Pharmaceutical Product Lifecycle Management : A Regulatory Consideration

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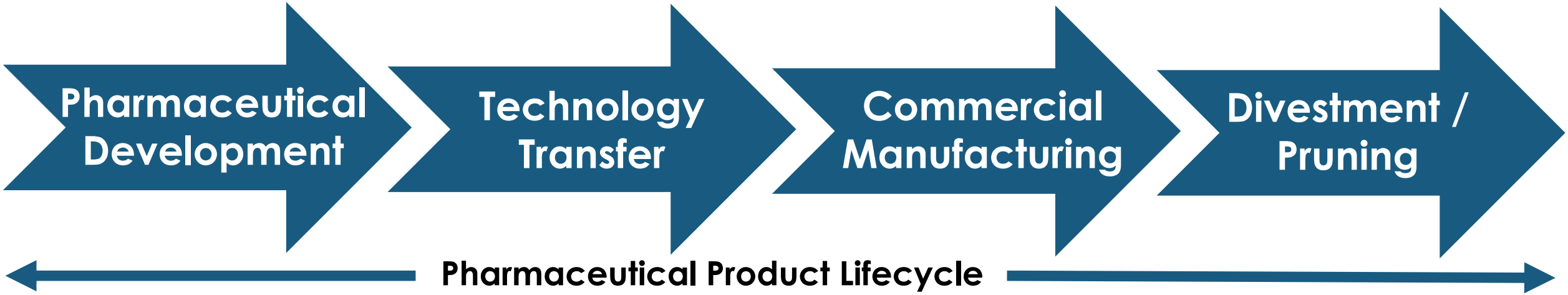
Introduction

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH-Q8).



Product Lifecycle Management:

Process of managing the entire lifecycle of a Pharmaceutical product from its inception, through development and manufacture, to service and divestment/Pruning.

Drive for Lifecycle management

Optimization of industry and regulatory resources utilization.

Support innovation and continual improvement to assure drug product supply.

Facilitate reduction in amendments/variations submissions through increased product and process knowledge.

Enhance transparency between industry and regulators.

Facilitate management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner.

Current situation vs Reality

Internal and External Complexity
Lack of harmonized Data Source
Advancement in Research and Development

The envisioned post-approval 'operational flexibility' has not been achieved.

Lack of harmonized approaches for technical and regulatory aspects.

Technology Transfer
Intellectual Property Portfolio
Integrated Quality and Risk Management
Global Product Registration

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Dimensions

Manufacturing and control

Supply and Logistics

Environment

Cost and Profit

Financial reforms
and
Economic Crisis

Therapeutic value

Regulatory

Categorization of Changes

A well-characterized, risk-based categorization of regulatory communication requirements is important to the efficient use of industry and regulatory resources.

Categories for regulatory communications:

-Prior-approval: sufficient risk changes
requesting approval from the regulatory authority

-Notification: Certain moderate- to low-risk change
notifying the regulatory authority

-Lowest risk changes
simply recording CMC changes with associated information requirements and where applicable, timeframes for decision.

Knowledge and Change management

Knowledge management:

Systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Change management:

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

✓ Change management

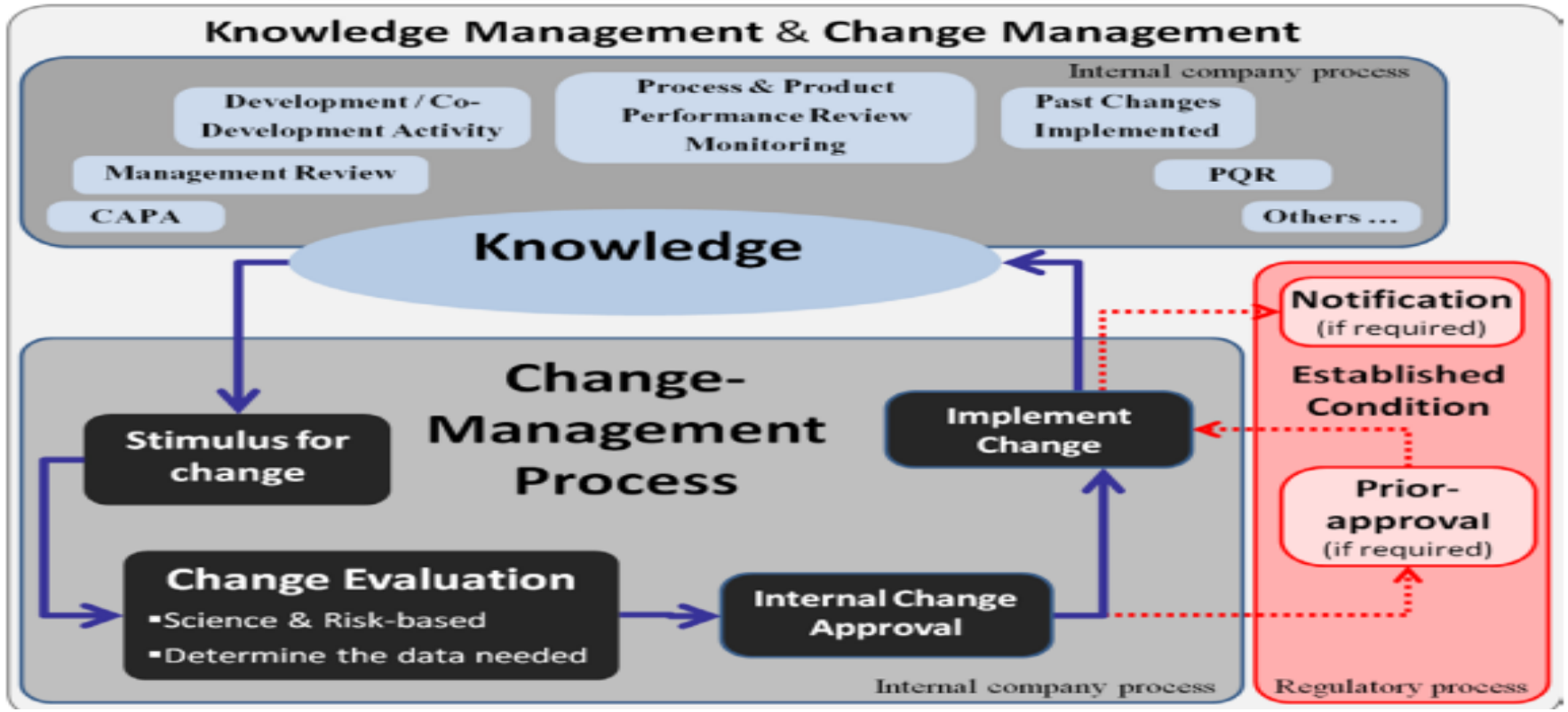
- Step 1: Proposal
- Step 2: Evaluation and Data generation to support proposed change
- Step 3: Review and approval from HA
- Step 4: Implementation

Problem statement

- Change management is not visible to regulatory assessors
- Health Authorities want visibility to change as it has significant impact on quality, safety and efficacy e.g. Valsartan genotoxic impurity
- Data rich submissions have seemingly translated to more post approval submissions with higher reporting categories
- Industry wants flexibility to manage post approval improvements to minimize supply chain complexities

Knowledge versus Change management

INSPECTION



REVIEW

PQR: Periodic Quality Review
Regular periodic review of API or drug products with the objective to verify process consistency, to highlight any trends and to identify product and process improvements
CAPA: Corrective Action and Preventive Action, APR: Annual Product Review
LCMP: Lifecycle Management Protocol, PACMP: Post-Approval Change Management Protocol
Reference: -ICH Q12 draft guideline

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Future Management

Harmonized regulatory tools and enablers to manage post approval changes

- ✓ Pharmaceutical Quality System(PQS)
- ✓ Corrective action and preventive action (CAPA) system
- ✓ Established Conditions (ECs)
- ✓ Post-Approval Change Management Protocol (PACMP)

PQS: Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

CAPA: System that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their occurrence. (ICH Q12)

Established Conditions (ECs)

ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

- ECs in a submission are either implicit(derived from regulation) or explicit(proposed by MAH).

- Identification of ECs
  - parameter based approach e.g. process parameters, in-process control
  - enhanced approach (Focused on important input parameter along outputs)
  - performance based approach (Focused on unit operation output)

Established Conditions (ECs)

Many "details" are provided in regulatory dossier to enhance understanding of the manufacturing process and/or control strategy. Maintenance of those "details" is a burden.

Examples of a variations for a drug substance (small molecule):

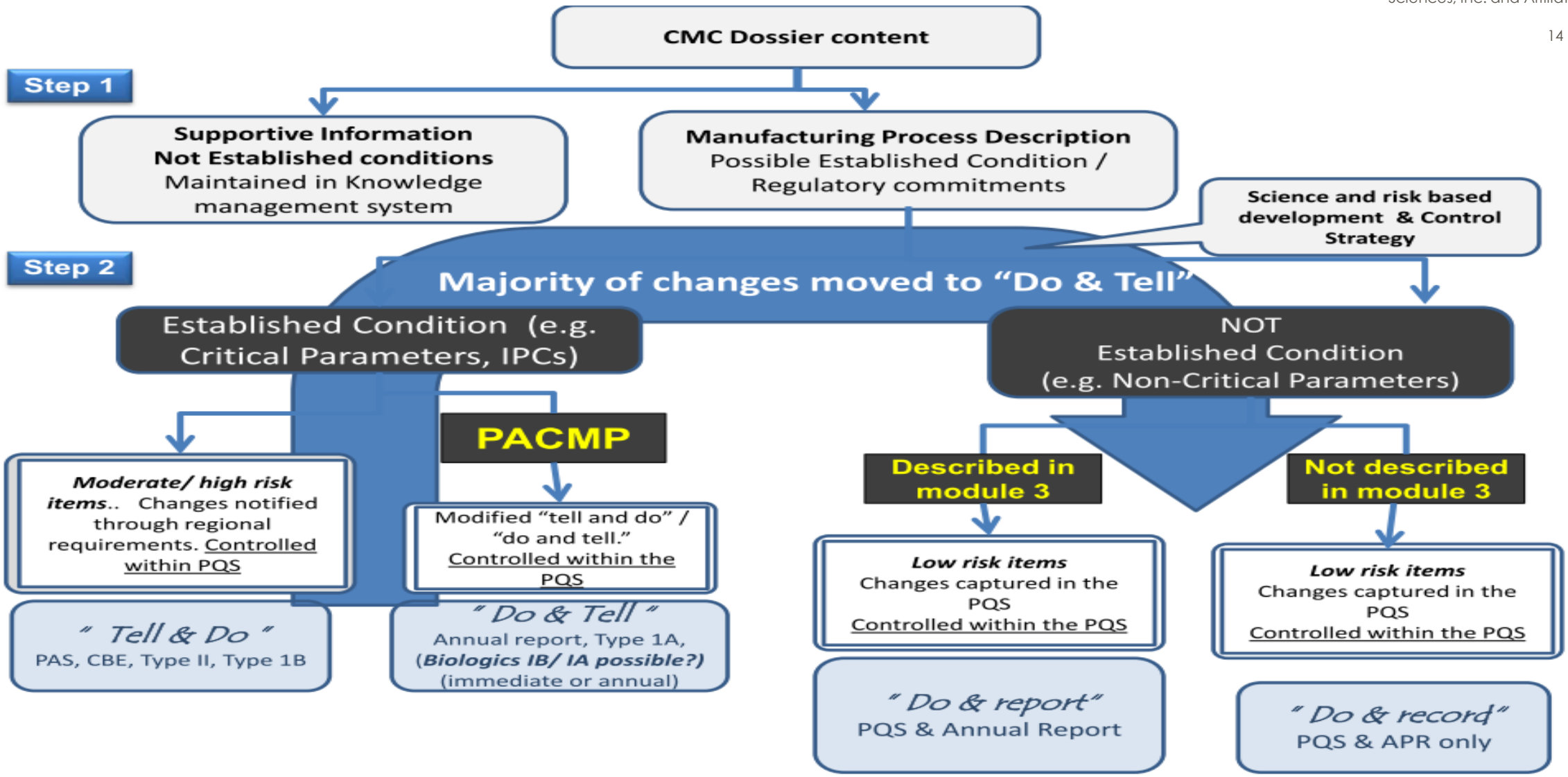
– Change in starting material quantity: from 200-235 kg' to '195-235kg'

– Use of lower concentration of NaOH leading to higher volume loaded into the reaction (stoichiometry respected)

– Lower amount of class 2 solvent used (from '2200-5650 kg' to '2000-5650 kg')

– Stirring time changed from 'approximately 2 hours' to 'at least 1 hour' based on process experience (completion of reaction)

Established Conditions (ECs)



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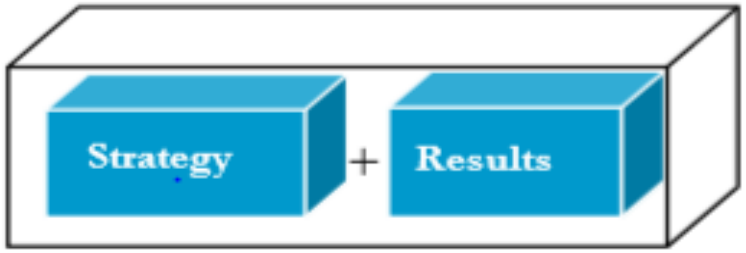
Reference:
https://www.ema.europa.eu/documents/presentation/presentation-case-studies-established-conditions_en.pdf

Post-Approval Change Management Protocol (PACMP)

A post-approval change management protocol describes **specific changes** that a MAH would like to implement during the lifecycle of the product and **how these would be prepared and verified**. It is a **step-wise approach in the assessment** of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy



Currently
Evaluation of a proposed variation as a 'whole' (Strategy + Results)

Early Step 1:

Submission of a Change Management Protocol

Type II Variation

Fast Step 2:

Reporting of implementation of a change in accordance with an approved protocol

Type IA$_{IN}$ or IB

Post-Approval Change Management Protocol (PACMP)

- Regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change.
- The PACMP describe changes intended to be implemented along with specific conditions and acceptance criteria to be met.
- PACMP can be submitted with the original MAA or subsequently as a stand-alone submission.
- PACMP requires approval by regulatory authority and the conditions and acceptance criteria outlined in the protocol must be met in order to implement changes.
- PACMP address one or more changes to be applied for single products or multiple products.
- PACMP could facilitate lower reporting category and/or shortened review period.

ICH Harmonization efforts

Q8
Pharmaceutical Development

Q9
Quality Risk Management

Q10
Pharmaceutical Quality System

Q11
Development and Manufacture of Drug Substances

Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

comments received on ICH guideline Q12

For further reference:
-ICH guidelines
-https://www.ema.europa.eu/documents/comments/overview-comments-received-ich-guideline-q12-technical-regulatory-considerations-pharmaceutical_en.pdf

Take Home Message

- Life cycle management must be prioritized for rapidly changing environment
- Better insights towards Global harmonization
- Integration is the key to successful life cycle management strategy
- Regularize use of tools and enablers leads to Agile Product Lifecycle Management

Evolving space: Harmonization of regulatory framework between ICH regions and beyond..

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