Drug Design & Manufacturing using Product Lifecycle Management

WHITE PAPER

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HCL
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Abstract

Product Life Cycle Management has evolved in Automotive, Aerospace & Defence and Hi-Tech verticals providing a collaborative platform to automate their Product development R&D processes and data management. Similarly PLM can provide an integrated platform to automate the pharmaceutical processes from Drug discovery to secondary manufacturing or simply *lab to launch*. Most organizations use a number of tools & solutions to manage the recipe, material & equipments, batch processes, Lab data management, document management during pre-clinical and clinical trials in the drug discovery and generic drug development areas. These solutions to a large extent are fragmented & do not streamline the R&D process as a structured program.

Drug Discovery & Design is a lengthy process which needs to driven under the ever increasing competitive pressure and fear of loss of profit margins due to Patent Expiration.

This whitepaper focuses on explaining how drug discovery & development process driven in PLM environment can help to ensure shorter time to market, system driven and consistent pharmaceutical processes, a common collaborative platform to manage eCTD and technology transfer for bulk manufacturing.
## Abbreviations

<table>
<thead>
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<th>Sl. No.</th>
<th>Acronyms</th>
<th>Full form</th>
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<tbody>
<tr>
<td>1</td>
<td>PLM</td>
<td>Product Lifecycle Management</td>
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<tr>
<td>2</td>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>3</td>
<td>eCTD</td>
<td>Electronic Common Technical Document</td>
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<td>4</td>
<td>GxP</td>
<td>Good Practices</td>
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<td>5</td>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>6</td>
<td>eDDR</td>
<td>Electronic Drug Development Record</td>
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Market trend/ Challenges

- Phlegmatically evolved PDM in pharmaceutical Industry
  PLM is evolved from automotive, aerospace & defense industries and then embraced by other verticals like Hi-Tech & Pharmaceutical. It has undergone the journey of evolution from PDM to PLM in these industries. Pharmaceutical domain does not have standardized product data modeling software and collaborative electronic data managed like CAD software. Some of the companies in Pharmaceutical domain are using PLM for product portfolio management & artwork and packaging. PLM products are still need to evolve for managing pharmaceutical product design data and act as collaborative platform within internal departments across the enterprise and with external groups.

- Smaller companies cannot afford cost of implementation
  Pharmaceutical domain specific solutions are available at very high cost. This investment is huge for a small biotech companies. One of the solutions for this could be using the open source PLM platform. Other way would be using on-demand PLM model on cloud. There are open source PLM solutions coming up in the market these days. The vendors of these solutions and also current PLM product market leaders has to come up with lighter version of the solutions with pharma specific processes, that will help SMB segment of pharma companies to meet their demand and budgets.

- Pharmaceutical Industry is mischarged for unrelated Engineering Complexity
  Pharmaceutical Industry involves totally different type of complexity world which could be related to physical and chemical complexity, storage, shelf life related complex problems. Current PLM products are much evolved to handle engineering complexities and hence the cost is also in proportion to the engineering complexities solved with PLM. The PLM vendors should have domain specific costing where one need not end charging more to pharmaceutical customer for engineering/ CAD complexities handled by the software.

- Less Matured pharmaceutical domain specific processes in PLM space
  As earlier stated PLM has started its journey from automotive/aerospace products and then embraced by pharmaceuticals, it is just a matter of time for PLM to evolve and become mature enough to cater the needs to industry. As current processes are more inclined towards automotive, aerospace, it will surely need some maturity to be widely accepted by pharmaceutical domain.
Functional Building Blocks of a Pharmaceutical Product Lifecycle Management system

Current PLM is mostly used to manage projects, documents, Artwork & Packaging and related CAD data management. There are many other areas in Pharmaceutical where the PLM processes can help to automate and streamline many areas.

Broadly PLM can useful for

- Enabling Drug Discovery & Design on principles of GxP, QbD, API formulation,
- Pre-clinical trials,
- Clinical Supply Chain Management, Recipe Management.

The following diagram summarizes the functional building blocks of a Pharmaceutical Product Lifecycle -

Structured Electronic Drug Development Record (eDDR)

- Standard Drug Discovery & Development Life Cycle

Drug design is an iterative process which begins when a chemist identifies a compound that displays an interesting biological profile and ends when both the activity profile and the chemical synthesis
of the new chemical entity are optimized. Traditional approaches to drug discovery rely on a step-wise synthesis and screening program for large numbers of compounds to optimize activity profiles. Over the past ten to twenty years, scientists have used computer models of new chemical entities to help define activity profiles, geometries and reactivities. Major Phases and sub-phases in a typical drug discovery process have been depicted in diagram below.

![Diagram of Drug Discovery Process]

PLM can help to store the electronic drug record in phases. The electronic drug record includes drug formulations at every intermediate state, the linked test results, drug regulatory related information, product quality assurance & control documents, drug packaging/artwork, geography specific packaging, regulatory information.

Currently all the drug development records are either available in non electronic format or available at different places in various formats. There is a single collaborative platform available in PLM for document management which can be extended for electronic drug development record (eDDR) management.

**Drug Design & Discovery Data Version Management**

In data rich industry like pharmaceuticals, knowledge tends to be weakened unless there is proper knowledge management, transfer mechanism.

Current drug development process does not facilitate the idea of Central repository where all the research data can be stored, version controlled and collaboratively used by all the stakeholders while work is in progress. Multiple stakeholders can work with multiple protocols, processes together to achieve the common goal by offering visibility, flexibility across various isolated islands of a Pharmaceutical organization.
With PLM systems, as the data is available centrally the backups related to data can be ensured. Only designated people can be given access to the product data. There will be standardization in terms of the research processes if the product data is available in collaborative portal.

The following diagram depicts how PLM application helps.

PLM provides a common collaborative platform for maintaining eDDR. Various important stakeholders for drug development like pharmaceutical scientist, engineer, and change analyst and manufacturer engineer can have life cycle specific view of the electronic drug record at various stages of drug development. PLM provides basic lifecycle management and traceability with all corresponding artifacts effective at specific period of time.

**Drug Portfolio & Project Management**

An efficient drug portfolio management is the key factory for to improve the drug development productivity. Like any other product the drug product life cycle consists of many offshoot projects which need to be managed throughout.

PLM’s Portfolio and project management features provide an effective way to monitor and control the timeline and cost in drug development process which is a pressing need to keep profit margins under control in the competitive environment. It also helps to track and control the risks associated with various phases of project/ sub-project phases. This is a proper tool to track the accountability and better resource management.

As mergers and acquisition (M&A) activities continue companies are in need of a common platform to harmonize their product portfolios.
and enhance the visibility across entire product line & customer pipeline. This also helps to achieve better utilization of shared resources, optimize the supply chain and logistics for the newly merged entity.

**Integrated Clinical Supply Chain Management**

Following are the factors which are driving a stronger need of a Clinical Supply Chain Management in a pharmaceutical industry:

- Continuous Mergers & Acquisitions causing lots of similarities in generic portfolio, The opportunity of cross selling ensuring better optimization, resource utilization of the newly merged entity leading to proper portfolio harmonization.

- The Adaptive Clinical Trials (ACT) methodology is accepted by the Pharmaceutical industry as a way to accelerate drug development, reduce costs and improve time to market. It allows statisticians and scientists to configure and evaluate different alternate designs, different adaptive elements of design. This involves a great deal of collaboration with external agencies. PLM provides a highly collaborative common platform for successful integration of supply chain management.

- An effective Drug development technique, like quality by design (QbD) allows shortening drug approval time span and efforts for Commercial Manufacturing.

- Logistics optimization improves better utilization of infrastructure, consumable resources.

**Technology Transfer**

Development and transfer of knowledge artifacts is a critical process for drug development.

**Internal/ External Secured Collaboration**

Technology Transfer is consisting of sending unit(s) and receiving unit(s) to transfer electronic design record of Product, Process or Methodology. Technology Transfer is considered successful if a receiving unit is able to reproduce the transferred product, process or methodology as per specification agreed with sending unit.

- It is a bridge to join gaps between customer, regulatory authority and pharmaceutical organization.

- Technology Transfer is used to transfer following types of documents in pharmaceutical industries:
- Drug Formulation
- Development Process
- Quality Control
- Mass Production
- Clinical Trials

Knowledge Management

Due to increasing attrition there is lot of leakage in knowledge base of an organization. Due to widespread geographical locations, there are many cases of reinvention of wheel. There are certain challenges in Technology Transfer executed traditionally which can be addressed by PLM like:

- Dilution in Knowledge base leading to reinvention of the wheel
- Confused ownership of responsibilities
- Delayed approvals

Personalized Drug Development

Personalized Drug Development model provides tailored healthcare to suit individual patient in whatever possible manner. Advancement in the field of molecule profiling may allow a greater deal of help in personalized drug development. As the time progresses there will be a need to combine the genetic information of patient, medical history of patient with drug development process. Pharmacogenomics optimizes the drug therapy as per the patient’s genotype to ensure maximum efficiency and minimum side effects. PLM has capability to facilitate the personalized drug development.

The following diagram illustrates how PLM can help for personalized drug development.
The principle of personalized drug design can be very easily adapted for product development of artificial biomedical implants like dental implants, pacemakers, orthopedic implants & Prosthetic Limbs. In place of the genomic database there need to be physical dimensions specific to the patient needs to taken into consideration.

Integrated Quality & Risk Management

Drug Regulatory Harmonization

Harmonization is a process of integrating national standards of drug development with international standard for efficient drug development.

Generic drug development has a typical harmonization process for getting the product approved by regulatory authority like FDA; similarly the branded drug also needs to confirm certain norms and compliances. PLM can provide a strong platform to achieve harmonization needs of any pharmaceutical industry.

Globalization has brought into greater importance of an approach to uniformity in the formulae of the more powerful remedies, in order to avoid chance to patients when a prescription is dispensed in a different country from that in which it was written. Attempts have been made by international pharmaceutical and medical conferences to settle a basis on which an international pharmacopoeia could be prepared.

The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration. Harmonization would lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

Risk Management

The process of identifying risk, creating mitigation plan, contingency plan to ensure the drug discovery, development & manufacturing executions.

In early 2002, the FDA announced its “Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk-Based Approach.” The FDA defines a Risk Management Program (RMP) as, “a strategic safety program designed to decrease product risk by using one or more interventions or tools.”

The Risk Management Plan consists of various elements like
• Risk Management Plan
• Risk Identification Techniques
• Risk Evaluation Techniques
• Risk Response Planning
• Risk & Issue Management Plan

PLM provides tools for effective risk management.

Packaging & Collateral Management

Packaging and collateral are basically 2D/3D graphic designs, video material which are useful for packaging and selling the drug. These graphic components are subject to various changes, co-authoring by group of people and require certain sort of approvals to be effective. PLM already has a strong platform to integrate with various graphic designs CAD tools which can be extended for 2D/3D packaging data management. Rest graphic content can be version controlled using document management functionality of PLM.

Packaging Data Management

Packaging is defined as collection of neutral foreign component which surrounds pharmaceutical product from the time of production till consumption.

Manufacturer are under constant pressure to meet ever increasing need of packaging and artwork management to fulfill consumer demand, increasing awareness of environment friendly packaging, meeting different external environment specific requirements like:

- Protection against external influences that can alter the properties of product.
- Protection against biological contamination
- Protection against physical damage
- Tamper proofing, Child proofing, Anti counterfeiting

As most of the products in pharmaceutical domain come with an expiry date, there has to be a mechanism to correlate the pharmaceutical product with packaging and same has be executed by the product assembly lines, by the Manufacturing Execution System after taking input from Product Lifecycle Management system.

Packaging CAD data management, collaboration and visualization is a necessary feature as the design and development of packaging has to incorporate various legal, scientific, branding collateral parameters taken into consideration.

The QC testing needs to done on packaging and results need to be available for following type of testing.
Visual inspection
- Dimensional Test
- Physical Test
- Chemical Test
- Microbiological Test
- Pressure Test
- Temperature Test

Collateral/Artwork Management

The labeling in current pharmaceutical industry has been complex due to evolution in technology. The label has to contain human readable information like:

- The artwork
- Statutory legal information
- Ingredients and allergy information,
- Storage instructions
- Dosage information
- Placeholder for printing the manufacturing date/ expiry date.

It should also contain placeholder for printing machine readable information like:

- Bar Code
- RFID
- Hologram stickers for identifying genuine product.

As mentioned in above sections the 2D/3D graphic design content, document facilitating the electronic records of packaging CAD and collateral can be collaboratively maintained using PLM.

Global Product Registration

Product Registration

The product registration artifacts are mandatory requirement and need to recreate every time an organization is going for the product registration under different geography as part of statutory and legal requirement. PLM provides facility to create reusable product registration artifacts, which is definitely a saving in terms of effort and money.

Electronic Common Technical Document (eCTD)

It was developed by the International Conference on Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). As of January 1, 2008, the U.S. Food and Drug Administration announced that the eCTD is the preferred format for electronic submissions. To date; over 98,000 eCTD sequences have been submitted to the FDA.
It is an interface for the pharmaceutical industry to agency transfer of regulatory information. The content is based on the Common Technical Document (CTD) format. The eCTD is a message specification for the transfer of files and metadata from a submitter to a receiver. A cumulative eCTD message can be viewed using an eCTD viewer. FDA revealed during the 2009 DIA Annual Meeting that it is looking at draft legislation to require eCTD.

Providing facility to manage eCTD will be a mandatory requirement for generating the compliance, harmonization results.
Conclusion

Pharmaceutical Industry can ripe the benefits of PLM not only in medicine packaging but also can be very well used for controlling and managing the R & D processes. The typical functional areas which can benefit with PLM Implementations are:

- Drug Portfolio & Project Management
- Drug Design & Discovery Data Management
- Drug Discovery Data Version Controlling
- Personalized Drug Development
- Drug Regulatory Harmonization
Reference

Abstract


Personalized Drug Development

http://en.wikipedia.org/wiki/Personalized_medicine

Regulatory Harmonization


Pharmaceutical Risk Management


Clinical Supply Chain Management

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