Plan Now or Fail Later

Exploring how raw materials matter and impact the success or failure of a pharmaceutical development project

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INTRODUCTION

Accelerating the development of mRNA vaccines and therapeutics requires the selection and use of raw materials designed to meet critical process, scale, quality, and regulatory needs. Choosing appropriate materials saves time and money. This article reviews several examples of how raw material selection either accelerated or stalled regulatory approvals. It focuses on some of those critical decisions that need to be made when developing an mRNA therapeutic or vaccine, and why choosing the right raw material can lead to the ultimate success or failure of a pharmaceutical development project.

GOALS AND CRITERIA IN RAW MATERIAL SELECTION IN MAKING AN mRNA OR THERAPEUTIC

When it comes to selecting raw materials for an mRNA vaccine or therapeutic, Quality is always the first requirement. This includes not only analytical quality, but also the availability of material origin traceability that allows you to know where that material came from, and that it is animal-free in origin and β-lactam free as well. Flexibility is an important criterion too, because during process development, there's usually some degree of customization with material about concentrations or formulations. No matter what materials are chosen, they will all need to stand up to intense regulatory scrutiny.

Consistency is also important, as batch-to-batch variation will impact the final product and cost of manufacture. Vendors must be able to supply consistent product at the manufacturing scale required to meet the anticipated project timeline and production demands.

Selecting a raw material for a vaccine or therapeutic that has been previously utilized for mRNA therapeutic or vaccine production and has successfully passed

regulatory scrutiny significantly reduces the risk of project delay or failure. A complete regulatory documentation support package should also be supplied by the vendor. This will help prove to the regulatory authorities that the raw material choices have met all required quality guidelines and are acceptable for use in a therapeutic or vaccine.

Last, but not least, is considering the need for scalability. Some vendors may not have the experience or equipment required for consistently providing materials at large scale production levels. It is therefore important that many questions are asked of vendors to help ensure they can provide adequate quantities of materials at different stages of the process in line with the project timeline.

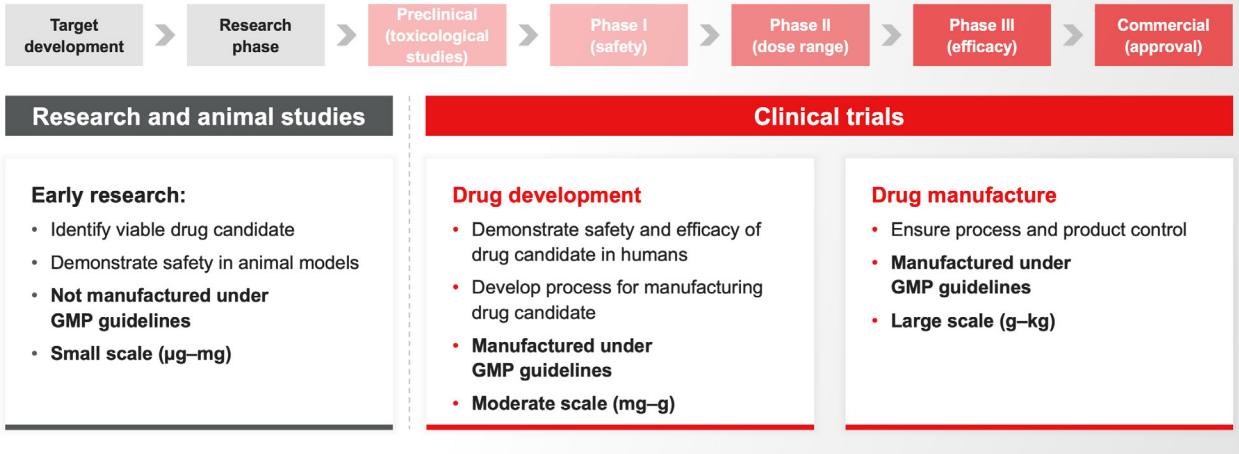
KEY RAW MATERIAL DECISION POINTS AND IMPORTANT SELECTION CRITERIA

Making raw material decisions typically come in phases, beginning with process development, and continuing through to clinical trials. What needs to be achieved for raw material selection is usually a little different for each of these phases as shown in **FIGURE 1**.

The criteria used for raw material selection depends heavily on the phase of development the project is in. In early development, the overall focus of raw material selection will be the suitability of the materials for use in process development and optimization. Materials must be able to be customized, meet quality and purity standards and be animal-free origin. They must also be scalable to follow the process development and scale up needs of the project. In addition to these, it is important to keep a line of sight to GMP production. Incorporating key quality aspects in raw materials as early as possible will help reduce the workload later in development. To help accelerate progress, the chosen raw material products should ideally be proven by having been previously utilized for commercial GMP manufacture of an mRNA therapeutic or vaccine.

The later phases of development and manufacture for raw material selection focuses on large scale GMP production. At these stages, having used proven raw materials in the early development stage should provide the confidence that materials used are suitable for GMP production and help accelerate the overall project timeline. High purity levels and animal-free origin are also now a must for the raw materials being used. Incorporating aspects of GMP production in early development including scalability, consistency, and regulatory support, will now also pay dividends in accelerating GMP production efforts.

FIGURE 1: Key Phases for Raw Material Decision Points



RAW MATERIALS IN mRNA VACCINE PRODUCTION

Although the SARS-CoV-2 virus initiated development of mRNA vaccine technology, COVID-19 created the opportunity for mRNA vaccine technology to really take off. mRNA technology enables the ability to create tests and bring vaccines to market in record time. This scientific achievement cannot be underestimated, as the billions of mRNA vaccine doses that have been manufactured and delivered using this technology have greatly benefited all mankind. Not only did this require a revolution in medicine in terms of the mRNA technology, but there was also a revolution in the manufacturing technology to enable this breakthrough in modern medicine. Without a commensurate revolution in manufacturing and delivering raw materials, mRNA technology would not have been as successful as quickly as it ultimately was. A large part of this success was in choosing a good partner for supplying raw materials and making the right choices for materials at each stage of development to overcome the significant hurdles relating to the raw material quality, scale, and consistency.

Producing mRNA vaccines is related, but significantly different than manufacturing traditional vaccines. mRNA vaccines are produced biosynthetically rather than utilizing culture cells. Consequently, the steps used to make an mRNA vaccine differ from traditional vaccine manufacture. There are a number of steps for mRNA vaccine production including plasmid production, mRNA synthesis, mRNA purification, and formulation. A significant number of raw material choices occur in the mRNA syntheses step, as the bulk of the raw material used in the mRNA drug substance reside here. **FIGURE 2** outlines the workflow for mRNA vaccine production.

The raw materials for mRNA production can be broken down into three different components which include mRNA building blocks, in-vitro transcription (IVT), and mRNA modification. The building blocks for mRNA therapeutics and vaccines are typically nucleotides or modified nucleotides. The IVT reaction utilizes enzymes and associated materials as well as a plasmid DNA template. The enzymes used for IVT include restriction enzymes and T7 RNA polymerase, as well as accessory systems like inorganic pyrophosphatase and RNase inhibitors. The mRNA produced by the IVT reaction will also require the use of modification systems for capping and tailing the mRNA to enhance biological activity and stability as well as reduce the immunogenicity of mRNA. While the materials and steps for making an mRNA vaccine are somewhat simpler

FIGURE 2: Workflow for mRNA Vaccine Production

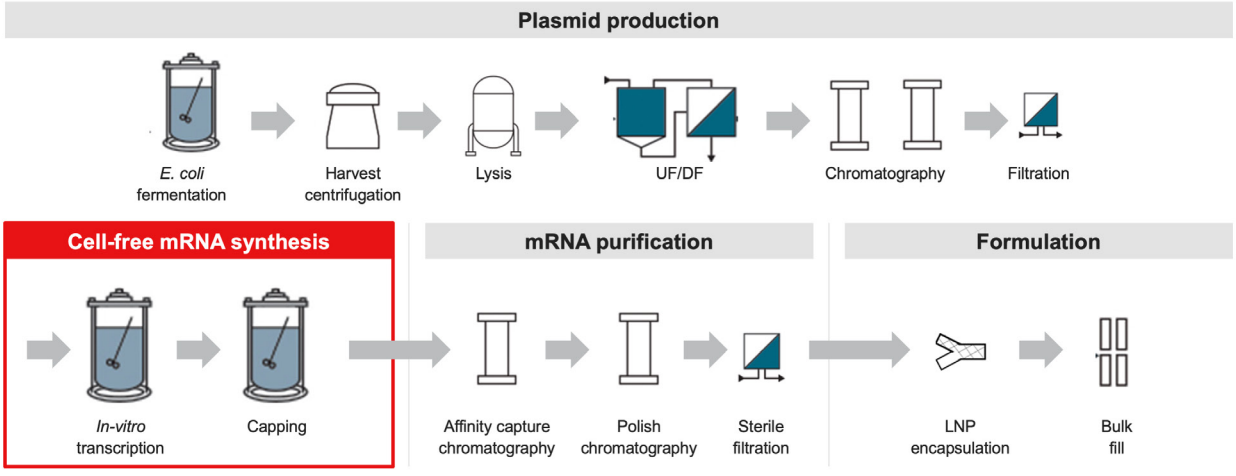
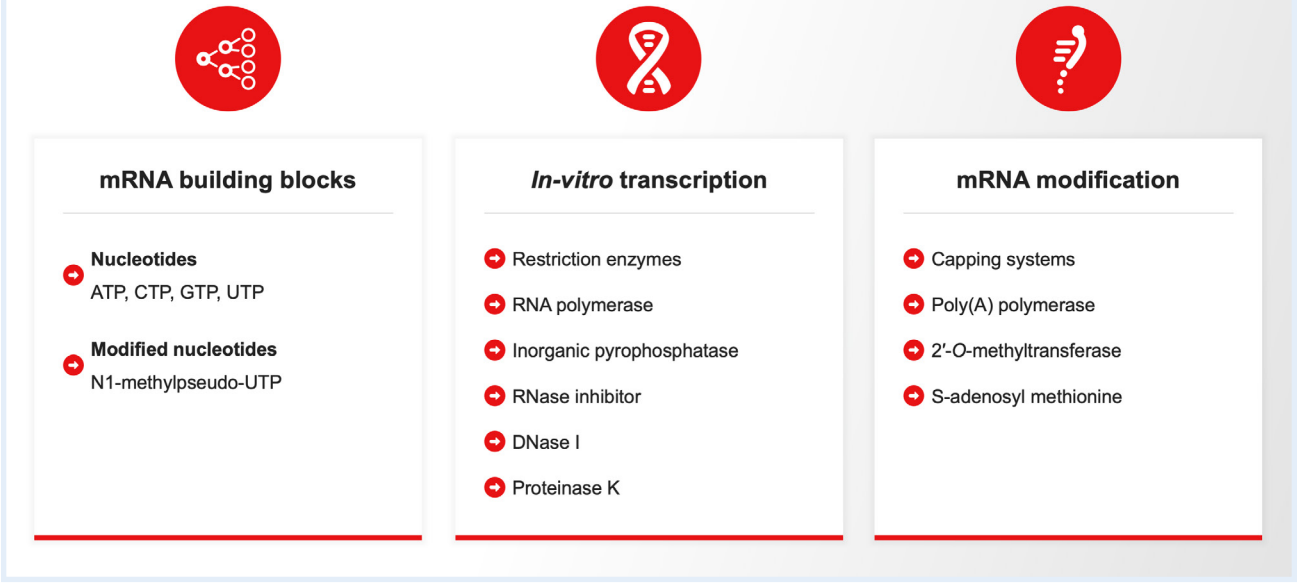


FIGURE 3: Materials for Making a mRNA Vaccine



than the more traditional vaccine manufacture, they are still complicated. The three components are summarized in **FIGURE 3**.

CASE STUDY 1 - THE FAST AND THE FURIOUS

This case refers to a biotech company that saw an opportunity with mRNA vaccines. They quickly determined their target gene and came up with their sequence and DNA plasmids. Their objective was to develop an mRNA vaccine that could immunize 30 million patients. In a hurry to get to pre-clinical and clinical stages, they used a non-standard research grade restriction enzyme. They invested a lot of time scaling up, manufacturing the plasmid containing the target gene sequence, and producing the mRNA in preparation for their clinical trial. However, because they used a non-standard research grade enzyme, regulatory authorities asked for verification that the material was animal-free in origin, as well as required full traceability of the enzyme's origins. Unfortunately, the vendor was unable to meet these requirements. There was no alternate vendor that could comply. As a result, the project is currently delayed for years, while other vaccine developers have passed the approval process and have brought their vaccines to market. Ultimately, they will have to re-synthesize the material again and have taken an estimated revenue loss of $300 to $700 million.

CASE STUDY 2 - HOUSTON, WE HAVE A PROBLEM

In this case study, the company was using process development grade material for an mRNA vaccine and two impurities were identified in the mRNA product. These impurities were not only impacting the overall purity of what they were manufacturing, but also reducing the transcription efficiency of the reaction. Knowing these impurities were product rather than process related, it was ultimately determined that they were coming from the raw materials.

The company went back to the supplier, and unlike the example in Case 1, the supplier worked with the company to identify the source of the impurities. The supplier formed teams with their pharmaceutical partner and traced the source of the impurities to the supplied nucleotides. A pre-validated alternate supplier was found that didn't have the

issue with impurities, and the impurities were removed from the nucleotide raw materials. Good partnership and good science resulted in a quick resolution to a roadblock. The production of clinical trial material was not affected, there was no rework of clinical trial material, and the company brought their product to market on time. This demonstrates the importance of working with a vendor with a good quality control system in place.

CASE STUDY 3 - GO WITH THROTTLE UP

This case is different than the previous two examples in that it involved a pharmaceutical company looking for a partner. They were working on a global scale mRNA vaccine and needed multiple enzyme and nucleotide raw materials as fast as possible. They searched for an existing supplier that could supply multiple raw materials on a global scale and couldn't find one. After approaching multiple vendors, they found one that agreed to develop the materials to meet their very strict requirements. A partnership with a dedicated project team was formed with the pharmaceutical company. The pharmaceutical partner worked on the drug development, while the supplier worked on a new innovative raw material manufacturing process.

Just as much as there was a revolution in mRNA technology, there was a revolution in providing the raw materials that were needed to fuel the mRNA vaccine revolution. Because the vendor and a pharmaceutical partner worked so closely together and were very much aligned, they were able to meet the accelerated timeline the pharmaceutical company demanded. The mRNA vaccine got to market on time, and now production is up to billions of doses.

THERAPURE AND THERAPURE PLUS PRODUCTS

Thermo Fisher and TheraPure products are specifically designed to be used in the manufacturer and development of mRNA vaccines and therapeutics. Thermo Fisher has a comprehensive portfolio of products and services that meet the critical process, scale, quality, and regulatory needs. The TheraPure product portfolio is central to that entire process because these products have been designed to fit the development and manufacturing process.

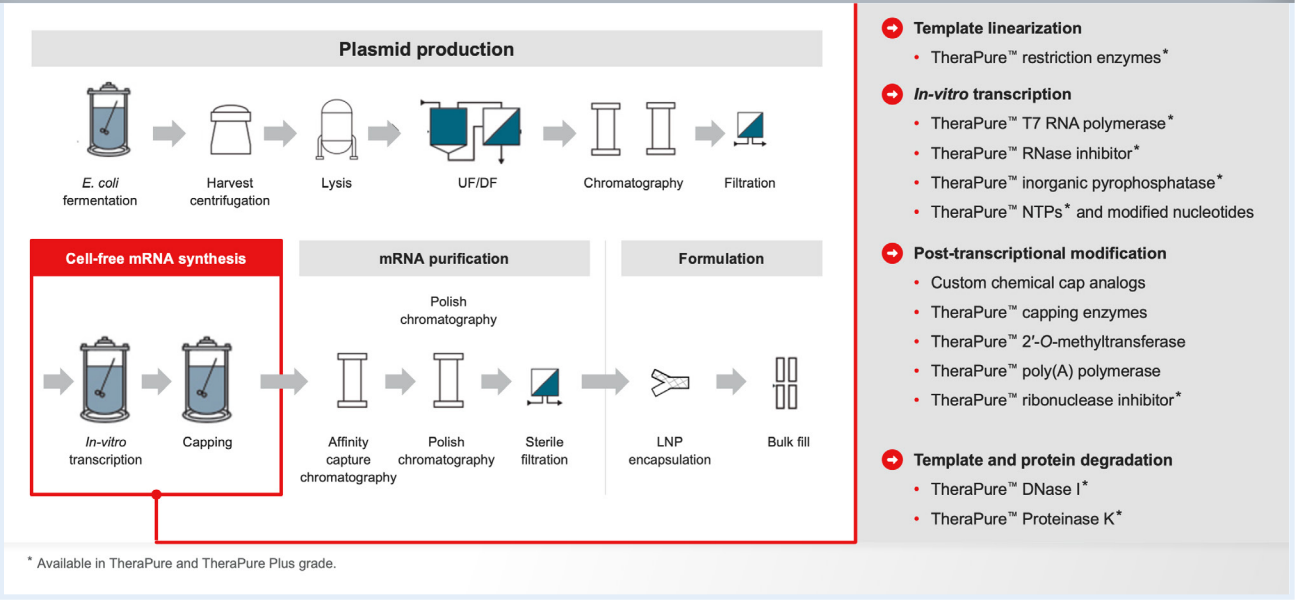
Thermo Fisher offers two grades of raw materials, TheraPure and TheraPure Plus grade. The TheraPure grade is recommended for early-stage development where some flexibility and customization may be required. In addition to a degree of flexibility, TheraPure grade products also have some line of sight to GMP production, in terms of purity, animal-free origin, and process scalability.

TheraPure products are specifically designed to be used in the manufacturing and development of mRNA vaccines and therapeutics.

The TheraPure Plus products, on the other hand, are designed to meet the needs of late-stage development and clinical and commercial manufacture. They are heavily supported with a robust quality management system, in terms of purity, animal-free origin, scalability, consistency, and regulatory support. They have been used in the production of mRNA vaccines and therapeutics that are on the market today.

The TheraPure portfolio is focused in on the IVT mRNA synthesis step of the process. It includes all the materials needed for mRNA production, from the restriction enzymes to the IVT enzymes, post-transcriptional modifications, and post-reaction cleanup enzymes (**FIGURE 4**).

FIGURE 4: The TheraPure Portfolio



CONCLUSION

There are many considerations when making raw material choices for development and manufacturing of mRNA vaccines and therapeutics. Quality is number one, as well as the quality management system that supports a particular raw material. In addition to quality when choosing raw materials, flexibility, consistency, and scalability need to be closely considered.

Regulatory support for raw materials is another key, as the regulatory scrutiny on the initial mRNA vaccines will be thorough. Supporting the process development and manufacturing timelines and scale up requirements will require a reliable supply chain that is capable of meeting the typical aggressive demands of drug developers.

Going with raw material products that have successfully gone through the process before and are produced by a partner who works closely with their pharmaceutical clients provides a strong level of confidence when choosing a raw material. It avoids the extreme risk of being the first company to go to a regulatory agency with a material from a vendor whose materials have not been through the approval process before.

From early-stage to late-stage, TheraPure products for mRNA production are raw materials that have the quality to fit the mRNA development and manufacturing process. They've been successfully proven and selected by several companies for use in the production of their mRNA therapeutics or vaccines, even on a global scale.