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Life Cycle Management in Pharmaceutical Industry

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ABSTRACT:

Implementing a PLM system is a must for all trading companies today. To ensure the effective installation of PLM system solutions, commercial organizations follow the various implementation recommendations available. In some situations, the available implementation guidelines may cause implementation / reimplementation to fail. Every time you try to fail / reimplement, both sides waste time, money, and effort. A review of existing available implementation guidelines is needed, detailing the situation in India, especially the actual PLM implementation projects in the process manufacturing industry. This white paper focuses on the process manufacturing industry and presents the challenges for implementing effective PLM in the Indian process manufacturing industry. This reduces the failure rate associated with PLM deployment. In addition, existing Lifecycle Impact Assessment (LCIA) methods cannot model multiple drug-specific impact pathways (such as endocrine disruption). Preliminary considerations for developing drug PCR and including drug-specific pathways in LCIA are presented, providing important impetus for further research.

Key words: Product life cycle management, Challenges, Regulatory, Market authorization.

Introduction:

Pharmacies are one of the highly regulated industries in which companies must comply with Regulations and comply with local governments such as the FDA (Food & Drug Association), EMA (European Medical Agency), and PMDA (Pharmaceuticals and Medical Devices Agency). It is one. Japan), CDSCO (Central Drugs Standard Control Organization, India), SFDA (Saudi Food and Drug Administration), etc., all stages of the product life cycle, including Regulations on research, preclinical, registration, and clinical. Processing,Manufacturing equipment, equipment verification, quality maintenance, packaging, labeling, etc.Adhering to a life cycle within defined regulations is an integral part of the pharmaceutical Industry, on which FDA approvals are granted to companies. The purpose of the Ordinance is to promote and support guarantees of drug use. These regulations Consistently define the drug life cycle at all stages. The Product Lifecycle Management (PLM) strategy is used to tackle complex Product-related tasks involving people, processes, and technology [1]. The Product Lifecycle Management (PLM) strategy begins with the product concept and becomes widespread.Commercialization and product retesting. Product Lifecycle Management operates products at Different production stages, as shown below. Life cycle assessment is still a long way to go before it becomes commonplace in the pharmaceutical industry [7,8]. In addition, existing pharmaceutical LCA is very heterogeneous in some respects.Selection of functional units or impact categories. This reduces the robustness and reproducibility of the Results and makes industry-wide insights into the potential strategies of “hotspots” or “more environmentally friendly” drug designs in a typical Environment useless. ..Of course, the various goals of pharmaceutical LCA are partly involved in the diversity of research methodological choices. However, given the high degree of Flexibility provided by the ISO 14040/14044 standard, it is assumed that even two Studies of the same drug performed by two different LCA practitioners show significant differences. It’s rational. To be precise, this realization has recently required so-called “product category rules” (PCR) for specific product categories, resulting in a parallel increase of [9]. Last year, a three-year project entitled “Development of a Sector-Specific Environmental Risk Assessment Approach for Pharmaceuticals and Processes”(German abbreviation: SERUM) was launched at Technical with the aim of developing PCR for the pharmaceutical sector. I did. University of Berlin.

- Pharmaceutical development
- Formulation (including container and closure system design)
- Experimental product product development and manufacturing
- Delivery system development (if applicable)
- Manufacturing process development and scale-up
- Development of analytical methods
- Transfer of technical knowledge Transfer of new products takes place during the development process of And continues into production.
- Transfer within a manufacturing facility or between a manufacturing facility and a testing facility for Commercial products
- Manufactured in the commercial sector
- Materials are procured and managed in a variety of ways.
- Providing facilities, utilities, and equipment is a prerequisite

PRODUCT LIFECYCLE MANAGEMENT (PLCM) DOCUMENT:

The PLCM document outlines a specific plan for product lifecycle management. This includes EC, reporting categories for EC changes, PACMP (if used), and all CMC post-approval obligations. Its purpose is to encourage future lifecycle management plans by marketing authorization holders and facilitate regulatory evaluation and inspection. PLCM documentation should be updated as needed throughout the product life cycle. The PLCM document acts as the EC's MAA central repository and reports Categories for making changes to the EC. This includes the important elements described below and References to relevant information elsewhere in the MAA (see Appendix IF). The PLCM document template Is important when MAH proposes an EC in line with the risk-based Approach in Chapter 3. The elements of the PLCM document are summarized below.

- EC (see Chapter 3): The EC of the product must be listed in the PLCM Documentation. EC identification and justification can be found in the appropriate section of the CTD.
- Notification category for changes to approved EC (see Chapter 3). The Notification category for changes to EC should be listed in the PLCM document. Detailed reasons for the Report category can be found in the relevant section of the CTD
- PACMP (see Chapter 4): A PACMP submitted to positively manage and implement Must list one or more post-approval changes.
- CMC Post-Approval Obligations: Certain CMC development activities were agreed between marketing approval holders and regulators at the time of Approval (eg, monitoring of specific Processes, additional testing). What was done should be listed in the PLCM documentation The PLCM documentation outlines a concrete plan for product lifecycle management. This includes EC, reporting categories for EC changes,

PACMP (if used), and all CMC post-approval obligations. Its purpose is to encourage future lifecycle management plans by marketing authorization holders and facilitate regulatory evaluation and inspection. PLCM documentation should be updated as needed throughout the product life cycle.

APPROACHES FOR CMC POST-APPROVAL CHANGES:

In addition to the other tools described in this guidance, to make Specific CMC changes for products that do not include market approval, simplifications include identifying ECs with relevant reporting categories. Requires an approach. In this chapter Structured approach for frequent CMC changes and includes A discussion of the data Requirements for CMC changes (e.g., stability). The strategy described for structured approaches to frequent CMC changes is Exemplified with a Description of an approach for analytical procedure changes in Annex II. Similar structured Approaches could be developed and applied for other Frequent CMC changes such as scale, Packaging, etc. These approaches may be applied When the following conditions exist:

- The Company's PQS change management process is effective and in compliance As described in Chapter 6 and incorporates an appropriate risk management System.
- A structured approach can be found in Annex II and describes the scope and the Steps to Be followed, including, where appropriate, data to be generated and Criteria to be met. Compliance with the requirements of relevant Internationally-agreed Standards and/or regulatory Guidelines may be specified As part of the structured approach. If the approach is followed and all criteria are met, the change can be made with Immediate or Other post-implementation notification, as appropriate, to the relevant Regulatory authorities. The flexibility provided in Annex II may not be available in all Regions and in all situations; Some specific changes may require prior approval as Defined in regional guidance.

STABILITY DATA TO SUPPORT THE CMC CHANGES

The data required to submit to regulators to support post-approval amendment Is determined by local regulations and guidance. This guidance provides an additional scientific and risk-based approach that can be used to develop Confirmation Stability Research Strategy That supports post-approval changes, and more timely submission, approval, and implementation of changes. Make it possible. Such an approach can be included in PACMP (see Appendix ID and IE). In contrast to the formal stability test recommended by the ICH Q1A (R2), this aims to establish useful shelf life and storage conditions for new drugs not yet on the market.Substance / Drug, Stability Testing Objectives If Required Supporting CMC changes after approval of Is to confirm previously approved shelf life and storage conditions. The scope and design of such stability Studies is based on the knowledge and experience of Drugs and APIs acquired since approval. An approach to the design of such a Study should be properly justified and may include: A good tool for assessing the impact of proposed changes. This includes:

1. Study of drug and / or drug acceleration and / or exposure on representative material (may be pilot or laboratory scale rather than 1: 1 scale)
2. Pre-change and on representative material Comparability study after modification
3. Statistical evaluation of relevant data, including existing stability studies
4. Predictive degradation and other empirical or first-principles kinetic models
5. Use of relevant corporate knowledge and prior knowledge, including scientific Literature

- Use of the modified Confirmation Stability Study, not the submission of data, as part of the Regulatory change submission. Obligation to start or complete continuous In the long term, if applicable. Stability testing in the modified batch ensures that the approved shelf life and Storage conditions continue to apply after the CMC changes are implemented.

APPENDIX 2: PRINCIPLES OF CHANGE MANAGEMENT

Consistent with the basic requirements of ICH Q10, the effective change control system Supports the principles of this policy and is described below.

- Ensures a complete understanding of the scope of changes and the impact on Aspects of the process and control strategy, including the impact on EC and non-EC aspects of marketing authorization affaffecte
- Use your existing knowledge of process performance and product quality.
- Scientifically sound risk management and risk classification of proposed changes are required. The Considers the potential impact if the intended changes are not implemented.
- Determine the data (existing and / or generated) neededimplemented Changes, and accordingly the method, expected Acceptance criteria, and additional Performance after implementation of the description. Develop research protocols that include and / or product quality monitoring as needed;
- Ensuring submission to the appropriate regulator, if necessneede
- Use the defined change management process to approve or reject the intended changes. TheInvolves appropriate stakeholders, including but not limited to manufacturing, quality, and regulatory stakeholders.
- Verify that the implementation of the change is based on: Make sure that theChanges implemented are consistent with the relevant investigation protocol, PLCM documentation, or PACMP.
- Evaluate the generated data to indicate that the purpose of the change and acceptance criteria are met.
- Allow risk mitigation measures to be developed in the event of deviations from the acceptance criteria of Or the identification of unexpected risks.

Pharmaceutical Lifecycle Management Challenges

- Increased internal and external complexity
- No single data source for products and related information
- R & D improvements
- Technology transfer
- Integrated quality and risk management
- Comprehensive Packaging
- Global Product Registration
- Intellectual Property Portfolio
- Manage complex joint outsourcing networks.
- Corrective and preventive measures system (CAPA)
- Burden of system verification

Review of LCAs in the Pharmaceutical Industry

A comprehensive review on the state of LCA-application in the pharmaceutical Industry, Specifically human pharmaceuticals, was initially performed in order toIdentify common LCApractices within the sector (e.g. choice of functional unit),Regularly identified ‘Hotspots’ in The life cycle of drugs, as well as often encoun-Tered challenges and remaining gaps. Results of The review were meant to lay theGround for harmonized sector-specific rules—in the form of PCRs—and revealThematic focal points for achieving greater LCA-application within the Pharma-sector. Given the unique characteristics of the pharmaceutical industry (e.g.Exceptionally high standards of cleanliness maintained during production) and the Relatively young age of ‘green pharmacy’-practices, the focus of the literature Review was on LCA case studies of human pharmaceutical products (i.e. APIs or Final drug, incl. packaging) or Pharmaceutical processes, performed in or after the Year 2000. LCAs of precursor chemicals (e.g. enzymes) were only included if Downstream application in the pharmaceutical industry is Clearly intended. The Search thus excluded LCAs in the broader field of green chemistry and in The Healthcare sector in general (e.g. medical equipment). Using search terms such as “Google Scholar’s “Cycle Assessment”, “LCA”, “footprint” and “pharma-cuticle ” or “fine Chemical *” combinations have so far been a very limited number of “pure” pharmaLCA (< 30 studies) have been produced. A peer-reviewed journal has been published. These LCAs were performed for a variety of purposes, including different synthetic routes, treatment modes (such as batch and continuous treatment), formulations, different doses, and comparative evaluation of package options. All LCA studies investigated so far, with a few exceptions, have performed cradleto-gate analysis, often criticizing the lack of sufficient data beyond the production stage.

shows a generic product system for pharmaceuticals and various ways to define system boundaries. The life cycle perspective is very important in the pharmaceutical context. First, because outsourcing of specific synthetic or pharmaceutical steps (and therefore "outsourcing" of effect) is widespread in the industry. Second, the environmental impact of upstream processes(eg, input chemical production and "background" energy production) usually reduces the impact of the actual internal synthesis process [10,11]. -Drug longevity can have significant Environmental impacts, especially if the‘s environmental and human toxic effects from drug injection into the sewage system (and ultimately surface water) are included in the Analysis. (See below for more information). Section). Therefore, pharmaceutical companies should aim for a complete cradle to graveyard analysis of A closer look at the existing pharmaLCA quickly revealed that the individual studies were highly nonuniform in many respects.Selection of functional units (FU), definition of system boundaries, use of Background database and data quality, selection of impact assessment methods, and Impact categories to be considered. Brunet et al. [12] FU was set at 20,840,000 kg of Penicillin V produced over a 20 year period, De Soeteetal. [13] selected a once-daily dose of From PREZISTA (anti-HIV drug) as the FU. However, most of the studies reviewed chose the 1kg API as the FU. Wernet et al. [10] decided to use five different impact assessment methods to assess 16 impact categories(both average and endpoint levels), Kimetal. [14] We considered five impact categories in just one way. Given the different objectives and scope of the studies reviewed and the unique uniqueness of the individual active substances / formulations, some methodological differences between pharmaceutical companies' LCA are logical and unwise. Nevertheless, lack of sufficient experience and guidance has led to major discrepancies.Concerns about the use of LCA in the pharmaceutical sector. This often jeopardizes the consistency and reliability of the Pharmaceutical LCA. Therefore, there is a clear need for PCR in the pharmaceutical industry To guide and promote future pharmaceutical LCA. Preliminary considerations for Drug PCR can be found in the section.Concerns about the use of LCA in the pharmaceutical industry. This often jeopardizes the consistency and reliability of the Pharmaceutical LCA. Therefore, there is a clear need for PCR in the pharmaceutical industry To guide and promote future pharmaceutical LCA. Preliminary considerations for Drug PCR can be found in the section.

Life Cycle Impact Assessment (LCIA) in Pharma-LCAs :

The LCIA phase of the reviewed pharma-LCAs was carried out using quite Divergent impact Categories and impact assessment methods. A streamlined LCA Tool developed by the American Chemical Society Green Chemistry Institute (ACS-GCI) Pharmaceutical Roundtable (hereinafter‘the Roundtable’) sets forth Nine impact categories/indicators to be assessed in LCAs of drug Synthesis routes [11]. lists these nine impact categories, next to the top five assessed Impact Categories in the reviewed pharma-LCAs, as well as a preliminary selection of eight Categories recognized by the authors as the most relevant for pharma-LCAs. The Latter list was Determined in consultation with the SERUM advisory committee,Which comprises experts from Academia, politics and the pharmaceutical industry.Quite notably, impacts—especially Toxicity related impacts—which have been Identified as relevant for the pharmaceutical industry Within the SERUM project are Not often considered in LCA studies nor recommended in the Roundtable's Streamlined tool. Given the desired functionality of

pharmaceuticals—e.g. to kill Rapidly dividing cells (anticancer), affect the action of neurotransmitter chemicals in The brain(antipsychotic), kill or inhibit microorganisms (antimicrobial)—and the Growing body of Literature providing pertinent evidence of potential unanticipated Eco-toxicological effects of APIs (reviewed in [3, 15–17]), it is concerning that none Of the existing pharma-LCAs Considered impacts related to the presence of phar-Maceutical residues in the environment.The Discrepancy between practice, recommendation and (perceived) relevance of The categories‘human toxicity’ and ‘eco-toxicity’ for pharma-LCAs is largely the Result of a number of Methodological constraints on toxicity modelling within LCIA, the most prominent of which are:

1)Lack of characterization factors (CFs) for pharmaceutical compounds in.Existing toxicity Models

2)Several impacts or impact pathways associated with pharmaceuticals and their Toxic mode of Action are neglected in current impact assessment methods.

In an attempt to address the first constraint and enhance the assessment of Pharmaceuticals' Toxicity in LCIA, several studies have recently updated or cal-Culated new CFs for APIs in the Categories human toxicity, freshwater, marine or Terrestrial eco-toxicity using mostly USEtox,But also EDIP97 and/or USESLCA 2.0 [18–20]

Product Category Rules (PCRs) for the Pharmaceutical Industry

PCR is usually defined for a group of products with equivalent or similar functionality, and Makes them widely comparable. Despite a compelling discussion of a harmonized framework in the form of PCR to guide LCA of pharmaceuticals, only PCR for vaccines has been developed so far [25].

Based on this PCR, Pfizer has implemented and published IMPROVAC's Environmental Product Declaration (EPD). This is an immunological product used as an alternative to physical Castration in pig farming [26]. However, IMPROVAC EPD is no longer valid after 2015.For the development of new PCR, there are no rules on how to define product category As "narrow" or "wide". In other words, the "particle size" of PCR is entirely up to the designer. Based on Feedback received in consultation with pharmaceutical experts, the development of PCR at two different Levels / particle size proves to be practical for the pharmaceutical industry (see figure). 2). First, a Generic PCR for the Pharmaceutical sector (‘horizontal rules’) should be developed, determining Broad LCA-modelling provisions which capture some of the industry-wide characteristics (e.g. The importance of including treatment processes of solvent waste within the System boundaries). Such a generic "frame-PCR" is subject to a considerable Degree of uncertainty/inaccuracy, as it Intends to provide common modelling rules For quite distinct products of a given sector, while Having to rely on numerous Assumptions and a significantly simplified representation of the Industry as a whole.Therefore, in a second step and in close alignment with the frame-PCR, specific (‘vertical rules’) should be cumulatively developed for:

- Pharmaceutical products categorized into different drug classes according to the International Anatomical Therapeutic Chemical (ATC) Classification System (productPCRs) and
- Drug manufacturing processes (process-PCRs).The product-PCRs are to be developed for the different drug classes available at The third level Of the ATC-code, i.e. the different therapeutic/pharmacological Subgroups of APIs, and would Serve the objective of assessing drug alternatives According to the same harmonized scheme on The basis of their common function (therapeutic purpose) and pharmacological properties. Process-PCRs Would guide LCAs which are primarily focused on process optimization.

Conclusion:

Due to the complexity of the more efficient drug research and manufacturing processes are needed.Today's pharmaceutical industry. Even in this extremely Complicated environment, PLM has The potential to Improve the efficiency and reduce the risk of Pharmaceutical manufacture. Product lifecycle Management is the process of creating and managing a Company's productrelated intellectual Capital from the Conception of an idea to its eventual decommissioning.

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