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Overcoming Challenges in Oligos Manufacturing: Within an Enterprise Framework

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Abstract

This article explores the diverse and intricate challenges associated with the manufacturing of oligonucleotides, which are synthesized DNA fragments crucial for various applications in research, diagnostics, and therapeutics. The manufacturing process of oligos is highly complex, encompassing numerous technical and logistical hurdles that must be addressed to ensure both efficiency and quality. We will examine the specific challenges in oligonucleotide production, including ensuring high fidelity in synthesis, managing the variability of starting materials, and maintaining stringent quality control standards throughout the production process. Additionally, we will examine how contemporary manufacturing solutions can be effectively integrated with enterprise architecture frameworks, particularly SAP, to create a robust and streamlined operational model. By harnessing advanced technological innovations and integrating them into an established enterprise system, manufacturers can overcome long-standing challenges in the oligonucleotide synthesis industry, leading to improved productivity, reduced costs, and enhanced product reliability. This article will offer insights into these strategies and their potential impact on the industry landscape.

Keywords: Oligos, Manufacturing, MES, Production Planning, Detailed Scheduling, Synthetic DNA, SAP, Capacity Planning, SAP Detailed Scheduling board, Production order

1. Introduction

Introduction about Oligos

Oligonucleotides, commonly known as oligos, are concise sequences of nucleic acids, which can either be DNA or RNA. These segments are gaining significant traction in the biopharmaceutical manufacturing sector due to their versatile applications. Their design allows for tailored manipulation, making them valuable tools in research, diagnostics, and therapy.

In therapeutic contexts, oligonucleotides can be engineered to alter the expression of proteins associated with various diseases, offering innovative approaches to treatment. While many currently available oligonucleotide therapies target rare diseases, there is a noticeable trend towards the development of treatments for more prevalent health issues, including widespread conditions like cardiovascular diseases. This shift is indicative of the expanding potential of oligonucleotide-based therapies to address a broader patient population, which is particularly exciting for the field.

Despite the promise these drugs hold, the biopharmaceutical industry faces significant hurdles that must be overcome to increase the production of oligonucleotides to a scale capable of meeting the demands of a large patient base. Challenges such as the synthesis process, cost-effectiveness, quality control, and regulatory hurdles will need strategic solutions to enable wider access and utilization of these innovative therapies. In this article, we will delve deeper into these obstacles, exploring current issues and potential pathways forward to enhance the efficacy and availability of oligonucleotide treatments.

2. Challenges in manufacturing oligos

The manufacturing of oligonucleotides at a large scale presents multiple complex challenges, particularly concerning operational scalability, cost-effectiveness, and sustainable practices.

a) Scalability

Solid-phase synthesis is a widely utilized methodology in the chemical production industry that enables the stepwise assembly of molecules while they are covalently attached to a solid support. This technique has been foundational for synthesizing oligonucleotides mainly in academic research and limited-scale production environments. However, transitioning to large-scale manufacturing with solid-phase synthesis poses significant hurdles.

As the demand for longer oligonucleotides rises—especially those intended for therapeutic applications like antisense oligonucleotides—the challenges associated with their synthesis become increasingly pronounced. The confined space of the solid support limits the efficiency of coupling reactions, leading to incomplete reactions and potential misincorporation of nucleotides. Such occurrences contribute to a noticeable increase in sequence errors, which can severely compromise product quality and consistency across batches. These factors are critically important for regulatory compliance in the production of oligonucleotides meant for clinical applications.

Moreover, despite the burgeoning interest in oligonucleotide-based therapies, the current global manufacturing infrastructure remains considerably underdeveloped. Many manufacturers are not equipped with the specialized tools and processes necessary to scale oligonucleotide production while adhering to rigorous quality assurance and quality control standards mandated for the creation of clinical-grade products.

b) Cost & Efficiency

The commercial-scale manufacturing of oligonucleotides grapples with substantial efficiency challenges, largely driven by both economic and technical factors.

One of the foremost drivers contributing to the high cost of oligonucleotide manufacturing is the expense of high-purity raw materials required for synthesis. The production of reliable oligonucleotides necessitates the use of high-quality reagents and specialized solvents to ensure accurate nucleotide incorporation throughout the synthesis process. As the complexity and length of oligos increase, so do the costs associated with these critical components.

Inefficiencies are prevalent throughout the oligonucleotide manufacturing process, primarily due to the need for excess materials to initiate and ensure the completion of chemical reactions. The limitations inherent in solid-phase synthesis become evident with each nucleotide addition, as reaction yields marginally decline, leading to cumulative product losses as oligos grow longer. This inefficiency not only diminishes overall yields but also results in the wastage of costly reagents, thereby escalating the total manufacturing costs.

The purification phase of oligonucleotide production represents a significant bottleneck, accounting for nearly 50% of the total materials consumed during manufacturing. Given the significance of removing any impurities to guarantee product quality and regulatory compliance, this stage presents both logistical challenges and heightened costs. Additionally, the solvents and chemicals employed in oligo synthesis and purification processes often present toxicity issues, necessitating meticulous disposal methods. Adhering to environmental regulations and managing waste effectively incurs substantial operational costs, which can be particularly burdensome for companies engaged in large-scale production.

c) Sustainability

The inefficiencies described earlier, including the excessive use of reagents and the financial burden of waste management, significantly hinder the sustainability of oligonucleotide manufacturing practices.

While there are aspects of oligonucleotide production that align with “green chemistry” principles—such as the inherent low toxicity of oligos and their ability to decompose into naturally occurring degradation products—certain characteristics of the oligonucleotide manufacturing process pose challenges in adopting green chemistry solutions. For instance, the extensive generation of organic and aqueous waste during synthesis and purification remains a significant hurdle. Additionally, the structural complexity of oligonucleotides limits the effectiveness of emerging green chemistry techniques, including enzymatic synthesis, which could otherwise provide more sustainable manufacturing alternatives.

Furthermore, the lack of circular economy practices in the oligonucleotide production process exacerbates sustainability concerns. Unlike the production of small-molecule pharmaceuticals, where some materials can be recycled or repurposed, oligonucleotide manufacturing rarely integrates circular economic models. The precise nature of the synthesis required, combined with the utilization of unique, specialized reagents, hampers efforts to recycle or recover materials, resulting in a predominantly linear production model that is inherently unsustainable.

3. Solutions in manufacturing oligos

The intricate nature of technical and infrastructural challenges outlined previously emphasizes the critical need for ongoing innovation in the processes involved in oligonucleotide manufacturing. As the demand for these advanced therapeutics continues to rise globally, it becomes increasingly vital to invest in expanding production capacity to meet this need effectively.

One of the most daunting challenges in oligonucleotide manufacturing is the purification process, which stands out as one of the most complex and labor-intensive phases. This process necessitates meticulous management of substantial fluid volumes, which demands not only advanced equipment but also highly skilled personnel to ensure precision at every step. The purification stages require stringent adherence to quality control standards, as even the slightest variation can compromise the therapeutic efficacy and safety of the final product.

Moreover, the manual labor involved in these purification processes often results in inefficiencies that hinder productivity, particularly in large-scale manufacturing environments. By tackling these specific pain points—such as optimizing automation techniques, enhancing process scalability, and streamlining workflows—industry stakeholders can significantly bolster overall manufacturing efficiency. Addressing these challenges is not simply a matter of improving operational capacity; it is also essential for keeping pace with the fast-evolving landscape of oligonucleotide drug development and ensuring that patient needs are met effectively and promptly.

A) Manufacturing Execution System with SAP

Manufacturing processes can be significantly enhanced through the implementation of advanced Manufacturing Execution Systems (MES). However, the true potential of these systems cannot be realized unless they are seamlessly integrated and effectively communicate with the broader enterprise framework. When it comes to optimizing the planning and manufacturing of oligonucleotides, achieving this level of integration is crucial.

To tackle the complexities associated with oligonucleotide manufacturing, utilizing advanced connectors and features that integrate the MES fully with Enterprise Resource Planning systems, such as SAP, is essential. This strategic alignment enables an end-to-end solution, addressing the unique challenges faced in oligos production. By ensuring that these systems work in harmony, manufacturers can streamline operations, enhance data accuracy, and improve overall efficiency in their manufacturing processes.

This scope item outlines a comprehensive integration of SAP S/4HANA Cloud with a third-party Manufacturing Execution System (MES) deployed on-premises, facilitating enhanced production operations.

The integration aims to seamlessly connect the MES directly to the SAP S/4HANA environment. This connection benefits manufacturing personnel by offering them a consolidated view of ongoing production activities and significantly enhancing the analytical capabilities available to management teams. In this context, SAP S/4HANA serves as the primary system of record for all master data, while the MES or shop floor system maintains the authoritative records for all work in progress (WIP) data.

Process Steps:

1. Production Order Creation and Management

Initiate, schedule, and release production orders directly within the SAP S/4HANA system.

2. MES Production Order Handling:

Subsequently, create and release these production orders within the MES or an equivalent shop floor system.

3. Data Synchronization:

Update production orders in the MES, ensuring that relevant information is communicated back to the SAP S/4HANA system promptly.

4. Confirmation Process:

Confirm the production orders directly in the SAP S/4HANA environment after the necessary updates.

B) MES Integration with Production Order

With respect to the integration process, any modifications made to a production order in the SAP S/4HANA system are synchronized with the MES using Data Replication Framework (DRF) functionalities.

If DRF integration for the production order is established, replication is automatically triggered under various scenarios, particularly within the relevant transactions, provided that the production order has been released. During this operation, the system evaluates filter criteria and additional prerequisites to facilitate the distribution process. In instances where a distributed production order is altered, the system automatically initiates another distribution to the MES. Customization options allow you to determine which types of changes can be permitted after the initial distribution.

It is important to note that distribution through the transaction titled “Select Transaction Data for Transfer” (POIT) is no longer applicable for production orders that adhere to the specified filter criteria within the DRF.

Prerequisites

To optimize the integration with production orders, it is advisable to utilize the Customizing activities available under the section for Production Integration with a Manufacturing Execution System. Within this framework, the guideline "Integrate Production Orders with a Manufacturing Execution System" serves as an essential resource. Additionally, the section “Enhance IDocs for Integration with an MES” encompasses a Business Add-In (BAdI) tailored for the adjustment of the IDoc LOIPRO05.

Recent Enhancements in Production Order Integration:

1. Order Confirmation:

- In order to maintain data consistency between SAP ME (Manufacturing Execution) and the SAP S/4HANA framework, direct entry of quantity confirmations for distributed production orders is restricted. Instead, confirmations for production quantities and scrap pertaining to distributed orders must be conducted exclusively through the MES. However, other data inputs, such as working times for these distributed production orders, remain permissible. Once a confirmation is processed, it cannot be reversed. The integration now also allows specifying batch characteristics for batch-managed materials and serial numbers for materials subject to serialization during the confirmation phase with the MES.

2. Serial Number Management:

- Each production order can be transmitted multiple times from the SAP S/4HANA system to the MES. Serial numbers intended for finished products can be predetermined within the production order itself. The communication of these serial numbers to the MES is facilitated using the IDoc LOIPRO05. Additionally, serial numbers designated for entry or deletion undergo stringent checks as part of the serial number management process. These checks, configurable in the Customizing settings, prevent inadvertent deletions of serial numbers that have already been assigned.

3. Documentation and Long Texts:

- Users now have the capability to append long texts and document files to the production order. This encompasses all document types related to the order header, operations, or production resources/tools. For instance, if work instructions need to be linked to a production order, they can either be integrated directly or included as part of production resources/tools. Documents categorized as 'Released' will also be transmitted to the MES. The technical keys and URLs linking back to the original documents stored in the system are included in this transmission. Users can access the original documents from the MES simply by using these provided URLs.

4. Benefits

Advantages of Integrating Advanced Solutions into Manufacturing Processes:

1. Enhanced On-Time Delivery: The adoption of sophisticated algorithms and real-time analytics allows manufacturers to refine and optimize their production schedules significantly. These advanced systems leverage historical data and market trends to produce highly accurate forecasts. Consequently, manufacturers can better align their production timelines with customer expectations, ensuring that products are delivered punctually. This not only boosts reliability but also elevates customer satisfaction, fostering long-term relationships and repeat business.

2. Increased Operational Efficiency: The implementation of automated scheduling systems significantly reduces reliance on manual input, conserving valuable time and mitigating the risk of human error. These automated systems dynamically adjust schedules according to the availability of machinery and the allocation of workforce resources. By identifying and addressing potential production bottlenecks in real-time, manufacturers can streamline workflows, increase overall throughput, and reduce downtime, leading to a more efficient operation.

5. Conclusion

The intricacies of contemporary manufacturing scheduling pose significant challenges; however, these hurdles can be navigated effectively with strategic approaches. By harnessing the power of real-time data and predictive analytics, modern scheduling solutions are revolutionizing the way manufacturing firms manage their production timelines. These innovative systems utilize optimization techniques, permitting real-time adaptations that respond to variations in customer demand, equipment availability, and labor capacity.

Furthermore, the user-friendly interfaces of these scheduling tools empower manufacturers to quickly interpret vast amounts of data and make informed decisions swiftly. This empowers organizations to minimize the inefficiencies typically associated with traditional scheduling methodologies. The shift towards advanced scheduling solutions not only enhances operational productivity but also positions manufacturers to react promptly to evolving circumstances, ensuring agility in a fast-paced market.

For manufacturers seeking to gain a competitive edge, adopting these state-of-the-art scheduling solutions is crucial. By integrating such technology into their operations, they can significantly improve operational efficiency, enhance on-time delivery rates, and gain a substantial competitive advantage in an increasingly competitive landscape. Adopting these progressive practices enables manufacturers to meet the industry's demands and thrive in a vibrant and dynamic manufacturing environment.

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