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Review

The complexity and cost of vaccine manufacturing – An overview

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ABSTRACT

As companies, countries, and governments consider investments in vaccine production for routine immunization and outbreak response, understanding the complexity and cost drivers associated with vaccine production will help to inform business decisions. Leading multinational corporations have good understanding of the complex manufacturing processes, high technological and R&D barriers to entry, and the costs associated with vaccine production. However, decision makers in developing countries, donors and investors may not be aware of the factors that continue to limit the number of new manufacturers and have caused attrition and consolidation among existing manufacturers. This paper describes the processes and cost drivers in acquiring and maintaining licensure of childhood vaccines. In addition, when export is the goal, we describe the requirements to supply those vaccines at affordable prices to low-resource markets, including the process of World Health Organization (WHO) prequalification and supporting policy recommendation. By providing a generalized and consolidated view of these requirements we seek to build awareness in the global community of the benefits and costs associated with vaccine manufacturing and the challenges associated with maintaining consistent supply. We show that while vaccine manufacture may prima facie seem an economic growth opportunity, the complexity and high fixed costs of vaccine manufacturing limit potential profit. Further, for most lower and middle income countries a large majority of the equipment, personnel and consumables will need to be imported for years, further limiting benefits to the local economy.

Contents

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1. Introduction

Despite the market dominance of vaccine manufacturers based in high and middle-income countries, there are many reasons why a low-income country or regional grouping of countries may want to establish their own vaccine supply [1]. These include: supply security, control over production scheduling and sustainability, control of costs, socio-economic development, and rapid response to local epidemics including emerging infectious diseases. Where Expanded Program on Immunization (EPI) vaccines are provided, vaccine uptake has increased and childhood morbidity and mortality have fallen [2]. Given the importance of vaccines in public health programs, governments and donors have invested in vaccine R&D and production in low-resource settings [3]. However, there are many factors to consider prior to commitment to this capability – the high failure rate of preceding efforts [1]; the high cost and time required to establish complex processes, and capabilities for production of a broad portfolio of vaccines [4]; fragmented or inconsistent demand [5]; diverse regulatory requirements; and limited local competence and experience [6]. Additionally, to produce at low cost requires strategic commercial planning and adoption of various cost saving approaches. While some manufacturers have successfully produced vaccines for decades, others have faltered or failed, and relatively little information is available in the literature on the challenges, complexity and cost of vaccine manufacturing. This paper consolidates information from disparate sources to begin to fill this void and to drive better understanding of the costs associated with robust vaccine production capabilities.

2. Vaccine manufacturing overview

Vaccine manufacture is one of the most challenging industries. Even the most basic manufacturing steps necessary to produce vaccines in a manner that is safe, effective, and consistent over the life cycle of a vaccine are difficult to execute [7]. Outcomes can vary widely due to the nearly infinite combinations of biological variability in basic starting materials, the microorganism itself, the environmental condition of the microbial culture, the knowledge and experience of the manufacturing technician, and the steps involved in the purification processes. To add to the complexity, the methods used to analyze the biological processes and antigens resulting from vaccine production often have high inherent variability. Failure to manage these risks can result in costly product recalls, and suspensions and penalties may be assessed if a manufacturer fails to fulfil supply agreements. In addition, lack of supply can disrupt routine immunization programs and negatively impact national public health outcomes.

Regulatory authorities license not only a specific biological entity, but also the processes by which that entity is produced, tested, and released for use. Subtle changes in the production process may alter the final product and change its purity, safety, or efficacy. Further, the *in vitro* analytics required to release the product may not detect a change in process and a clinical trial may be needed to validate a new process and to maintain licensure of a product. This compounded risk of biological and physical variability makes vaccine manufacturing more challenging than typical small molecule pharmaceuticals and is a primary root cause of the high proportion of vaccine manufacturing failures and supply shortages [7,8]. This is also the main reason why the number of vaccine manufacturers that succeed and thrive remains low despite unmet demand for many vaccines globally. Moreover, individual vaccine prices do not always decline, even after the patents expire, in contrast to pharmaceutical products. In fact, many vaccine patents protect the manufacturing process rather than the antigen that is produced by the process, which is not always the analogous case for small molecule pharmaceutical products. These process patents may present a more significant barrier to entry than the patent on the vaccine composition itself.

2.1. Process development and maintenance

Significant changes in the manufacturing process, such as new facilities, manufacturing equipment or changes in raw materials, will typically trigger new regulatory requirements, including clinical trials. These requirements will confirm that the vaccine is still effective and comparable to the product produced by the original vaccine process and studied in the original clinical studies. As this is a significant obstacle for continuous process improvement and process modernization for vaccine manufacturers, it is optimal to have visibility into how the product will be made at commercial scale early in the development process. This prevents having to maintain a suboptimal manufacturing process for the long life-cycle of the vaccine. Emphasis on process development is a major success factor in being first to market with new biopharmaceuticals and inadequate process development is often implicated in late stage product development failures [9,10]. Manufacturers are challenged to balance the competing goals of speed to market and process optimization; getting to market earlier increases revenue in the short term, but locking in a further optimized process may generate cost savings over the entire vaccine life-cycle.

2.2. Life cylce and lead time

Most vaccines have a long life-cycle; some vaccines used today were developed in the 1940s and 1950s and remain essentially unchanged [7]. To maximize a vaccine's life-cycle, raw material and component supplies must be available and consistent in composition for decades. Optimal and efficient process development requires a sustained supply of quality raw materials from reliable vendors. Competitive pressure from other industries for the same materials can increase cost and interrupt supply. Likewise, production processes may need to be adapted as technologies advance and production components (e.g., filters and resins) change over time.

The lead time to produce a vaccine lot ranges from several months (e.g., influenza vaccine) to three years [8] (e.g., pentavalent and hexavalent combination vaccines) and vaccine shelf-life generally ranges from one to three years. The vaccine must conform with release specifications for the duration of manufacturing and storage, and stability of the product must be confirmed through long-term stability studies. Even when vaccines have been licensed, several lots are tested for stability each year to confirm that any process changes made did not have a deleterious effect. Stabilization may be achieved simply by managing pH with the appropriate buffer preparations, or for products that are inherently unstable such as some live viral vaccines, by lyophilizing (freeze-drying) to remove water. Lyophilizing creates a dry form that is

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