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REGULATORY ASPECTS OF PRODUCT DEVELOPMENT STAGES

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ABSTRACT

The pharmaceutical market requires more efficient drug development and production. Product Lifecycle Management (PLM) has the opportunity to make pharmaceutical production more effective and lower risk. The product lifecycle management creates and manages a company's product-related intellectual capital starting from an idea to its final development. The Pharma industry, it benefits through enhancing the life of patient and pricing strategies. Improved patient compliance, growth, expanded clinical benefits; cost advantages, Leaders are actively implementing PLM and are reaping the benefits of fewer problems, lower costs, higher yields, and audits that make everyone more confident. The present manuscript focuses on problems and the key solutions for a successful product lifecycle management in pharmaceuticals.

INTRODUCTION

Product lifecycle management (PLM) is the processes that entire lifecycle of a product from its conception, through design and manufacture, to service and disposal. PLM forms the product information backbone for a company and its extended enterprise [1]. The multiple elements includes: foundation technologies and standards, information authoring and analysis tools, core functions, functional applications and business solutions, that incorporate best practices and methods. For the completion of the product development two elements are required: 1) proper processes 2) a complete set of design specifications, standards, and tools. [1]. . Objectives Objective of Product Development Phase involves: • Building the system • Testing and integrating the units into larger components • Preparing the technical environment for the system • Approval to progress to the Test Phase [2] Goals The Development Phase is to convert the system design prototyped in the Design Phase into a working information system that addresses all documented system requirements. At the end of this phase, the working system will enter the Test Phase. [2]. Product development Stages Product development Stages involves: - Project approval, Preformulation Studies, formula development, process optimization, documentation, exhibit batch manufacturing. 1.

PROJECT APPROVAL:

S1A- Project Initiation The project initiation phase is the critical phase within the project life-cycle, so also called the project preplanning phase and about starting the basic characteristics of the project. The researcher need to which basics steps are required to carry out to develop a business case, undertake a feasibility study, develop a project. Details of project goals and objectives are critical success factors by which achievement of the objectives will be judged [3].

S1B-Literature search: A literature review is an essential chapter of a thesis. The purpose of the researcher is to analyze critically a segment of a published body of knowledge through, classification, summary and comparison of prior research studies, reviews of literature, and theoretical articles.

Literature reviews should comprise the following elements:

An overview of the subject, issue or theory under consideration, along with the objectives of the literature review.

Division of works under review into categories (e.g. those in support of a particular position, those against, and those offering alternative theses entirely)

Explanation of how each work is similar to and how it varies from the others [3].

S1C-Procuretment of materials The act of obtaining or buying the process includes preparation and processing of a demand as well as the end receipt and approval of payment. it includes :- purchase planning, standard determination, specification, development, supplier research ,and selection. The company's strategy is the ability to purchase certain material will determine if operation will continue.

2. PREFORMULATION STUDIES: Preformulation studies involves (a) selection of the drug candidate itself, (b) selection of formulation components, (c) API & drug product manufacturing processes, (d) determination of the most appropriate container closure system, (e) development of analytical methods, (f) assignment of API retest periods (g) the synthetic route of the API, (h) toxicological strategy. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve enhance product quality, public safety standards [4].

S2A- Active Pharmaceutical Ingredients Evaluation

Physical Characteristics of Active Pharmaceutical Ingredients Involves:

A. Bulk characteristics of Active Pharmaceutical Ingredients Involves: Particle Size &Surface area, polymorphism, crystallinity, hygroscopicity, flow properties & bulk density, compressibility, drug-excipient compatibility, electrostatic charge, osmolarity, rheology, wettability [4].

B. Solubility Analysis of Active Pharmaceutical Ingredients Involves: Aqueous Solubility, Solubilization, partition coefficient, thermal effect, common ion effect, dissolution [4].

S2B- Compatibility Studies of drug & excipients Objective of compatibility studies involves-

- Drug: active part of dosages form and it is mainly responsible for therapeutic value.
- Excipients: substances which are included along with drugs being formulated in a dosage form so as to impart specific qualities to them [5].

Different Analytical techniques used to detect DrugExcipients Compatibility: It involves:- Thermal methods of analysis involvesDifferential Scanning Calorimetric, Differential Thermal Analysis, FT-IR Spectroscopy and Diffuse Reflectance Spectroscopy. Chromatography involves- Self Interactive Chromatography, Thin Layer Chromatography, High Pressure Liquid Chromatography, and Miscellaneous involvesRadiolabel Techniques Vapor Pressure, Fluorescence Spectroscopy [5].

S2C – Analytical Method Development

What does analytical methodology consist of?

Techniques, method, procedure, protocol [6].

What does analytical methodology provide to an analyst?

Analytical methods provide required data for a given analytical problem, the required sensitivity, the required accuracy, the required range of analysis, The required precision i.e. the minimum requirements which essentially are the specifications of the method for the intended purpose: To be able to analyze the desired analyte in different matrices with surety and certainty.

The following steps are common to most types of projects:

Method development plan definition, background information gathering, laboratory method development, generation of test procedure, methods validation protocol definition, laboratory methods validation, validated test method generation, validation report. [6]

3. FORMULA DEVELOPMENT:

S3A- Prototype Development Prototype development is a stage in the new product development process. The idea is a descriptive statement that can be written or only verbalized. The idea is refined into a product concept that includes consumer benefits and features of the product. The concept is developed into a prototype, i.e. a working model or preliminary version of the product. After several iterations the prototype is perfected into the final product [7].

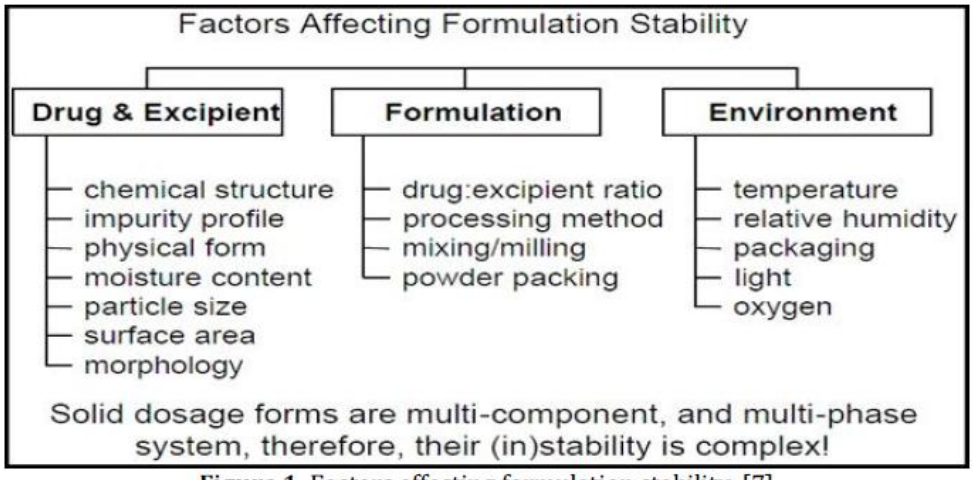

Figure 1. Factors affecting formulation stability. [7]

Phases of Prototype Development: There are five phases in the prototype development process:- 1) Identify the basic requirements of the product. 2) Develop a design meeting these

requirements and implement it. 3) Have users experiment with the prototype. 4) Revise the prototype, thereby redefining and completing the requirements [7].

S3B - Lab Stability Studies Initiation Importance of stability Extensive chemical degradation - a substantial• loss of potency Degradation products may result in adverse• events or be unsafe Instability may cause undesired change in• performance, i.e. dissolution/bioavailability Substantial changes in physical appearance of• the dosage form causing product failures requirement for approval by regulatory agencies [7].

Figure 1. Factors affecting formulation stability. [7]

S3 C –Comparative dissolution profile When dissolution profiles or a similar term is used in this guidance, data should be generated in a comparative manner as follows: It measures the portion (%) of the active pharmaceutical ingredients that has been released from tablets/capsules and has dissolved in the dissolution medium during controlled testing conditions within a defined period. The tablet thus first disintegrates, then the active pharmaceutical ingredients will be able to dissolve, slow disintegration, slow dissolution The % active pharmaceutical ingredients dissolved are determined with an appropriate validated method: UV/VIS, HPLC, AA, GC, etc. [7, 8]

It is a requirement for comparative dissolution data for the bio-batch and innovator batch:

Same batches as used in bioequivalence study

Submit report with data, profile comparison & discussion (see report requirements) This report forms part of pharmaceutical development report

Inclusion of the same report in the bioequivalence study report is recommended [7,8]

Variables affecting dissolution:

Characteristics of the API e.g., particle size, crystal form, bulk density

Product composition e.g., drug loading, and the identity, type, and levels of excipients Manufacturing process e.g., compression forces, equipment

Effects of stability storage conditions e.g.,temperature, humidity [7,8]

Comparative dissolution testing Dissolution conditions (study design):

Table 1. Comparative dissolution testing, dissolution conditions. [7,8]

Apparatus (choice)	**Paddle, 50 (75) rpm or Basket, 100 rpm**
Dissolution media All three media for,full comparison	Buffer pH 6.8,simulated intestinal fluid without enzymes, Buffer pH 4.5 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, (60, 120) min. (typical)

Table 2. Determination of similarity of profile [7, 8]

Example 1-A		
	% API dissolved	
Time (min)	**Tablet A (Ref)**	**Tablet B (Test)**
10	87	94
15	96	99
20	99	99
30	100	99
45	101	99
60	101	99
F2 required?	No, ≥ 85% in 15 min	
f2 (n = N/A?)	profiles similar	

Table 3. Determination of similarity of profile. [7, 8]

Example 1-B		
	% API dissolved	
Time (min)	**Tablet,D (Ref)**	**Tablet E (Test)**
10	55	57
15	72	78
20	85	91
30	97	100
45	102	100
60	103	101
F2 required?	Yes	
f2 (n = 3?)	64 (similar)	

4. PROCESS OPTIMIZATION:

S4A-Scaleup and stability study of batch Pharmaceutical Technology - is the development of a new drug product progresses, the batch sizes manufactured generally increase. Current International Conference on Harmonization (ICH) guidelines state that data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container-closure system as proposed for the marketed formulation [9].

Laboratory-scale batches: These are produced at the research and early development laboratory stage. They may be of very small size (e.g., 100–1000 times less than production scale). Laboratory-scale batches may be used to support formulation and packaging development. Laboratory-scale batches can also be analyzed to assist in the evaluation and definition of critical quality attributes (CQAs) [9].

Pilot-scale batches: These may be used in the process-development or optimization stage. For oral solid dosage forms, this size should generally be 10% of production scale or 100,000 units, whichever is greater. The choice of pilot scale is often difficult for the project team as members must balance parameters such as anticipated product volumes [9].

S4B -Process Optimization Studies Process optimization is the discipline of adjusting a process so as to optimize some specified set of parameters without violating some constraint. The most common goals are minimizing cost, maximizing throughput, and/or efficiency. This is one of the major quantitative tools in industrial decision making. When optimizing a process, the goal is to maximize one or more of the process specifications, while keeping all others within their constraints [10].

S4C – Analytical Method Validation The steps of methods development and method validation depend upon the type of method being developed. However, the following steps are common to most types of projects: ● Method development plane, background information gathering, laboratory method development, generation of test procedure, methods validation protocol definition, laboratory methods validation, validated test method generation, validation report. Pharmaceutical analytical methods are categorized into five general types: Identification tests, potency assays, impurity tests: quantitative, impurity tests: limit, specific tests. [10, 11] Validation requirements depend upon the type of test method, including

Specificity: ability to measure desired analyte in a complex mixture.

Accuracy: agreement between measured and real value.

Linearity: proportionality of measured value to concentration.

Precision: agreement between a series of measurements.

Range: concentration interval where method is precise, accurate, and linear. Detection limit: lowest amount of analyte that can be detected

Quantitation limit: lowest amount of analyte that can be measured.

Robustness: reproducibility under normal but variable laboratory conditions [10, 11].

S5 DOCUMENTATION: S5A – IPR and Regulatory clearance Regulator is usually a Government or Professional body that 'regulates' - meaning makes up the rules for certain types of businesses. Getting regulatory clearance can apply to many things and you have not provided a context. For example, if researcher wanted to become a Financial Advisor then researcher employer would need to submit an application, probably to the Financial Services Authority, to seek approval along with a list of researcher relevant experience, qualifications [12].

S5 B -Technology transfer dossier Technology transfer is the practice of transferring scientific findings from one organization to another for further development. Technology transfer is both integral and critical to the drug discovery and development process for new medicinal product. This process is important for to elucidate necessary information for technology transfer from R & D to product development laboratory & for development of existing products to the production for commercialization [12, 13].

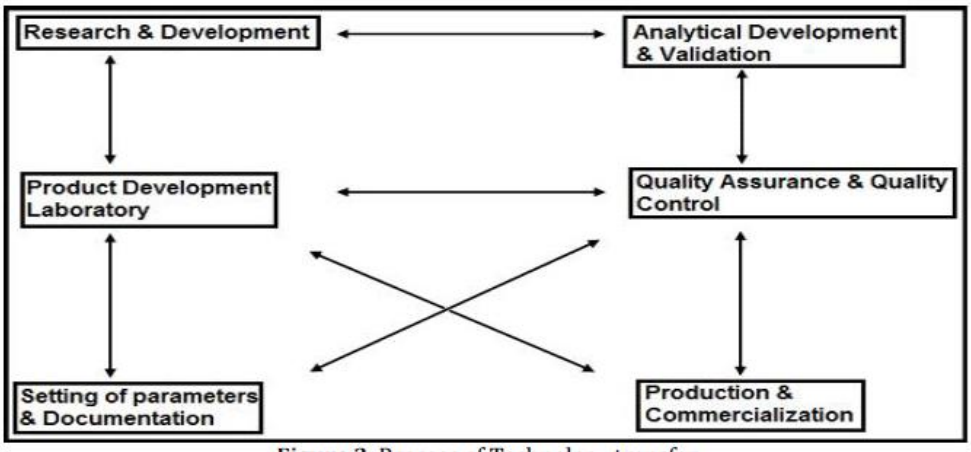

Figure 2. Process of Technology transfer

Technology transfer from R & D to production: R & D provides technology transfer dossier (TTD) document to product development laboratory, which contains all information of formulation and drug product as given below: [12,13]

a. Master formula card (MFC) includes: Product name along with its strength, generic name, MFC number, page number, effective date, shelf life and market.

b. Master packaging card: Gives information about packaging type, material used for packaging, stability profile of packaging and shelf life of packaging.

c. Master formula: Describes formulation order and manufacturing instructions. Formulation order and Manufacturing Instructions gives idea of process order, environment conditions required and manufacturing instructions for dosage form development.

d. Specifications and standard test procedure (STPs): Helps to know active ingredients and Excipients profile, in process parameters and specifications, product release specification and finished product details.

S 6 EXHIBIT BATCH MANUFACTURING:

S 6 A Validation Batch Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages similarly, the activity of qualifying systems and equipment is divided into a number of subsections including the following: Design qualification (DQ), Component• qualification (CQ), Installation qualification (IQ), and Operational qualification (OQ), Performance qualification (PQ). [14] The Validation Report: A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized. The report should include at least the following: Title and objective of study, reference to protocol, details of material, equipment, programmes and cycles used, details of procedures and test methods, results (compared with acceptance criteria); and recommendations on the limit and criteria to be applied on future basis. [14]

S 6 B Pivotal BE Studies: This batch shall be submitted to Regulatory authority Shall be charged for both Accelerated• & Long term stability testing Bio-study shall be done on the same. [15]•

S 7 C Dossier Compilation and filling: Dossier compiling, documentation and presentation in a compliant format is very involving and yet an part of the process of registration of any

pharmaceutical product in India as well as international markets. This is why companies look for ways to increase efficiency and cut time and costs in the dossier submission process. We understand the challenges of Pharmaceutical Dossier submission and registration, involving repeated interaction between the submitting pharmaceutical firm and the regulatory authority. We incorporate Quality by Design into your CTD and ACTD requirements and create the optimal Modules for dossier filling in different regulated, semi-regulated and non-regulated countries. Dossiers can be prepared in the Common Technical Document Format (CTD) [15].

CONCLUSION

Companies are constantly designing and developing new products, improve their Product development process [PDPs]. Companies have difficulty designing or selecting the process. This research used a series of case studies to define the components that distinguish Product development process from each other, providing companies with a more analytical method of comparison. This Product development process design is a directly applicable for research contribution, and provides companies with a framework for efficiently designing Product development process that suit specific project needs. Product development process into reviews and iterations can be helpful in product

design and development. Having good ideas for new products is not enough; to successfully bring those products to market, companies also need to design Product development process.

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