ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Training Material
Module 4 – Post-approval Change Management Protocol (PACMP)

Publication Date: 11 June 2021

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Post-Approval Change Management Protocol – Chapter 4 (1)

A PACMP is a regulatory tool to facilitate (benefit) post-approval changes

It provides:

- Transparency between industry and regulatory authorities about planned changes and
- Predictability regarding the acceptance and implementation of the change(s)

Post-Approval Change Management Protocol – Chapter 4 (2)

- **Transparency:**
  - Regulatory authorities are aware of future changes
  - The PACMP is assessed prior to the planned change(s) with regards to the information provided in the protocol needed to support a CMC change
  - Information to be provided:
    - Experimental studies to be performed
    - Conditions to be fulfilled
    - Implementation plan (including reporting level)

Post-Approval Change Management Protocol – Chapter 4 (3)

- **Predictability:**
  - After approval by the Regulators, a PACMP allows a timely implementation of the change(s) and, in some cases, may be used multiple times for a change

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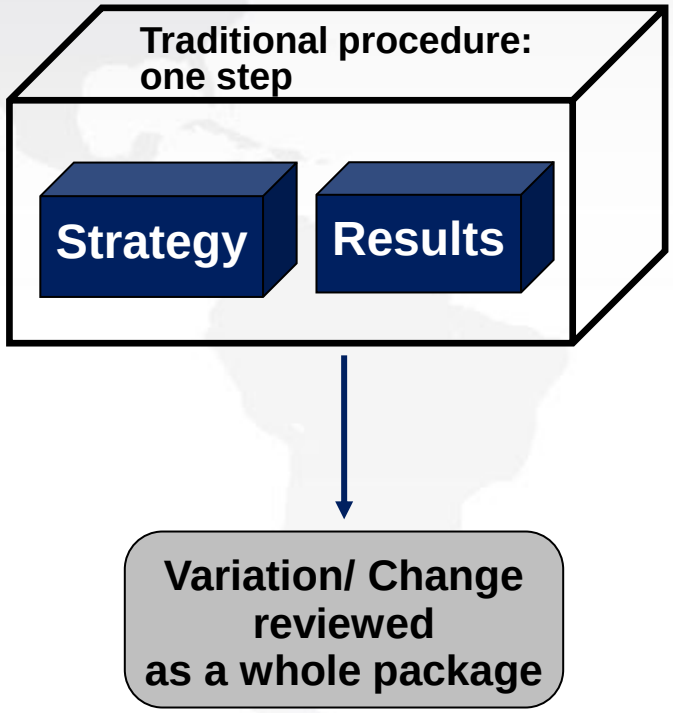
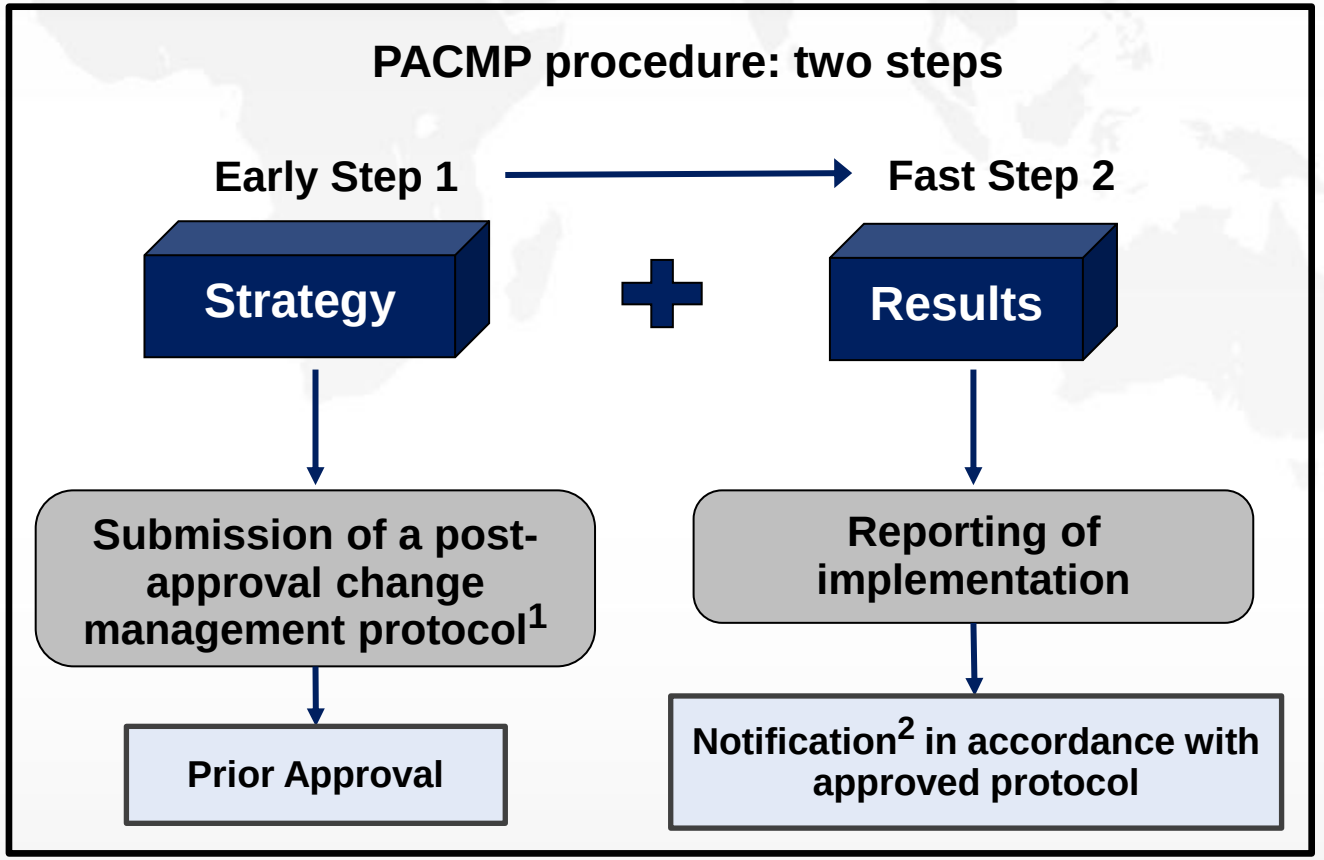
Traditional Change procedure compared to PACMP approach





1: PACMP may be submitted with the original MAA or subsequently as a standalone submission

2: Approval by the regulatory authority may be required prior to implementation

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Post-Approval Change Management Protocol – Chapter 4 (4)

Step 1

- Submission of a written protocol including:
  - Description of the proposed change(s) with rationale(s)
  - risk management activities
  - proposed studies and acceptance criteria to assess the impact of the change(s)
  - other conditions to be met
  - the proposed reporting category
  - any other supportive information
- Approved by regulator in advance of execution

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Post-Approval Change Management Protocol – Chapter 4 (4)

Step 2

- Carry out tests and studies outlined in the protocol
- If results/data generated meet the acceptance criteria in the protocol and any other conditions are met, submit this information to the regulatory authority according to the category in the approved protocol
- Depending on the reporting category, approval by the regulatory authority may or may not be required prior to implementation of the change

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Post-Approval Change Management Protocol – Chapter 4 (5)

- **MAH should demonstrate in the PACMP suitable scientific knowledge** and understanding of aspects impacted by the proposed change(s) in order to conduct an appropriate risk assessment
  - Where monitoring of the impact on product quality is required after implementation, a summary of the quality risk management activities should be provided
- A PACMP can be submitted independent of the level of development (minimal/enhanced)
- The level of product/process understanding should be proportionate to the complexity of the change (i.e., more complex changes require enhanced product/process understanding)

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Post-Approval Change Management Protocol – Chapter 4 (6)

- A PACMP may be submitted with the original Marketing Authorization Application or subsequently as a stand-alone submission (e.g., supplement/ variation)
    - Located in Module 3.2.R; may be located in Module 1 in some regions
- It may address one or more changes for a single product, or may address one or more changes to be applied to multiple products (see Q12 Annex I examples)

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Post-Approval Change Management Protocol – Chapter 4 (7)

- The change(s) outlined in a PACMP should not introduce any additional risks to patient safety, product quality or efficacy
- A **CMC change that would require supportive efficacy, safety (clinical or non-clinical), or human PK/PD data to evaluate the effect of the change** (e.g., certain formulation changes, clinical or non-clinical studies to evaluate new impurities, assessment of immunogenicity/ antigenicity) **is generally not suitable for inclusion in a PACMP**

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Post-Approval Change Management Protocol – Chapter 4 (8)

- **Modification of an Approved PACMP:**
  - A **modification to an already approved PACMP** such as replacement or revision of a test, study or acceptance criterion **should provide the same or greater capability to assess the effect of the proposed change on the product quality**
  - **Such changes would normally require a notification type** of communication with the regulatory authority
  - A **modification that more significantly alters the content of the protocol** may require **either prior approval of a protocol amendment or submission of a new protocol**, as agreed upon with the regulatory authority

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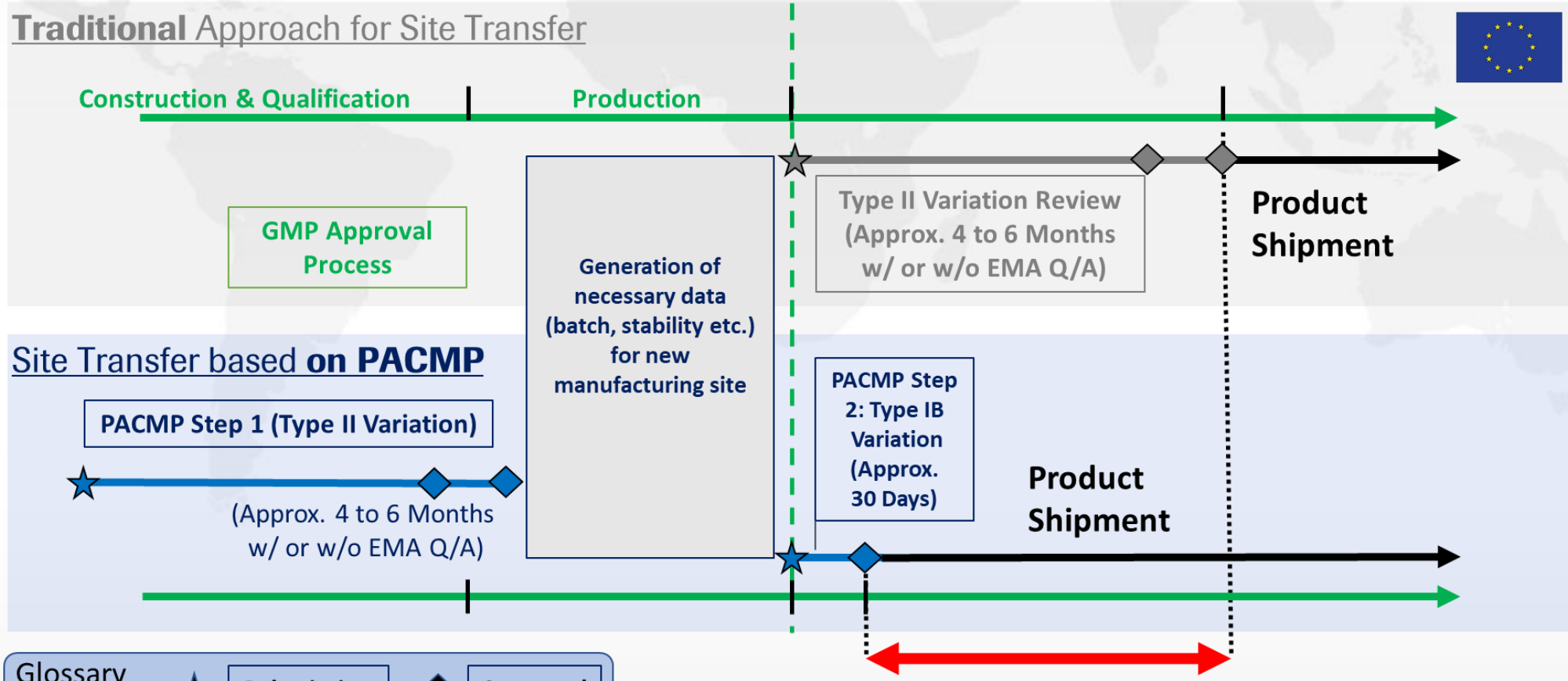
Example - Manufacturing site transfer: Timelines PACMP Approach vs. "Traditional" Approach* (based on EU/EMA case)



- Up to 5 months faster approval of the site change using a PACMP (time benefit similar in US)

*Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision

PACMP - Conclusion

- A PACMP is very much encouraged due to its transparency and predictability
- While submission of a PACMP is independent of the level of development, more knowledge allows better planning of the change and, as a consequence, more benefit from the use of a PACMP
- This benefit should be an incentive for innovation and continual improvement

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➔ Annexes

- **Annex I: Illustrative Examples**
  - Annex I A: Identification of ECs - Chemical Product
  - Annex I B: Identification of ECs – Biological Product
  - Annex I C: Identification of ECs – Analytical Procedure
  - **Annex I D: PACMP Example 1**
  - **Annex I E: PACMP Example 2**
  - Annex I F: Product Lifecycle Management Document – Illustrative Example

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Annex I D & E: PACMP- Illustrative Examples

- Examples provided are intended to illustrate the range of Post Approval Change Management Protocols (PACMPs) that are possible for a given type of change. They are not intended to serve as a binding template and other approaches may also be acceptable.
- **Example 1 outlines a protocol for a single change (a manufacturing site change for a chemical drug substance) to a single product**
- **Example 2 outlines a protocol for multiple changes (multiple manufacturing site changes for multiple biotech drug substances) that could be implemented for multiple products**
- These examples are not intended to suggest that the only type of change appropriate for inclusion in a PACMP is a manufacturing site change; many other quality-related changes (e.g., change in container closure, change in manufacturing process, or change in analytical procedure) may be suitable for a PACMP

Annex I D: PACMP Example 1 – Alternative manufacturing site for a small molecule drug substance

Outline for Step 1 Submission

- **1. Introduction and Scope**
  - PACMP is intended to allow for the addition of an alternative manufacturing site for the manufacture, testing, and release of the drug substance for a small molecule solid oral drug product
  - Based on the risk management activities described below (see next slide), the implementation of this change in Step 2 is proposed to be reported in a submission type that is a lower category than currently provided for in existing regulations or guidance, or a submission category eligible for shorter review timelines, depending on regional requirements

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Annex I D: PACMP Example 1 –
Alternative manufacturing site for a small molecule drug substance

Outline for Step 1 Submission

- **2. Quality Risk Management (QRM) Activities**

  QRM is conducted for the proposed alternative site and includes:

  - Identification and assessment of the potential risks associated with the proposed change, as well as the activities proposed to mitigate each risk
  - Accounting for known elements of the process, such as robustness, existing controls, and potential impact on product quality
  - Incorporating prior knowledge gained from development and commercial manufacturing experience

Annex I D: PACMP Example 1 – Alternative manufacturing site for a small molecule drug substance

Outline for Step 1 Submission

- **3. Acceptance criteria**

  Based on the risk assessment, the following acceptance criteria should be met:

  - In a comparative batch analysis, three consecutive batches of drug substance manufactured at the alternative manufacturing site should meet approved specification to demonstrate equivalence to batches manufactured at the currently approved site.

Annex I D: PACMP Example 1 – Alternative manufacturing site for a small molecule drug substance

- **Other conditions to be met prior to implementation:**
  - **Stability studies** will be initiated immediately on a suitable number of commercial scale batches of drug substance manufactured at the alternate manufacturing site and drug product manufactured with drug substance produced at the alternate manufacturing site. Stability data are to be reported to the regulatory authority subsequent to implementation of the new site according to regional requirements.
  - **Alternative manufacturing site to have acceptable compliance status** for small molecule drug substance manufacturing; depending on the region, this may be indicated by the last GMP inspection with acceptable outcome, through a valid GMP certificate, or other appropriate documentation (e.g., Qualified Person declaration)
  - **Alternative manufacturing site to use similar manufacturing equipment** or equipment with the same type of material of construction

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Annex I D: PACMP Example 1 – Alternative manufacturing site for a small molecule drug substance

- **Other conditions to be met prior to implementation (cont'd):**
  - **Technology transfer and process qualification to be completed**
  - **No change to synthetic route, control strategy, impurity profile, or physicochemical properties**
  - **No change to any specification or analytical method** for starting material or intermediates
  - **No change in analytical methods or specification for release and stability testing for drug substance manufactured at the alternative site**
  - Any additional regional requirements.

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Annex I D: PACMP Example 1 –
Alternative manufacturing site for a small molecule drug substance

Summary of Step 1 and Step 2 Submissions:

PACMP Component	PACMP Step 1 Contents (registration/approval of protocol)	PACMP Step 2 Contents (change implementation)
Overall Strategy (Scope and Limitations of proposed change)	Defined scope and limitations	Demonstrate requirements of scope are met
QRM	Description of QRM activities and summary of risk assessment	Confirmation that previously conducted risk assessment has not changed; or, if new information is available that impacts the risk assessment, an updated risk assessment is provided
Acceptance criteria	Tests and studies to be performed; description of any other criteria to be met, including plans to report outcomes from ongoing stability testing	Data demonstrating that acceptance criteria are met. Confirmation that other criteria are met. Updated CTD sections for S.2.1 Manufacturer(s) of Drug Substance and S.4.4

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

- **1. Introduction and Scope**
  - **Primary objective of this expanded (broader) PACMP is to support the mobility across biologic drug substance manufacturing sites**, i.e., the transfer of one or multiple products from one donor site to one or more recipient site(s) including CMOs (sites already licensed with appropriate inspection record) thereby **reducing the number of regulatory submissions of similar content and driving consistency**
  - **The expanded (broader) PACMP effectively leverages concepts of Quality Risk Management and ICH Q9**. Typical process adaptations linked to scale and equipment differences at the donor and recipient site(s) are in scope of the protocol (e.g., change in raw material sourcing) whereas the scope excludes opportunistic significant process changes (e.g., changes to increase productivity/yield)

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

- **2. Quality Risk Management (QRM)**

  QRM is performed for each individual site transfer, and includes:

  - Identification, scoring, and documentation of the potential hazard and harm associated with each manufacturing unit operation and process change, as well as the prevention and detection controls
  - Accounting for known elements of the process, such as robustness, existing controls, and potential impact on product quality

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

3. Comparability/Acceptance Criteria

The overall comparability plan in line with ICH Q5E comprises the following elements:

- The drug substance meets all release and in-process specifications, as well as comparability acceptance criteria, derived from the entire manufacturing history
- Analytical profiles from selected characterisation tests of post-change material are consistent with pre-change material in side-by-side comparison
- Process performance attributes, e.g., cell culture performance, purification process yields, and impurities levels are comparable between donor and recipient site
- Planned process validation at the recipient site
- Drug Substance degradation studies consistent with pre-change material

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

4. Site specific Considerations

a) Site Risk

- A risk assessment for the receiving site will be conducted by the MAH; the risk assessment includes:
  - the GMP compliance status, and should also include
  - facility experience, process knowledge, and any additional regional assessments such as QP declaration
- Outcome of the risk assessment will indicate to the MAH whether a site inspection by the competent regulatory authority may be needed and whether additional data to support the change should be generated (e.g., site-specific stability data)

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

4. Site specific Considerations

b) Process Validation

- An overview of the process validation project plan and validation master plan for the site transfer in accordance to the current PQS system should be provided at step 1
- A summary of validation studies performed to support the site transfers, e.g., studies adopted from the donor site and new studies at the recipient site are part of the step 2 implementation submission
- The number of proposed validation batches should be based on the variability of the process, the complexity of the process/product, process knowledge gained during development, supportive data at commercial scale during the technology transfer and overall experience of the MAH

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Proposed Outline for Step 1 Submission

4. Site specific Considerations

c) Stability

- Stability studies are traditionally rate-limiting to site transfer timelines
- Following successful demonstration of comparability by analytical characterisation methods, including accelerated and/ or stress stability studies (see Chapter 9) can leverage tiered regulatory submission reporting categories and commitments

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Annex I E: PACMP Example 2 –
Manufacturing Site Transfers of Biotech Drug Substances

Summary Expanded PACMP Step 1 and outline for Step 2 submission:

Component	Step 1 contents (registration of protocol)	Step 2 contents (change implementation)
Overall Strategy (Scope and Limitations)	Defined scope and limitations	Demonstrate requirements of scope met, including process changes associated with transfer
QRM	Description of QRM program and approach to site transfer risk assessment	Documented risk control strategy and executed risk management report summary
Comparability & Stability	Comparability plan, real-time stability commitments and acceptance criteria (product-specific)	Data demonstrating that acceptance criteria are met
Process Validation	Overview of validation program	Summary of facility/equipment differences and applicable validation; validation summary data support the process, facility/equipment, and method transfer
Site risk	Description of site inspection risk assessment	Outcome of site inspection risk assessment defines actual change submission requirements. Acceptable compliance status confirmed at the time of change implementation.