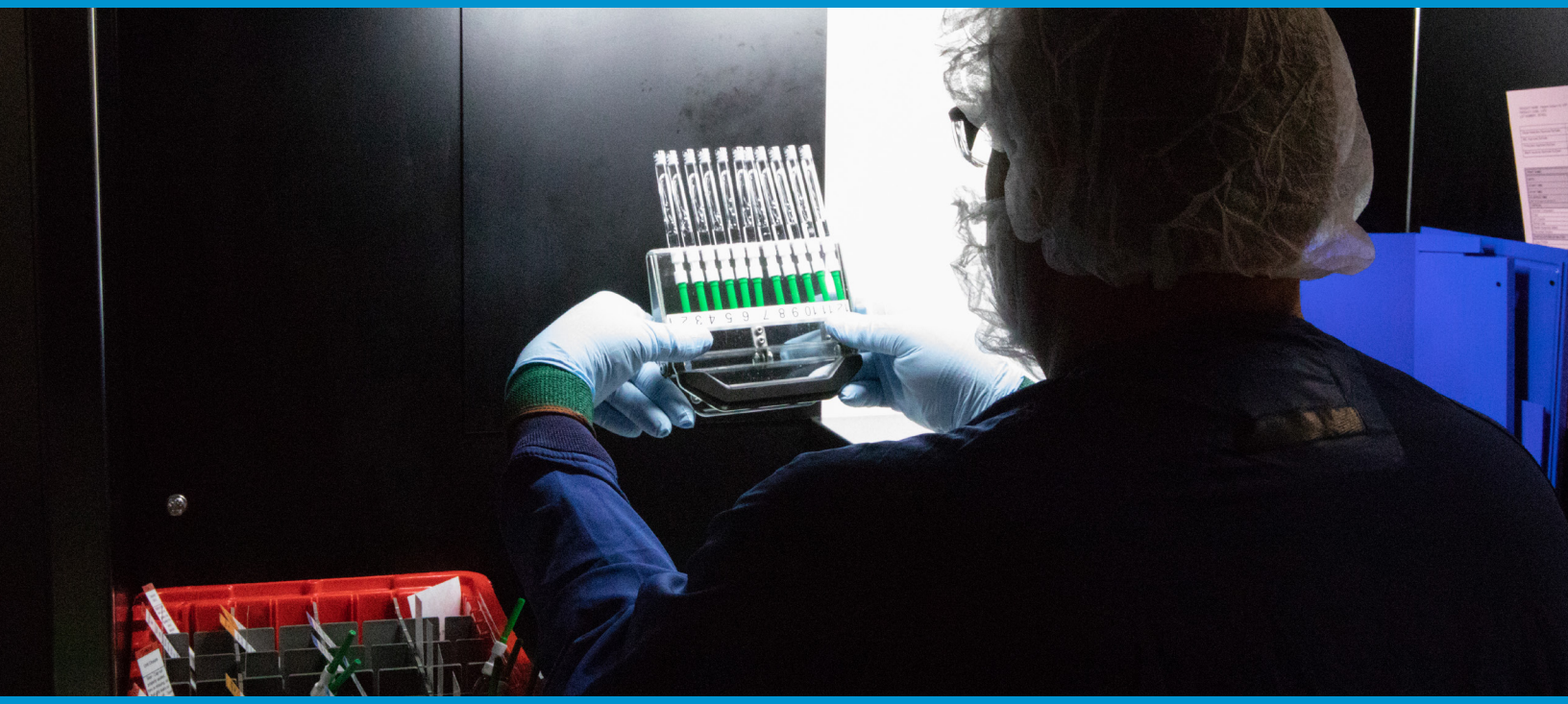
How successful CDMO collaboration sets the foundation for sterile injectable product success

Pfizer CentreOne

In the realm of Sterile Injectables (SI), sponsors come in a variety of sizes and with a range of experience levels. The oncology segment, which will drive much of the growth in the SI market (expected CAGR of 9.1%) in the coming years, is the focus of many drug developers with significant differences when it comes to history, footprint and experience.[1] The same is true for contract development and manufacturing organizations (CDMOs) and the dynamics of these outsourcing relationships have a huge influence on project success.

CDMOs work with all types of sponsors, from small, emerging, sometimes virtual companies, to large biotech and pharma companies. To accommodate such variety, CDMOs must make every possible effort to customize their operations to the sponsor's product technical needs without compromising quality or safety. The two mottos, "Right the First Time" and "No Cutting Corners Allowed" are pillars for a CDMO.

In this white paper, we discuss how a small or medium size biotech or pharma company can benefit from the experience and assistance provided by a CDMO.



Key considerations in the CDMO-sponsor relationship

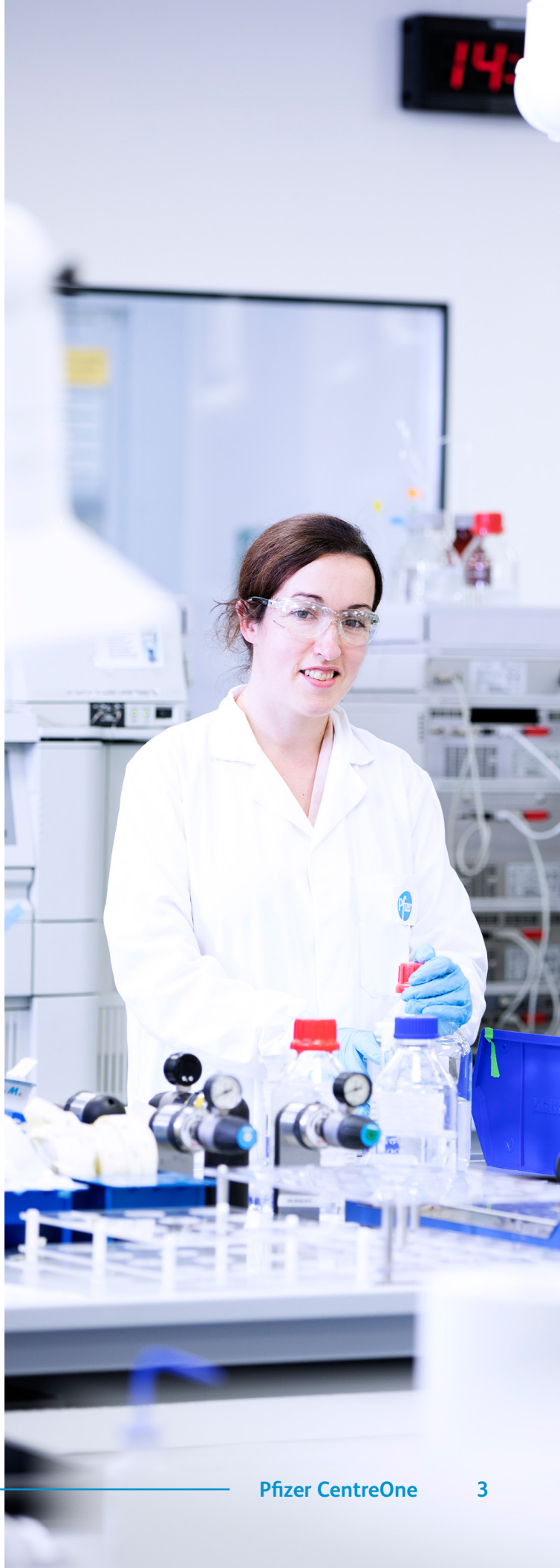
There are three main areas to consider in the CMDO-sponsor interaction:

1. The sponsor's needs for their product
2. The CDMO's flexibility to adapt to technical manufacturing requirements
3. The patient's need for a product that provides quality and safety

To a certain extent, the first two areas are influenced by the assigned budget tied to the manufacturing goods without compromising the safety and quality of the drug product.

A sponsor's main goal, irrelevant of its size, experience or capabilities, is to get its medicines to the patients who need them as soon as possible while gathering the most information about the drug product to support the product filing.

For CDMOs, the nature of the relationship will change depending on the characteristics of the sponsor. When dealing with a small company, for example, where the drug product manufacture and its accompanying process knowledge might be minimal, a great deal of CDMO collaboration might be required. This usually results in a more complex project when compared to more experienced pharma companies, which normally have a deeper understanding of their product and where the processes required to manufacture can be iterated from other or similar products in their pipeline. A CDMO can offer its experience, vast resources, and partnership to more inexperienced sponsors while having the capabilities and capacity to fulfill more transactional requirements from more sophisticated organizations.



On-boarding – from assumption to fruition

There are usually a good number of assumptions when a new sponsor presents a proposal for consideration. Both sides make projections and forecasts that can potentially make or break a fruitful partnership. Flexibility, transparency, and fluid communication, regardless of manufacturing experience and knowledge, are always the key to a successful endeavor, and they must start at this stage.

Sponsors need to map out their needs to jump start a project and make meaningful advances within a set timeline. CDMOs can facilitate this process with templated fact-finding documents or questionnaires to gather the necessary information.

Once there are both agreement and alignment between the parties, letters of intent/contracts are drawn and approved, and the initial fact-finding is complete, face to face technical meetings commence to define manufacturing and technical development requirements. During the first few discussions, a CDMO's experts might guide the sponsor to further evaluate or challenge some assumptions.

These challenges are often grouped into several key areas related to the overall manufacturing process activities. Relevant discussion and information-sharing needs to take place before embarking on each of these steps:

1. Product knowledge relating to basic analytical method and processes development
2. Early non-GMP batch manufacture and container selection
3. Batch record generation/Quality documentation
4. GMP batch manufacture
5. Process validation strategy/activities

In the following sections, Martin Gonzalez, Sr. Manager Formulation and Process Development at Pfizer CentreOne Technical Services, will provide an overview of each of these areas. Note that this is not a complete list of activities and assumptions.

Product knowledge – basic analytical method and processes development

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To bring a new product to market, critical knowledge of its properties, basic attributes, and its areas of opportunity are essential to success. A comprehensive understanding of the molecule and the processes involved in its manufacture are paramount to complete the difficult tasks that await later in the manufacturing process.

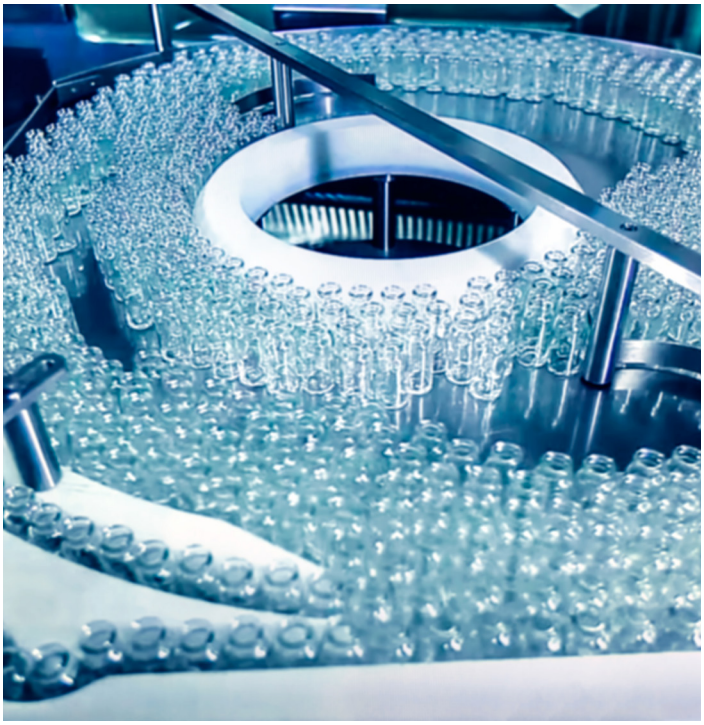
A small company usually has minimal resources to devote to basic early stage or even discovery activities related to its active pharmaceutical ingredient (API). Its immediate need is to produce enough drug product for early phase studies.

Characterization of the molecule is most likely minimal, the buffer composition and primary container specifications are not firmly established, dosage might change as result of Phase I-II studies (safety-efficacy), and product stability might be minimal or poorly defined for the different manufacturing steps.

In addition, various analytical methods might need to be developed and in place early on to allow product characterization/testing while executing development studies and batch release of material manufactured at lab scale. The release testing could be chemistry related as some products require USP testing for quality attributes such as pH, color, density, composition or potency by liquid chromatography (HPLC), or more complex analytical tests such as gas chromatography (GC-MS) or Capillary Electrophoresis (CE).

Method development might take several months to complete, depending on complexity, equipment suitability and availability, while ensuring the methods are suitable for commercial laboratory testing. A second set of activities following basic method development includes those same methods being validated and transferred to quality labs for final release of the drug product manufactured under GMP conditions. Resource constraints during these steps usually result in bottlenecks that can potentially delay project timelines.

It is at this stage where some unknown or unexpected situations tend to appear. Incomplete drug product characterization, lack of process understanding, or an undefined path forward usually means some additional development work needs to be executed. For example, lack of solid information about product stability, its capacity to withstand freeze-thaw cycles, and not being shear, light or oxygen sensitive might require basic studies to be performed prior to making lab scale batches to support other ancillary studies like filter validations or drug product-process surfaces contact compatibility. It's also at this point when questions about selecting a suitable final container for the drug product first arise. If basic stability studies are needed, sponsors want to use the most likely container that will be carried out all the way to product launch. When the sponsor and the CDMO are working closely together to identify those issues, the results can be impressive: a well set of scheduled development activities, shorter development times, a sound set of supporting documentation, and avoidance of surprises.



Early non-GMP batch manufacture-container selection

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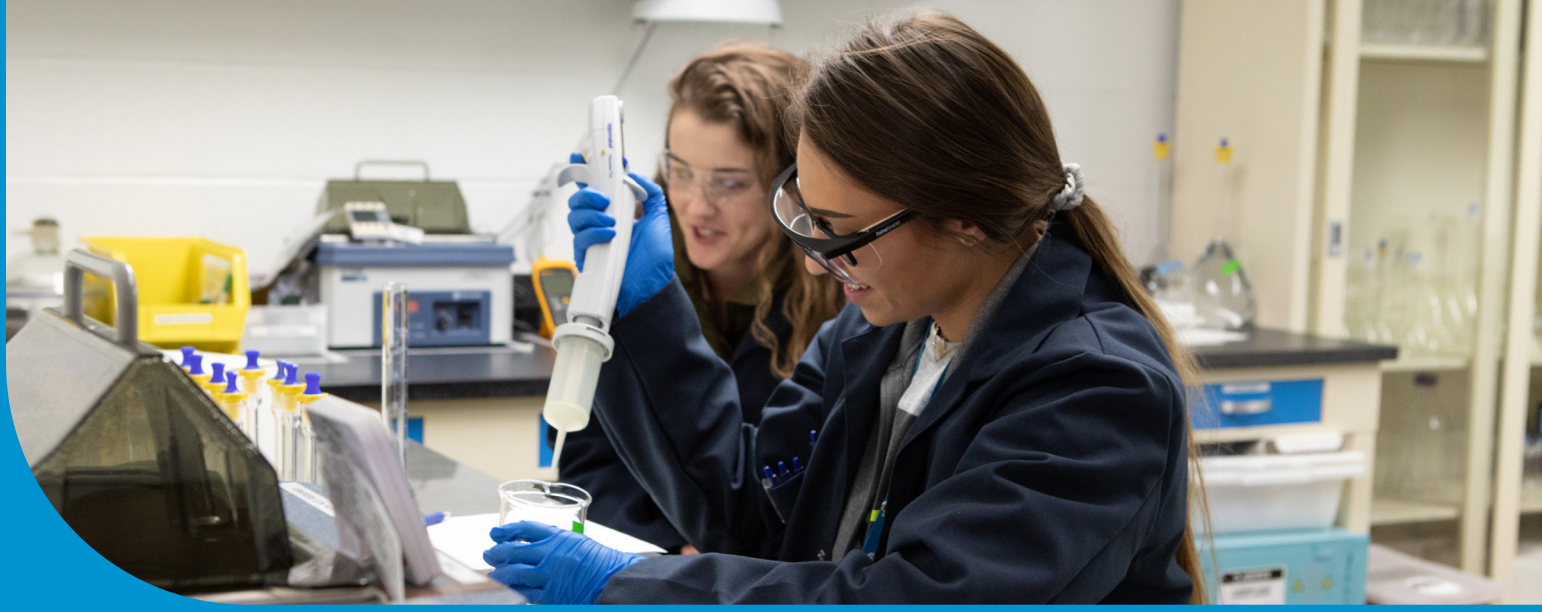
In preparation for GMP drug product manufacturing, the batch size scale-up, manufacturing and fill finish line equipment design, specifications and capabilities need to be considered. One main topic to be discussed when approaching this stage is drug product manufacturing line contact materials compatibility. Another is the selection of the right type of final container for the drug product in question as these are intertwined to a certain extent.

Batch scale up

Many early assumptions at this point require some precise answers:

- What is the scale-up magnitude?
- Are we going to use dedicated equipment or general use?
- Do we need to design special compounding vessels?
- What are the optimal mixing rates, temperatures and speeds?
- Are there any specific sampling requirements, process aides (nitrogen blanking, dim light, peristaltic pump or pressure-driven filtration and fill steps), order of compounds addition, pH adjustment strategy, or formulated bulk hold time and temperatures?

Most of those questions are addressed via laboratory studies with non-GMP material prepared at lab-scale (which could vary from 100's of milliliters to 10's of liters) using the same type of materials as those to be used in the manufacturing setting. Mix speed/time/hold time studies are done by properly scaling down the intended GMP batch sizes. The information gathered as a result of these studies is also needed later to support batch manufacturing record write ups and provide a starting point for process validation activities.



Fill finish line equipment design and product-surface contact

CDMOs usually have flexibility when deciding what kind of equipment to use in manufacturing lines, either by using restricted access barriers (RABs) or isolators. Often, they have both available and which one is used depends on product requirements and intended applications.

These technologies use either clean in place (CIP) or Vapor Hydrogen Peroxide (VHP) as the main sanitation method on these fill lines. VHP might theoretically present a problem for certain drug products that are prone to oxidation. A simple solution to avoid exposing the drug product inside the fill line enclosures to the VHP sanitation process, which produces vaporized H_2O_2, is to run the venting step longer to sweep away residual peroxide to achieve extremely low levels (such as <<1 ppm).

Nonetheless, it is important for the sponsor to understand those facts, while ensuring there is data to support that the product in question is not vulnerable to hydrogen peroxide.

An important consideration for fill lines is the use of single-use systems, which provide enormous manufacturing flexibility, thus enabling a great deal of customization with a wide variety of parts. But sometimes that flexibility comes with a price as it adds complexity to the overall manufacturing operations. Procurement, validation, and compatibility studies must be performed with the inclusion of different single-use parts.

For example, a typical batch of a biologic drug product uses a wide variety of single-use components, represented by shipped preformulated bulk in a disposable bag, to the tubing connectors for sterile filtration units, sampling ports, waste lines, pumping systems, and filling needles.

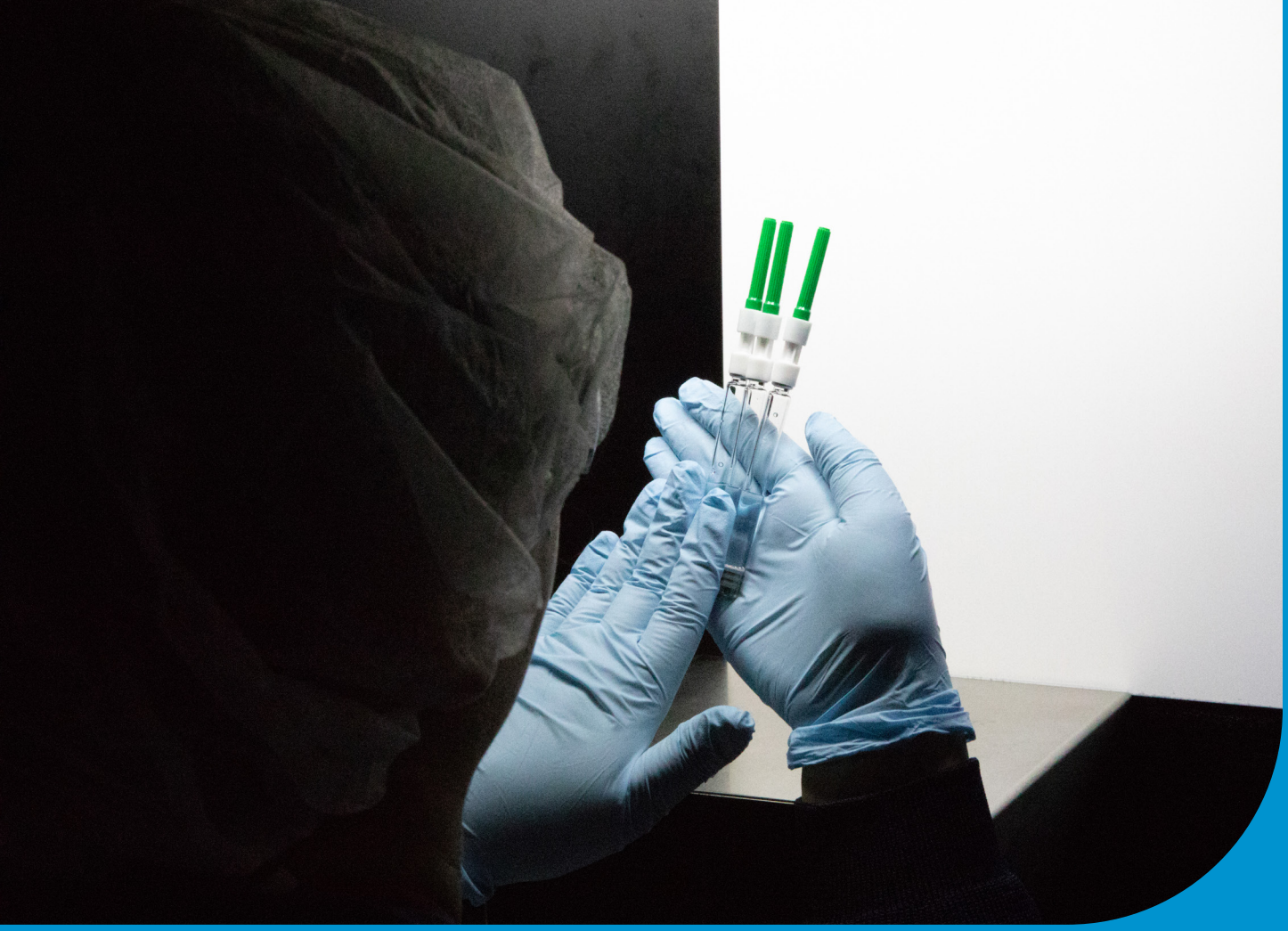
Single-use components are not always the most cost-effective option and at a certain scale for particular products, they do not make sense from a cost perspective. A general principle is that the smaller the volume of processed units, the more suitable disposable systems usually are.

A very important advantage, especially for high-cost biologics, is that single-use systems eliminate the need for cleaning and related validation, where multiple, expensive GMP batches might be needed.

A disadvantage to using single-use parts is that these change parts must be thoroughly characterized to assess the potential impact of extractable and leachables (E&L) on the final drug product.

In this case, it is very important to perform drug product-material contact surface studies to rule out any undesirable effects on drug product quality when presented to these single-use components. It is recommended to run these kinds of studies early in the development process, before any GMP batch is made. This also implies the need to have analytical tests in place to assess basic product stability/potency. This approach also includes filter compatibility studies that need to be executed prior to the manufacture of GMP batches.

Finally, there are also other in-parallel activities to carry out as early as feasible, such as the process of serialization for each finished unit (an inked numerical code applied to the outside of the container that unequivocally identifies every single unit produced). This is also a time-consuming task that requires significant collaboration and coordination efforts between the sponsor and the CDMO.



Final container selection

Bringing a new container and its closure (stopper or plunger for vial or Pre-Filled Syringe (PFS), respectively) to the manufacturing lines can be a time and resource intensive journey for both the sponsor and the CDMO. A large or specialist CDMO may have an advantage here as they normally have many choices readily available, as well as the required machine parts, and the data to support those selections, such as validation documentation and supply agreements in place with reliable providers.

When evaluating variables such as batch volume, fill line loss, line capacity, line speed, visual inspection capabilities, flexibility in PFS sizes, types (stake needle/luer-lok; silicone coating level, etc.), in-line fill volume checks and stopper seating options, a large CDMO can offer a great deal of options aimed to accommodate either small or large biotech or pharma company's needs.

When selecting a container closure system for a drug product, an important point of scrutiny by regulatory agencies is the presence of particulate matter in the final drug product. The creation of glass particulates due to chemical interactions between the glass and the drug product are usually more difficult to address. These particulates, also known as delamination flakes, or lamellae, are hard to identify and can result from a number of interactions. Particulate matter in the form of glass flakes can shed from the interior of glass containers and form under certain glass manufacturing conditions or during glass handling and preparation at the fill finish facility, as a result of the product formulation (such as high pH, high salt concentrations), or freeze-thawing, and the presence of certain excipients or buffers (such as citrate or tartrate).

Drug products exposed to the inner surface of containers for extended periods of time, stored at room temperature, and those that have been terminally sterilized (which is done almost exclusively on vials) are also at a higher risk of potential for lamellae formation. An alternative polymer-based container could be a viable solution, even though glass is still the preferred material for vials due to its perceived inertness and compatibility. Many companies are making great efforts to put biologics into plastic containers such as clear olefin polymers (COP) to reduce the potential for delamination and the need for siliconization. Sometimes these materials can lead to product oxidation from gas permeation, which is a challenge when it comes to protecting sensitive compounds. The good news is that some of those companies started offering coated COP containers, which greatly reduce oxygen and vapor transmissions, making them a great alternative.

In addition, PFS manufacturing processes offer much better unit defects detection, thus lowering the number of defective units that might hit the fill line and visual inspection stations (manual or automated), which will result in greater product losses and batch yields, or even batch rejections.

The selection of a PFS is an attractive choice for many developers, especially those in the biologic drug product area where each individual drug product unit could cost hundreds of dollars.

Assuming most of the product stress points (e.g., mix time/speed; ingredients addition rates and order; pH adjustments; dissolved oxygen in solution; solution temperature; filtration, visual inspection; etc.) are identified and addressed during early process development stages, the specific factors that need a closer look when selecting a container system can be explored.

Container selection criteria

There are many variables related to the drug's container that may trigger some undesirable outcomes. For example, when dealing with a biologic drug product, protein aggregation, degradation or potency loss, are the most important effects to avoid. For synthetic drug products, oxidation, and degradation are issues to avoid. There is a common theme here, drug products, regardless of their nature, can all suffer a critical quality attribute loss by selecting the wrong container. Factors such as shipping and storage conditions, rubber components, silicone oil and tungsten are often high on the list of culprits.

Identifying a container that will best protect a drug product requires a container-selection process that screens for:

- Silicone levels
- Tungsten traces content
- Rubber formulas, including whether they are siliconized, coated or non-coated, and the composition of the coating
- Headspace: present or not, gas overlay
- Container size (to minimize headspace)
- Intended storage conditions, including stress conditions and shipping simulations
- Potential visual-inspection stress conditions, such as high-voltage leak detection, high-intensity light and spinning (used in High Voltage Leak Detection Systems-HVLD)
- Selection of reliable component providers, with a long-term expectation that parts won't be substituted

Silicone is necessary to provide a PFS with a smooth drug product dispensing operation by reducing the required force to eject the liquid from the device (typically measured as part of the product quality functionality test and referred to as the gliding and break-loose forces). Cross-linked (or immobilized) silicone is an alternative to sprayed silicone into the glass tubing barrel that provides lower amounts of free silicone that can migrate into the drug product solution. Once the silicone is applied inside the syringe barrel, it is immobilized by a cross-linking process involving a light source that promotes the bonding of silicone to the glass. The amount of silicone used in this process is significantly less than the spraying process (by >100 times), thus providing a meaningful reduction in the possibilities of particulate matter formation. It is thus recommended to select syringes with very low silicone content. Biologic drug products are especially sensitive to silicone, so close attention is required when dealing with these types of products.

Tungsten is a strong oxidizer. Tungsten-free or reduced-tungsten syringes are now available from some syringe manufacturers. Tungsten is introduced into the syringes while forming them. A tungsten pin is used for making the hole at the neck of the syringe, and by that action, minute traces are left behind, which could eventually act as a strong oxidant to metal-sensitive drugs or proteins and other biologic molecules. Therefore, it is essential to avoid or minimize this occurrence by selecting PFS with free-or low-tungsten content.

Selecting a cross-linked silicone and/or tungsten-free type syringes depends mostly on the product's ability to withstand stress. If the drug product is not silicone-sensitive or prone to oxidation, selecting a standard syringe system might be an acceptable compromise between risks and product quality and safety.

Rubber formulas come in a few options for PFS. Developers need to consider two different product-contact locations: the plunger stopper, which bears the largest contact surface with product, and the tip plug, which closes the orifice in the luer-lok style PFS (alternatively, there is a sheathing covering the needle in the stack needle's style PFS that could also become a product contact-surface). Sponsors need to be aware that all those parts can also be polymer-coated (like Teflon), so when designing studies to select a closure or to address the effect of those parts on the drug product, these need to be included as well. Synthetic drug products normally have harsher formulation buffers, represented by lower pH, the presence of several types of salts, and strong buffers and organic solvents. On the other hand, biologics have "softer" formulation components, such as weak organic or inorganic buffers, low content of salts, and sometimes surfactants associated with the active molecule. A wide variety of studies can be undertaken to assess those parameters in a rationale way, for example, by using design of experiment (DOE) tools.

The presence of headspace in a PFS can sometimes be problematic. First, the headspace is usually comprised of either air or nitrogen (when nitrogen blanketing is applied to the PFS right before inserting the plunger stopper). If the drug product is sensitive to oxygen, it could induce oxidation. Second, air shipment prompts plunger stopper movement due to external pressure changes during the transit. This could trigger intrusion of drug product into the plunger ribs and grooves and cause product rejection or complaints. Third, if the plunger stopper moves out and then in, it could compromise the container closure integrity, leading to contamination and potentially rendering the

drug product unsafe to use. Lastly, especially true for biologics, an excessive headspace can let the liquid shake and move more freely and, if the drug product is shear-sensitive, lead to product aggregation. Selecting the appropriate container size can prevent most of these undesirable consequences.

Selecting the appropriate storage conditions could also prevent alteration of the drug product quality. An incorrect storage temperature for example could lead to accelerated degradation of the product, induction of glass particles formation, migration of silicone into the drug product, or excipients (or product) crusting around the stopper plunger, thus preventing the correct actuation of the device. To prevent those issues from happening, a CDMO can work with the sponsor to develop and execute studies to address storage temperature selection under normal and accelerated conditions and carry those studies for as long as necessary to support container selection and regulatory filing.

The finished drug product normally goes through a visual-inspection step at the end of the manufacturing operation. Depending on how that is done, certain unavoidable stress conditions are applied to each individual container. One of the container closure integrity tests used is the High Voltage Leak Detection systems (HVLD). The HVLD equipment, which uses a pass-through high voltage electric current (25KV) administered to the outer side of different parts of a container, followed by shinning high intensity visible light (25K lux, for a few seconds max) while the container spins (usually at about below 2000 rpm, but could be as high as 4500 rpm, again for a few seconds max). This type of visual inspection (automated) might not be suitable for biologic products but is appropriate for synthetic drugs.

A well-established CDMO offers the sponsor a good selection of final container components from reliable sources. There is an expectation that parts won't be substituted without prior notice and enough time to seek a resolution in case the change is permanent and cannot be replaced with an alternate vendor.

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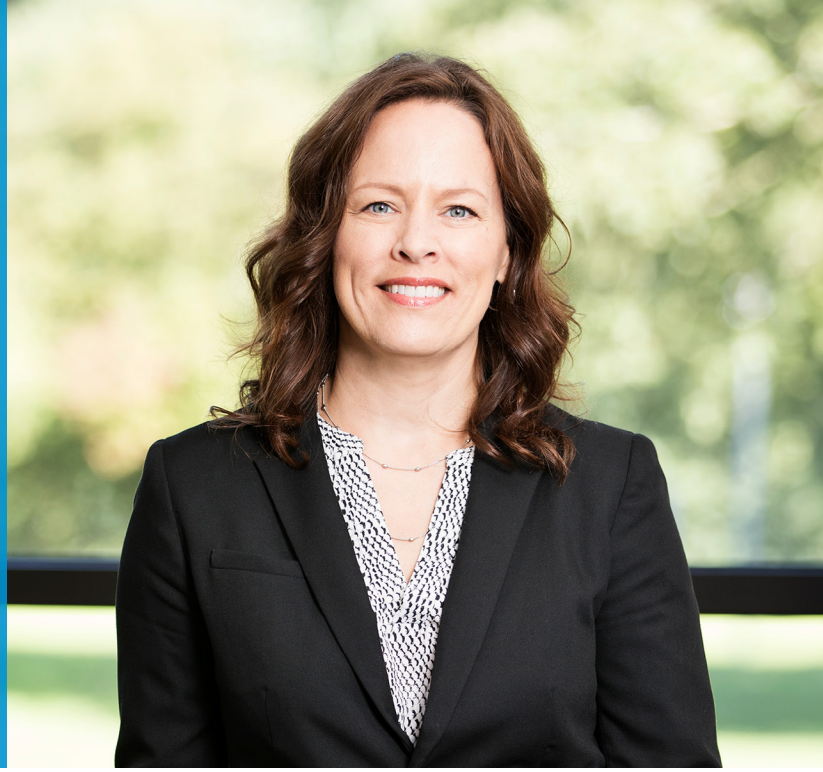


Batch record generation/Quality documentation

When preparing for batch manufacture, it is critical to start drafting the various manufacturing SOPs that drive the drug product manufacture. Many inputs need to be generated before the first component is added to the vessel, and this ought to be done in early process development studies or provided by the sponsor as identified critical quality attributes (CQA) and critical process parameters (CPP).

For a non-GMP batch where the intent is to evaluate basic manufacturing conditions and commodities suitability, the batch is usually run using checklists, which are basically draft documents of what the specific process step SOP will look like once the project moves into GMP batch production.

Fluid dialogue and transparency between the sponsor and the CDMO's technical team is key to ensure that CQA and CPPs are captured in specific SOPs, like dispensing, compounding, filling, capping, testing and inspection instructions. Also, it is essential that those quality attributes align with final release testing specifications, sampling conditions, and validation documentation. This will result in timely release of batches and proper documentation support for submission purposes.

GLOSSARY

Quality Attributes: A quality attribute is a property of a product or output of the process that is reflective of the process performing as expected. Critical quality attributes (CQAs) correlate to critical process parameters.

Critical Process Parameter (CPP): A process parameter whose variability will have an impact on CQAs. CPPs must be monitored and/or controlled to ensure acceptable variation in the output of a process stays within allowable limits to provide assurance that the process manufactures product meeting expected levels of quality.

In-Process Control (IPC): Checks that are performed during the unit operation to determine if additional processing is required (i.e., pH adjustment).

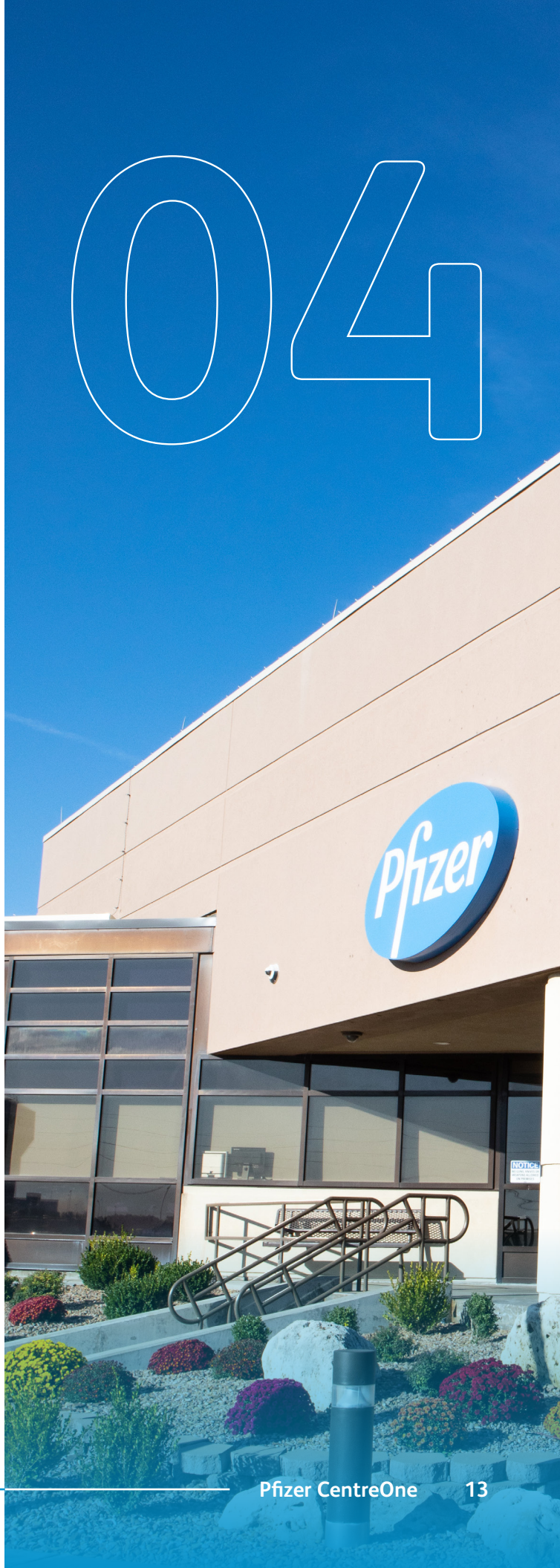
In-Process Test (IPT): Tests which are performed to determine the acceptability of the in-process product (i.e., bioburden test).

GMP batch manufacture

By this time, most of the CQA, CPP, IPC and IPT ranges and/or parameters have been set, defined and may be challenged during process performance qualification batches manufacturing. These are batches that are done at full scale and/or within the batch size ranges defined for the product. These batches are crucial for the success of the program as there are complex preparations taking place to support them and they will form part of the submission documentation. These include:

- Batch scheduling
- Additional studies to be performed
- Commodities and components ordering, and released by Incoming Quality group
- Approval of batch records
- Writing of process performance validation plans for the different manufacturing steps
  - Compounding
  - Equipment cleaning
  - Batch testing
  - Filter validation

Preparing for GMP batch production mobilizes quite a few people. It involves coordinating through the Program Management Organization with many business units. Procurement must ensure all the commodities and drug product components are on site well in advance of the scheduled manufacturing dates. Incoming Quality must test and release commodities for production. Quality chemistry labs, equipment prep, compounding, fill line, visual inspection and packaging lines, among many others, must be ready and have all the information and documentation necessary to execute the batch.



Process validation strategy/activities

The process validation stage is often where the challenges to a well-designed manufacturing process surface. Sometimes things don't go as planned and issues are identified that require additional activities. For example, poorly defined CQAs might lead to the testing of incorrect attributes or failing the defined release specifications.

A failed batch usually means the whole validation process needs to be repeated and any previous released batches are made redundant, which could make the project budget soar. Failing cleaning validation activities can also delay the program timelines by several months until the cleaning process is fixed and required changes are addressed.

Where sponsors decide to have more than one API supplier, this brings extra complexity to the process. If a sponsor wants to qualify multiple suppliers at the same time as this step, it could lead to significant longer validation completion times. If there are qualitative differences between API suppliers, it could lead to unexpected failures on a batch (caused by different solubility, impurity profiles, or even ingredient availability) that will require a deviation investigation, forcing the batch to be placed on hold and not to be released.

Depending on the drug product dosage strengths, batch sizes range, or number of compounding vessels needed, the number of validation batches could start growing from a minimum of three batches to sometimes close to a dozen.

A CDMO usually has many checks in place to ensure the batches are done "Right the First Time," without improvisations and in a timely manner.

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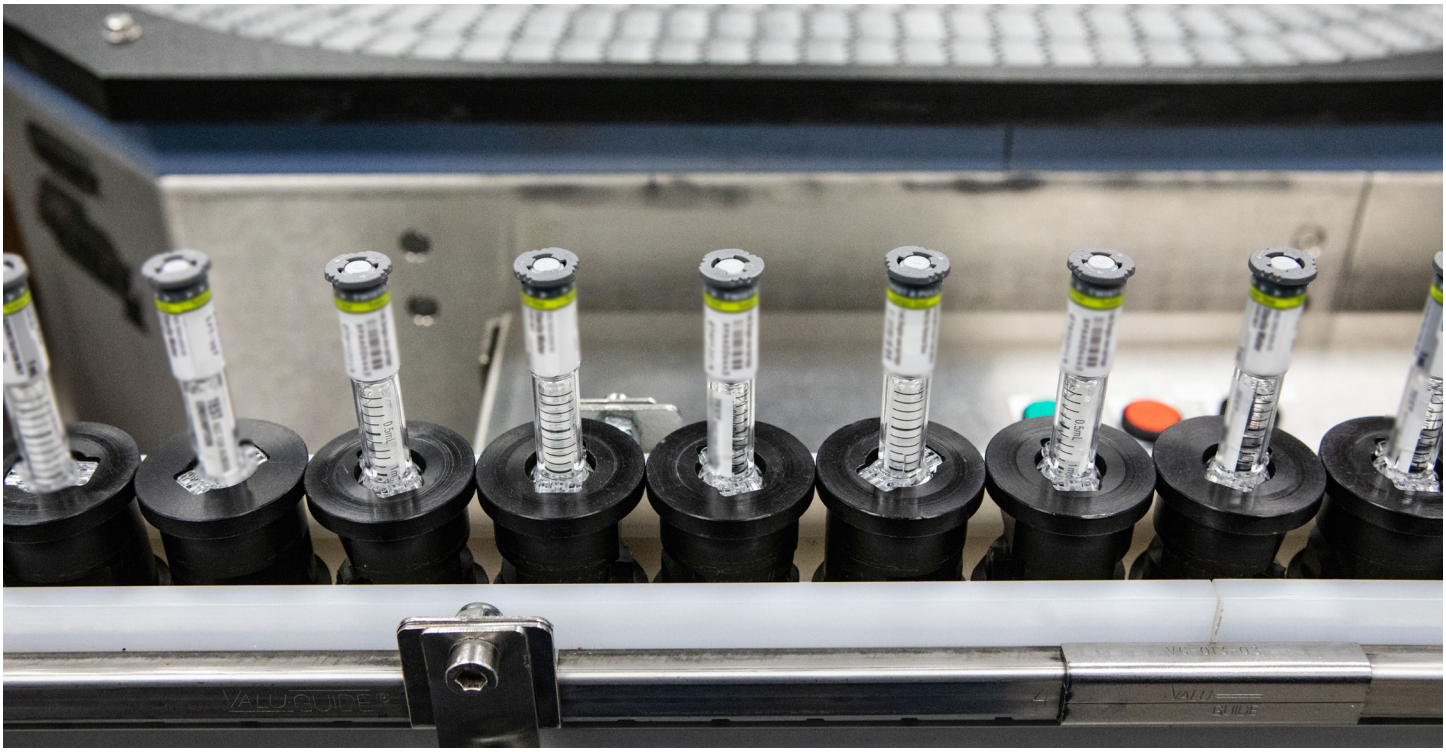

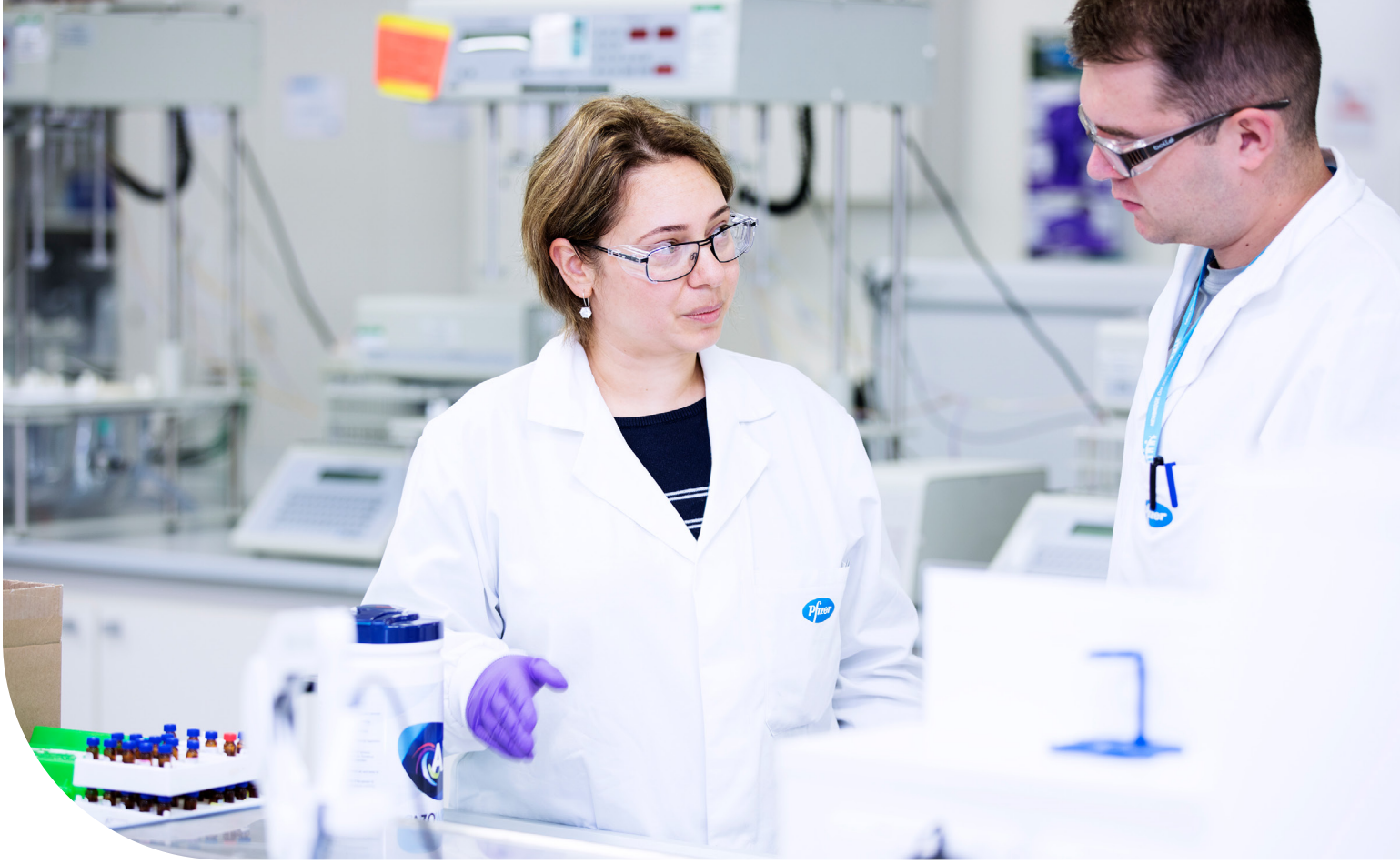

Conclusion

Sterile injectable product development and manufacturing is a complex endeavor that requires deep expertise backed by extensive capabilities. Where CDMOs and sponsors are bringing medicines to the patients who need them, fluid and honest conversations are essential to ensuring a successful product launch in a timely manner.

In every stage from initial project discovery where product knowledge and basic analytical method and process development details are shared, through to GMP batch manufacture and process validation, close collaboration and transparency is essential.

Due to the complexity and vastness of activities that need coordination over long periods of time, the forming of a genuine partnership between the sponsor's team and an extensive group of professionals under the umbrella of the CDMO's project management organization is often the difference between success and failure.

For more information about Pfizer CentreOne and its sterile injectable services, **contact us** to start the conversation.

Reference

1. https://www.datamintelligence.com/research-report/sterile-injectable-market