-time' Reliance/Collaboration

A single dossier is submitted simultaneously through a cloud-based platform to multiple health authorities who conduct **concurrent reviews in parallel** with the Reference Authority. - ex., Amgen's Vectibix PAC Reliance Accumulus pilot





- Currently it takes 3-5 years for global approval of a CMC variation
- The use of parallel "real-time" reliance/collaboration can reduce this time to 6-9 months
- US manufacturers benefit from faster approvals of one global dossier for PACs due to internal manufacturing capacity expansion and supply chain management simplification

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Questions?


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THANK YOU
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OBRIGADO
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Additional References

1. ICH Q2(R2)/Q14 Training Materials, Module 5: at www.ich.org
2. Pink Sheet: Decades-Old US FDA SUPAC Guidance May Be Updated To Help Onshoring Goals
3. *Pioneering the Future: Delivering the First Digitally Generated CMC Post-approval Change (PAC) Dossier to Global Regulators Simultaneously*. *J Pharm Sci* 2026 Feb; 115 (4), 104193, https://jpharmsci.org/article/S0022-3549(26)00042-0/fulltext.

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