



Regulatory Guidelines and Production Planning Strategies for Biosimilars in the USA

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Abstract: At present, biosimilar projects are ruling the pharma market. This article aims to show that project management is crucial in developing biosimilars. Bad project management will give a bad reputation to the organization, project cost overruns, project schedule delays, demotivation of the project team, sustainability risk to the organization, and more over huge loss. It is the main reason most companies are spending more on the training of employees, particularly on project management. Biosimilars are biological products that are highly similar to a reference product despite modest changes in therapeutically inactive components. Biosimilars have no clinically significant changes in product safety, purity, or potency compared to the reference product. With the imminent patent expiration of certain important high-cost biologics, biosimilar manufacture is becoming increasingly profitable for firms. However, the introduction of biosimilars necessitates the adoption of critical new rules. Because of the inherent differences involved with the production methods used by different companies and even different sites within the same company, the existing standards that regulate the approval pathways for generic pharmaceuticals are insufficient for biosimilars. Biosimilars are similar to but not identical to the original. Due to the exclusive nature of the manufacturing line and the techniques employed by these competitors, basic variances in methodology may exist between competing organizations. Even modest variations in the manufacturing process can result in micro heterogeneity, characterized by minor differences in molecular structure, stability, production cell line behavior, growth conditions, vectors, and purification methods. For these reasons, developing biosimilars takes a lot of work. ICBER regulates biosimilars in the US Market. The reference Medicine's Patent status and market potential should be considered when developing biosimilars. The main objective of this article is to show that the project management strategies and regulatory approval process are equally important to enter biosimilars into the market. Concerning quality in the project management of biosimilar products, budget, deadlines, and scopes are major constraints. A Gantt chart has been enacted to represent a graphical illustration of a schedule. Gantt chart helps to plan, coordinate, and track specific tasks in a project.

Keywords: Biosimilars, biologics, project management, software, regulatory.

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I. INTRODUCTION

A pharmaceutical drug, medicine, or medication is a chemical substance used to diagnose, cure, mitigate, or prevent diseases. Drug discovery and drug development is an intricate and exorbitant process by scientists, pharmaceutical companies, and academicians. Product quality is the ultimate goal of pharmaceutical development, and it is the manufacturing process that incessantly contributes to the pre-convinced performance of the product. Information obtained from pharmaceutical development studies is used for quality risk management. It is ideal to acknowledge that quality cannot be tested to procure it should be built design.² Biologics products are produced from living cells or specific components of a living organism, and they include a wide variety of products derived from animals, humans, or microorganisms by using biotechnology.³ Biologics products in the market brought tremendous success and profits. They are blood and blood components, vaccines, gene therapy, allergenic, somatic cells, tissues, and recombinant therapeutic proteins. It contains proteins, sugar, or nucleic acid.⁴

1.1 Biosimilar

Biosimilars are biological medicines that possess highly similar characteristics to other already approved biologics and for which there should be no clinically meaningful differences between the biological product and the reference product in safety, purity, and potency.⁵ Biologics treats those with chronic health conditions and autoimmune diseases. Pharmaceutical products are small molecules that are inorganic and synthesized through chemical processes. The final versions of this molecule came to be fully characterized by analytical techniques. Companies other than the originator can incorporate the same active ingredients structurally identical

to the innovator, also called generics. Comprehensive clinical trial data are optional for the approval of generic drugs as the company can depend on the safety and efficacy of data of the originator company and moderately careful bioequivalent studies.⁶ The final protein that makes up biological medicine varies in size and structure, like insulin, a simple protein. A Biosimilar is highly similar to its original counterpart regarding safety, structure, efficacy, biological activity, and immunogenicity profile. In the year 2006, The first Biosimilar was approved.⁷ It cannot be considered a generic version of biological medicine. The reason is the unpredictability and complexity of manufacturing biological drugs that inhibit the precise imitation of the originator.

1.2 General Approval of Biosimilar:

Biosimilar is also known as similar biologic or follow-on-biologic. It is identical but not similar to the innovator drug. Biosimilar has the same active substance as the originator but is developed by another company. The biosimilar developer extrapolates the data from the originator drug and compares the data between the two drugs to prove bio similarity to the FDA. The molecule is characterized structurally and functionalityally, and animal studies are conducted to compare the clinical studies if needed. The main advantage for biosimilar developers is that they don't need to furnish the complete clinical trial data set. Rather, they can depend on the originator by demonstrating to the FDA that there are no clinically meaningful differences with the originator.⁸ In short, it means that biosimilar developers shall conduct only some of the expensive and time-consuming clinical trials and can make the product easily marketable at a much-reduced cost without compromising safety and efficacy. The approval process for biosimilars is depicted in Figure 1

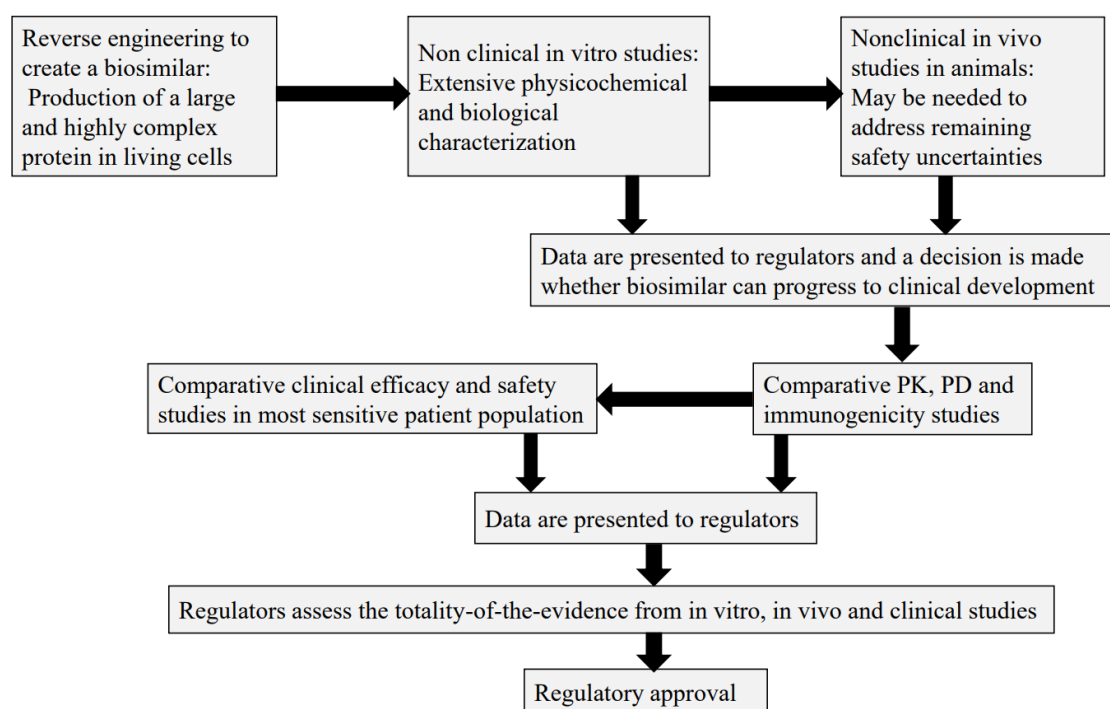


Fig 1: Approval process of biosimilars

1.3 The impact of the manufacturing process

Biosimilars must undergo a rigorous development procedure and exhibit no clinically significant safety, purity, and potency changes compared to reference medicine to receive regulatory approval. Given the complexity of the process, it is critical to comprehend how biosimilars are created. Biosimilars must go through the same manufacturing process as their reference biological product, which is costly and time-consuming. When comparing biosimilar development to that of the reference product, there is a potential time and cost savings because some stages are not required to manufacture a similar biologic product. Because the biosimilar administration regimen uses the same dosing as the reference product, the discovery/research phase and dose-finding studies (Phase II clinical trial) are unnecessary for biosimilar development. Phase III research establishing efficacy equivalence between the biosimilar and its reference product is required. However, it can be carried out with fewer participants. One phase of the normal clinical trial process is not specific to biosimilar development. Recently, the FDA announced advice for an expedited clinical program designed to accelerate approval of breakthrough medicines for life-threatening diseases, with a 40% decrease in time projected. Nonetheless, the discovery/research phase continues to be a differentiating factor in biosimilar creation. Using various expression systems to produce biosimilars vs. reference pharmaceuticals may alter post-translational modifications, such as the glycosylation profile of the protein, which could compromise the product's safety or effectiveness. Variations in the glycosylation protein pattern can affect the final product's immunogenicity or clearance. Furthermore, minor changes in the composition of biological products affecting inactive components or changes in principal packaging materials may modify immunogenicity. The creation of biosimilars to replace biopharmaceuticals whose patents have expired or are about to expire has resulted in novel production concepts. The manufacturing facilities relied on relatively rigid, hard-piped equipment, such as large stainless-steel bioreactors and tanks, to hold product intermediates and buffers, which are now being replaced with single-use counterparts to develop biosimilars and new products. Some benefits of adopting single-use or disposable technologies for biopharmaceutical manufacturing include (1) lower capital costs for plant construction and commissioning; (2) reduced risk of product cross-contamination in a multiproduct facility; (3) quick changeover; (4) lower utility costs due to reduced need for steaming-in-place (SIP); and (5) reduced need for cleaning validation.⁹

1.4 Microheterogeneity

Biosimilars are not identical duplicates of the original biologic, as opposed to generic small molecule medications in which the active pharmaceutical ingredients are exact replicas of the originator product. As a result, biosimilars can be compared to snowflakes. A biosimilar and its associated originator product are not identical, just as no two snowflakes are. Because of the complexity of the biologics structure, as well as the nature of the changes in the manufacturing process.¹⁰

1.5 BPCI Act:

As a part of (ACA), The Biologics Price Competition and Innovation Act of 2009(BPCI) was passed. Then President Barack Obama, on March 23, 2010, signed a law into an act.

The Act allows the biosimilar or interchangeable to be approved via the abbreviated license pathway about the original biologics drug.¹¹ Through this license pathway, the biosimilar can be under 315 k of the Public Health Service (PHS) Act. The reference product used to prove bio similarity with biosimilar is licensed under 351(I) of the PHS Act. The BPCI Act includes other provisions as follows:

- During approval of a 351-k application, 12-year exclusivity periods and 4-year exclusivity period from the date of the first license of certain reference products reference. It may not be made effective (section 351 (k) of the PHS Act.
- For 1st biological product, the exclusivity period is determined with interchangeable products.
- To resolve patent disputes, an application is submitted under section 351 (K) of the PHS Act.¹²

1.6 General requirements for 351k application:

The PHS Act also requires additional information to demonstrate bio similarity. Analytical studies ensure biosimilar to the originator with no minor differences in the clinically inactive components. Animal studies focused on detailed descriptions of toxicity studies. Clinical studies are suitable for assessing immunogenicity and pharmacokinetic pharmacodynamics, demonstrating purity, safety, and efficacy in varied conditions. In some cases, the FDA can consider any one of the above elements as unnecessary, but it is entirely upon FDA discretion.¹³

1.7 Regulatory submission to the CBER in Electronic format-

General requirements of biologics marketing applications are given in 21 CFR Section 601.2 and 314.5 for submission to the CBER. Form FDA 356h enlists the requirement for submission of a biologic or NDA.

- Refuse to File:** As per 21 CFR 601.2 and CFR 314.0, CBER may have the right to file a supplement or an application, and those reasons are reliable with the published RTF policy. RTF happens when an application or supplement's paper or electronic versions are uninterpretable, illegible, inadequate or inadequate, and incompatible formats. CBE Review and statistical analyses may be regarded only with a legit electronic database, resulting in an RTF decision.
- Review and Archival Copies:** Docket number 92s-the Agency has established 0251 in the Federal Register, where the submission that can be accepted in the electronic format will be published. Once the document that can be reviewed or archived in an electronic-only format is identified in the docket number, the applicant can provide all or portions of the copy in the electronic format. Those portions of an application that cannot be submitted electronically should be given in paper format. Suppose a submission includes both electronic and paper formats. In that case, TOC (Table of Contents) for submission must contain the location of information submitted as a copy and identify the site by electronic file by file and folder name. The area of information provided on paper only must be noted within the electronic submission using a placeholder. It is because the placeholder directs the

reviewer to the paper-based submission and gives the volume and Page number of the application. Each form of FDA 356h can be a complete paper /electronic document. Another agency guidance document must submit the paper part of the license application.

- c. **Supplements and Amendments:** The supplement and amendments submitted under this must be equivalent to the original submission of an application, and the following supplements
- d. **Electronic Signatures:** Before the advent of online submission without paper, documents that require an

original signature should be submitted by a paper copy, which is attached with a handwritten signature. Therefore, the reference document can be checked when the agency is accepting electronic signs.^{14,15}

Authorization of the FDA to assess and collect fees for biosimilar biological products is given by the Biosimilar Use Fee Act of 2017 (BsUFAII). The FDA can dedicatedly use the obtained fee to expedite the review process for biosimilar biological products. BsUFA plays an important role in facilitating the development of safe and effective biosimilar products. BsUFA Fees are given in Table I.

Table I: Biosimilar processing fees in the USA			
Use Fee type	Rates for FY 2021	Rates for FY 2020	Percentage Change
Initial BPD	\$102494	\$11987	-13.2%
Annual BPD	\$102494	\$117987	-13.2%
Reactivation	\$204988	\$235975	-13.2%
An application requiring clinical data	\$873373	\$873373	0
Application not requiring clinical data	\$873373	\$873373	0
Program	\$304162	\$304162	0

Table I illustrates the percentage change in biosimilar processing fees in the USA, comparing 2020 and 2021.

1.8 Project Management Strategies and Tools:

Several non-repetitive and temporary activities that are carried out to produce a product, a service, and a unique result is a project. Project management is a complex undertaking with many stages and processes. It should follow the full business lifecycle, from the definition and justification of the

project through to delivering demonstrable benefits for the business. Components of Project Management involve three factors. They are Objective, Schedule, and Required resources. Benefits of Project Management: Decreased risk, time, and Cost, increased quality and productivity. The basics of project management strategies are depicted in Figure 2.

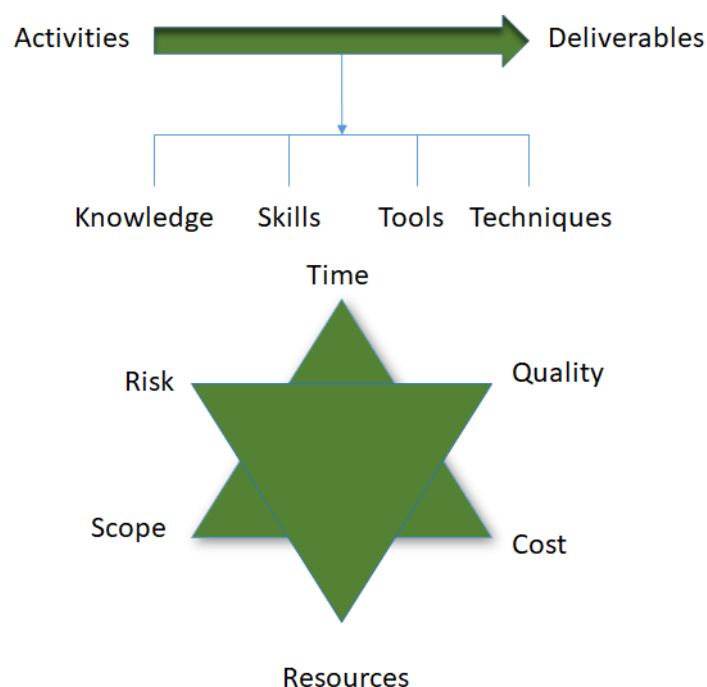


Fig 2: Basics of project management system

1.9 6C of Project management

1. Concept- High-level ideas about the project and a brief about the scope of the project.
2. Clarity- Requirements elicitation and analysis. Defining the requirements and then documenting them or implementing them into a system that can track changes

- and act as a control point. It includes a Project execution plan and a Project status update system.
3. Consensus- Socialization and approvals
4. Commitment- Addressing requirements in the solution design and allocating resources to build the solution.
5. Control- Understanding the impact of changes and analytical development.

6. Confirmation- Confirming designs in testing and implementation.¹⁶

The project manager performs multiple bases in an organization to ensure effective success. The project manager leads a major role in executing, planning, controlling, monitoring, and closing Individual projects. An organization can have one or more project managers. Every manager should possess some Hard and Soft Skills. Statement of Work (SOW) consists of all project dimensions. It lays the legwork

of the project as it consists of detailed explanations. Before the planning and execution of the project's landscape, it is one of the first documents to be created. It is a daunting process as all the methods should be explained clearly. The main advantage of this statement is that it can be shared with contrast and vendors who are bidding on the project, as the document is self-explanatory.¹⁷ Triple constraint theory triangle defines constraints that are integrated into project management. The limitations are made of three things: Cost, scope, and time, as depicted in Figure 3.

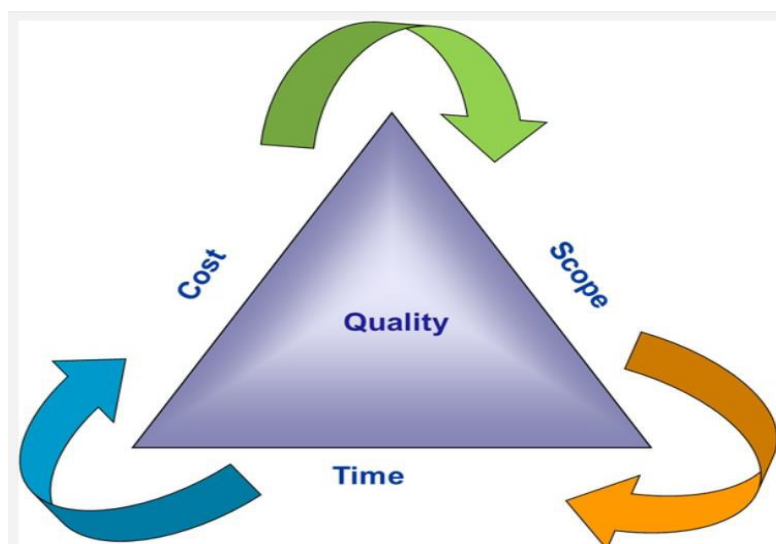


Fig 3: Triple constraint theory triangle

It is essential because it gives a framework for people to agree to work out things, just like when restrictions increase creativity. With this model, the project manager can know the project's status with its ups and downs.¹⁸

1.10 Methods adopted in estimating project cost

1. Historic data- by analyzing other similar projects.
2. Bottom-up, the Lowest to highest work package is estimated
3. Vendor bid- by calculating some average vendor bid
4. Quality analysis- estimating the Cost of the highest quality activity
5. Resource costs- the rate of costs for labor and goods is estimated
6. Reserve- cost for the activities is aggregated
7. Parametric- by calculating the statistical relation between historic and other variable

Project scope is concerned with tasks or specific requirements that aid in project completion. The project's scope is essential as it helps to finish its stipulated time frame within a given budget. The first central criticality in managing scope is prioritizing the task and effectively using resources. The second is fulfilling the prerequisite and stakeholders' expectations. The final criticality is to overcome the new demands that are put forth by the consumer, which is standard in long-term projects. Scope management is significant as it can delay a project's completion while increasing the budget.¹⁹ A work breakdown structure (WBS) is generally used to drive large project goals into a series of smaller ones, making it easy to prioritize and estimate the project's Cost. One of the ways to represent the project schedule is a Gantt chart, which gives a timeline for each particular task. The method is very

supportive when having historical data. The schedule can be managed by following the Project Management Body of Knowledge (PMBOK) steps. While it is evident that some variables are constant in project management, others are not. Using this model helps us figure out the adjustments that can be made. For instance, if the project lacks a schedule, some features can be reduced, reducing the scope. Then, more resources can be allowed to keep the schedule ahead. It increases the Cost. In this case, the end date of the work can be postponed to buy more time. All these scenarios are the classic example of applying the triple constraint model to manage the project. This model is nothing but a balancing act. A project manager has to take time to practice this model, as it is just like juggling.²⁰ Critical Path Method (CPM) and Project Evaluation Review Technique (PERT) are used for Program and work planning in management engineering science. CPM technique to upgrade central pharmaceutical supply functions. While these two methods are developed distinctly, the similarities are so much more; therefore, it is referred to as the CPM-PERT Technique. This combined technique serves as a network model in planning and scheduling the project's activities. The steps involved in the technique are given in Figure 4. The PERT Technique benefit is that the exact time needed for each task can be estimated accurately. From the above diagram, it is evident that adding all the task time gives 83 weeks to complete the work assigned. In this, several tasks can be done concurrently. Tasks B & C can be started immediately when task A is done. It gives the soonest date for the completion of the task. The longest and the most critical path is A-C-E-G-K-L, which requires 50 weeks to complete.²¹ The Log Frame method or the logical framework approach (Log Frame or LFA) (Figure 4) is one of the methods that has border applications.

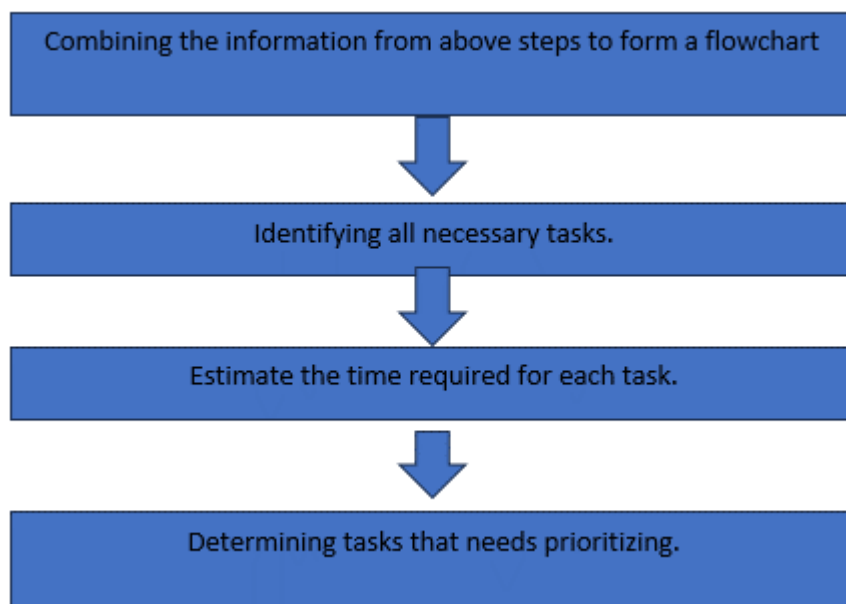


Fig 4: Steps involved in the CPM-PERT technique

A Guidebook on the approach of the Long Frame Method was published by the World Bank in 2005. The essence of this method is to combine all the key components of the project in one place and give them concisely. Logical inter-relatedness among project elements is ensured by this method, as given in Table 3.²²

Table 3: The Log Frame method			
Native summary	Verifiable indications	Means of verification	Assumption/risks
Goal	Quantitative ways of measuring or qualitative ways of measuring.	What source of information exists?	External factors are necessary for sustaining objectives in the long term.
Purpose	Quantitative ways of measuring or qualitative evidence to judge achievement and impacts.	What source of information exists?	External factors affecting the movement of purpose toward project goal.
Outputs	Performance questions and indicators for each output.	What source of information exists?	External factors affecting the movement of outputs to purpose.
Activities	Can include the needed inputs for activities.	What source of information exists?	External factors affecting the movement of outputs to purposes.

It provides a systematic basis for monitoring and highlighting the influence of external factors. Instead of using Log Frame as a final product, it can be updated throughout the project to continuously get a clear view of the objective. The drawback of this approach is that it can lead to an inflexible project design without a connection to realities in the changing current situations. The approach appears as a four-four-by approach.²³

1.11 Strategic planning

A shared vision of the fundamental purpose of the mission is strategic planning. It also talks about its effectiveness and direction of the Program. A Strategic thinker looks for the following questions:

- Who is meant to benefit from our services?
- Is the organization appropriately structured for achieving these goals?
- What are our priority goals?
- What are the most appropriate strategies for achieving our goals?
- What are the basic values of the organization?

1.12 Steps involved in strategic planning

- **Stage 1- Identify an area** - No matter which path companies take, two things are certain: Biosimilars are coming, and Pharmaceutical companies will need to evolve their commercial strategies to address them. As the pathophysiology of the disease is known due to technological advancements, Biosimilars help achieve target-specific treatment.
- **Stage 2- Analysis, Cost, Risk, and Benefit** - After analyzing current market trends and requirements, a perfect plan is executed, including cost estimates and counter-risk strategies. Examples of the types of analysis executed are SWOT analysis (strengths, Weaknesses, Opportunities, and Threats analysis),²⁴ PESTEL analysis (Political, Economic, Social, Technological, Environmental, and Legal analysis), NOISE analysis (Needs, Opportunities, Improvements, Strengths and Expectations analysis) and SOAR analysis.²⁵
- **Stage 3- High-level business requirement** - The main criterion to succeed is that the organization should be completely equipped and eligible to afford the best medical care to patients. Despite developing and getting approval for the right drug, the company has to market its drug to reach out to every patient in need. The pricing of the drug is also important.

- **Stage 4- Structure executed work plan** - Gantt chart work plan: A Gantt chart is a popular graphical representation of a project timetable. It's a form of bar chart that displays project aspects' start and end dates, including resources, planning, and dependencies.
- **Stage 5- Completion of the project** - The Project life cycle's Final stage is all woven around the completion of the project. The significance of the project lies in delivering what has been promised. If the customer is satisfied with the project's output, it implies that the project has to end. Distributing information to formalize the acceptance of the product, project, or service and performing project closure are key activities in the Final Stage of Project life cycle management.

2. CONCLUSION

The biosimilar industry will continue to change quickly. Developing and selling a biosimilar is a unique and conflicting problem. Commercialization tactics in biosimilars extend beyond the target audience team to encompass prelaunch, customer profiling, data management, program management, scaling production, data analytics, and quality control. Pharmaceutical businesses face huge hurdles during the lengthy and exceedingly complex product development process. This lengthy process involves management in various diverse business processes, such as technical development employing quality by design, regulatory strategy, clinical investigations, and supply chain, from the first study in the early laboratory stages to the end product market launch. To find

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the most cost-effective ways of speeding up the process of developing new products, particularly during the clinical trial phase, pharmaceutical companies had to introduce and implement project management, which was done in other manufacturing industries a long time ago. Identifying risks in each phase of the process and an effective risk mitigation plan were critical success elements for these companies, both financially and technically. However, using excellent project management to launch new medicines does not just enhance pharmaceutical firms' performance and profitability. Effective project management in the pharmaceutical business also makes new medical discoveries available to people in need sooner and at a cheaper cost, and by enabling treatment for a specific ailment, it helps human health maintenance and enhances quality of life worldwide.

3. AUTHORS CONTRIBUTION STATEMENT

The authors confirm their contribution to the paper as follows: Study conception and design: Prasanthi, Venkateswara Raju, Aditya, Srinivas; Data collection: Prasanthi, Aditya, Jeevan; analysis and interpretation of results: Lakshmi, Venkateswara Raju, Jeevan; Draft manuscript preparation: Prasanthi, Aditya, Srinivas, Lakshmi. All authors reviewed the results and approved the final version of the manuscript.

4. CONFLICTS OF INTEREST

Conflict of interest declared none.

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