
# Controlling raw materials variability for batch consistency when scaling up

Raw materials are a critical component of vaccine development. Variabilities in raw materials can lead to variabilities in batches, which can result in cascading problems for vaccine developers when scaling up. As such, the quality of raw materials is important in maintaining batch consistency, and steps to minimize variability in raw materials should be a top priority for a developer. From choosing a supplier with a robust supply chain and strict raw materials characterization methods, to strict analytical testing and the use of advanced products, there are several key considerations for vaccine developers.

## Sources of raw material variability

Within vaccine manufacturing there are several sources of raw material variability that must be considered to help control consistency. Raw materials of animal origin, such as serum, can be inherently variable due to their biological nature, with fluctuations in growth factors and nutritional composition. Additionally, variability in raw materials may be present in the form of trace impurities and microbiological contaminants, which can cause a variety of negative effects on both processes and products. When scaling up from the bench to a bioreactor, inconsistencies within the raw materials are amplified, resulting in reduced productivity and lower yields—or no yields at all if the process no longer works—between batches. Beyond these effects, raw material inconsistencies can also affect product performance; for example, trace impurities or contaminants that are carried over into the final product alter the efficacy and safety of the batch [1]. This may lead to batch failures, causing costly slowdowns as well as waste of expensive raw materials.

With these challenges in mind, it is critical to consider the potential variability of each raw material used in your process. There are many steps that should be taken to mitigate this variability from the early stages, so it does not become a problem during scale-up.

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## Vendor supply chains

A key factor in reducing the opportunity for raw materials inconsistency is partnering with a supplier with strict raw material characterization and global manufacturing and sourcing redundancy. Changes in a raw material at any point in the vaccine development process—for example, due to different raw material sources, manufacturer processes, or supplier changes—may introduce variabilities, and as a result, impact the process. It is therefore essential to work with a vendor that can provide a consistent supply of raw materials. In addition to strict characterization and quality control measures, a vendor should offer dependable supply chains with global sourcing to reduce the impact of local issues. Suppliers should have a robust qualification process for their own vendors, giving customers confidence across the entire supply chain. A reliable supplier will have multiple qualified vendors that can provide raw materials at the same high level of purity. This redundancy helps minimize vendor changes that can often introduce more variability into a process.

An additional consideration when choosing a supplier is the source of raw materials used in its non-GMP and GMP media. Ideally, raw materials for both should be obtained from the same source, helping to minimize any opportunity for inconsistency when transitioning from non-GMP to GMP during scale-up.

## Characterization

A reliable supplier will have strict and established methods for characterizing raw materials, including extensive programs for profiling trace impurities that may be transferred to the final product. Sensitive techniques, such as inductively coupled plasma mass spectrometry (ICP-MS), which can detect very low levels of trace metals, are important in creating these impurity profiles. It is also critical that suppliers have an in-depth knowledge of which impurities are most significant in their products and processes, with knowledge of these key contributors enabling them to monitor and maintain raw material consistency. In addition, it is necessary to characterize incoming raw materials to verify the identity of the products the supplier has received. Techniques such as Raman spectroscopy and Fourier transform near-infrared (FT-NIR) spectroscopy can be used to achieve this. Raman spectroscopy enables rapid and convenient identification and quantification of contaminants [2], while FT-NIR spectroscopy can rapidly characterize a raw material [3]. These types of analyses are relatively quick and easy and help provide confidence in the identity and consistency of the starting materials.

## Product considerations

An important consideration in managing raw material variability is product choice. Of the raw materials involved in vaccine manufacturing, serum in particular can cause challenges due to its undefined nature. With critical factors difficult to define, fetal bovine serum (FBS)—which is often used in vaccine manufacturing—can be inherently variable, and there are safety considerations surrounding its use relating to bovine spongiform encephalopathy (BSE), a prion disease. Careful sourcing and extensive qualification of serum are therefore essential to minimize variability and risk. Alternatively, another option is utilizing innovative, serum-free products. These products can provide the essential components associated with serum, such as adhesion or growth factors, while bypassing a significant potential source of variability in the process.

While serum is often flagged as the most potentially variable component, media and supplements can also introduce variability as they may be complex and made up of multiple components [4]. Chemically defined (CD) and animal origin–free (AOF) products offer greater consistency in terms of raw material composition, as their exact components are known so they do not contain any undefined or unqualified factors. These products can inherently reduce variability when compared to biological products, with undefined critical factors and potential biological contaminants. It is worth noting, however, that variability may still be present even in these advanced products and, CD does not necessarily mean “chemically pure”. Trace metal impurities or microbiological contaminants may still be found, emphasizing the continued importance of strict raw material characterization and analysis.

## Optimization and analytics

It is also important to consider variability in the initial development stages, enabling you to optimize your raw materials early on to provide you with the confidence that your process will work at scale. A supplier can employ techniques such as chemometrics and spectroscopy to understand the key drivers of variability and how these will affect your products, allowing these to be more carefully managed. Omics approaches enable modeling of the process in order to optimize performance and achieve consistent critical quality attributes [5]. Process analytical technology may also be used throughout media production to manage the quality of the raw materials produced and limit variability [6]. Other analytics, such as spent media analysis, can help troubleshoot a process to understand why there might be variability in performance or yield. By working with a supplier that can provide support with these analytical methods early on, raw materials can be optimized, preventing the need to make changes during scale-up that could result in inconsistencies.

## In-process factors

In addition to considering variability within the raw materials themselves, it is also important to consider how factors within the process could impact variability. This includes any required process steps, such as hydrating dry format materials or adjustments to pH and osmolality. These steps introduce more opportunities for inconsistency, but products employing advanced formats, such as innovative dry powder, can simplify these steps to help reduce the guesswork otherwise involved, therefore contributing to improved consistency.

## A combination of measures for raw material consistency

Properly considering your raw materials and having strict raw material characterization methods in place is essential to maintain batch consistency and quality of your products when scaling up vaccine manufacturing. In addition to in-house characterization and quality control, choice of supplier can be critical in facilitating consistency throughout the scale-up process. Suppliers play a vital role in controlling consistency in raw materials, and the extent of their analysis and qualification should factor into supplier choice. Partnering with a supplier with strict controls on raw material characterization and extensive vendor qualifications may provide developers with confidence in the supply of their raw materials. In addition, innovative products in advanced formats can help minimize the potential for variability by removing the need for variable components and reducing the opportunity for user error. Beyond this, advanced analytical services can help to optimize and troubleshoot, limiting the likelihood of inconsistencies. With a combination of these measures in place, it is possible to control raw material variability and limit batch-to-batch inconsistency during vaccine development and scale-up.

### References


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