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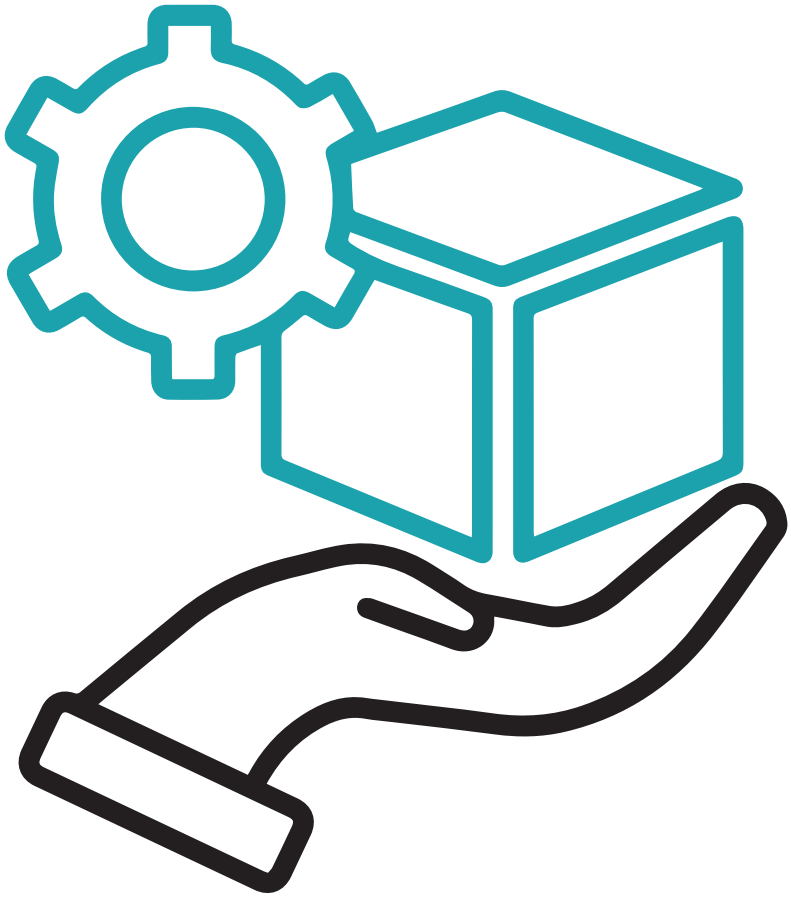


Delivering sterile fill & finish capacity fit for the future

Demand from pharmaceutical companies for sterile fill & finish capacity is putting pressure on contract development and manufacturing organisation (CDMO) partners to find ways to make their existing infrastructure more productive. Dr. Claus Tollnick, global head of sterile fill & finish operations at Recipharm, explores the challenges facing the sector in meeting present and future sterile filling requirements, and explains the steps Recipharm is taking to address them at its site at Monts, France.

By Dr. Claus Tollnick

THE DEMAND FOR STERILE FILL & FINISH

The global fill & finish manufacturing market is growing rapidly. The latest forecasts expect the segment to reach a value of US$12.6 billion by 2027 internationally, up from US$6.1 billion in 2019, growing at a CAGR of 9.6% throughout the forecast period.[1]

Several factors are driving this ongoing growth, particularly in the field of sterile fill and finish. The rise of the biopharmaceutical sector is one key driver, since these treatments tend to be administered parenterally. The global biopharma market was valued at approximately US$330.7 billion in 2021 and is expected to reach US$ 478.08 billion by 2026, growing at a CAGR of 7.65%.[2]

The biggest driver of growth in the sterile fill and finish market, however, is the ongoing COVID-19 pandemic, and the spike in demand for vaccine filling to fuel mass vaccination campaigns across the globe.

This surge in demand has put pressure on CDMOs, contract manufacturing organisations (CMOs) and other partners to find ways to optimise the efficiency of their existing production lines. More than that, it has challenged these partners to explore options to expand and optimise their capacity to meet near- to mid-term projections of high sterile filling demand.

EXPANSION AND PRODUCTIVITY CHALLENGES

Whether optimising existing aseptic fill and finish capacity, or expanding capabilities with new infrastructure, CDMOs are faced with challenges when seeking to meet increased customer demand for sterile filling. When CDMOs are operating at close to full capacity, the obvious answer is to build additional infrastructure. However, in the current climate, the order books of many equipment suppliers are full, and the COVID-19 pandemic has led to shortfalls in the supply of raw materials and components, extending lead times for new equipment. As a result, typical timelines for the construction of a new facility have increased dramatically. Moreover, it can be complex and difficult to upgrade existing production lines, due to the difficulty of integrating new components or technologies with older equipment.

This is a common problem for pharmaceutical companies across the globe. Many have legacy machinery that has been well maintained for many years and continues to provide valuable services, delivering high-quality filling capabilities. However, it can be difficult to source compatible replacement components for this equipment, or add-on technology to upgrade these lines to meet changing sterile processing legislation,

1 https://www.businesswire.com/news/home/20210329005556/en/Outlook-on-the-Fill-Finish-Manufacturing-Global-Market-to-2027---by-Product-End-user-and-Geography---ResearchAndMarkets.com

2 https://www.globenewswire.com/news-release/2021/08/25/2286455/28124/en/Global-Biopharmaceutical-Market-Report-2021-Market-is-Expected-to-Reach-478-08-Bn-by-2026-from-330-7-Bn-in-2021-Increasing-Investments-in-R-D.html#:~:text=The%20Global%20Biopharmaceutical%20Market%20is,at%20a%20CAGR%20of%207.65%25.

3 https://www.pda.org/topic-areas/eu-annex-1-revision

MONTS - FRANCE

Source: Recipharm

such as the European Union's (EU) upcoming Annex 1 revisions.[3]

Older filling technology is often slower than new machinery, and there is a limit on how quickly speed and output can be optimised, meaning upgrades to an existing line may not be an effective use of financial resources. Additionally, upgrading also requires shutting down production on the line that's being worked on. This leads to downtime and lower productivity, negatively impacting on the timely delivery of product to customers.

Tailoring isolators or restricted access barrier systems (RABS) - common features of modern sterile processing lines - to be installed around existing equipment can also be a major barrier to investment. It is often the case that major upgrades need to be made to other aspects of the building, such as new Heating, Ventilation and Air Conditioning (HVAC) systems, to support isolator equipment and maintain optimum sterile processing conditions.

All this complexity has the potential to limit future growth of the sterile fill and finish segment, with negative implications for the commercialisation of future drug products.

At Recipharm, we believe the answer is the development of prefabricated, modular sterile filling lines, and we are utilising this exact approach at our specialist aseptic manufacturing facility in Monts, France.

Monts is a key focus of our commitment as a business to meet not just present customer demand for aseptic filling, but future customer requirements, and we are investing significant sums in updating the facility and expanding its capacity. This site poses challenges of meeting this goal using traditional means and equipment. For this reason, we have opted to take a novel approach, utilising prefabricated modular sterile manufacturing units in order to deliver additional sterile filling capacity as quickly as possible.

UNDERSTANDING MONTS

Situated in the Centre-Val de Loire region of France, our site in Monts has an intriguing history as a pharmaceutical manufacturing facility. First built in the 1940s, the site was

retrofitted for pharmaceutical production in the 1980s, before being acquired by Recipharm in 2007.

In addition to a workforce of some 350 team members, the facility contains well-maintained legacy sterile fill and finish equipment that is of high quality and performance and continues to provide efficient, effective, and compliant service. The site specialises in filling for generic and biologic products, filling 2-100ml vials and 1.5-3ml ampoules.

Monts has long added to our full sterile filling capability, allowing us to meet customer demand for reliable and on-time delivery of sterile drug products in a wide range of dosage forms and packaging types.

At the height of the COVID-19 pandemic, Monts was at the forefront of our efforts to support the wider pharmaceutical industry to develop and manufacture vaccines. With a combination of unique team expertise, efficient existing equipment, and close client collaboration, the site was able to support a leading vaccine developer to commercialise and roll out its newly approved vaccine in record time.

As a result, Monts delivered large batches of compliant and high-quality finished products that played a key role in the success of the mass vaccination programmes in the EU, UK, and other markets/regions across the globe.

However, demand for sterile filling is set to further increase for the foreseeable future, and there are changes to sterile processing legislation on the horizon. To keep up, and to continue to meet customer expectations for rapid delivery of high-quality finished vaccines and other products in the future, Monts required both upgraded sterile processes and additional capacity. This needed to complement and integrate with the site's existing facilities.

THE BENEFITS OF PREFABRICATION

Prefabrication was chosen by Recipharm as the approach for upgrading and expanding the Monts site for several key reasons.

THE NEW FACTORY UNDER CONSTRUCTION

Source: Recipharm

*Programme of Investments for the Future / Project Ronsard 2

CONSTRUCTION OF MAJOR PROCESS EQUIPMENT AT THE SUPPLIER'S SITE

Source: Recipharm

The technique is highly time-efficient compared with alternatives - it can typically take three to four years from the decision to invest into a new line to onset of production using the traditional method. With prefabrication, the manufacturing cleanrooms are manufactured in modular sections off-site by a specialist supplier according to the needs of the line. All the required process components and equipment are sourced and fitted together within a RABS unit.

Once completed, each cleanroom section is then transported to the facility and integrated with neighbouring sections, and the process equipment is introduced. As each modular section is already set up ready for operation, significant time is saved in the integration process on-site.

Typically, the construction itself of a building and accompanying cleanrooms can take at least 18 months. This allows sufficient time for the process equipment to be designed and delivered. Prefabrication can reduce this time to no more than six months, placing time pressure on equipment suppliers to deliver just as quickly. As such, prefabrication allows the rapid creation and launch of new lines in just one year, instead of three to four, significantly streamlining the entire expansion process.

The prefabrication approach is cost-effective too. Dedicated suppliers already have relationships with sterile filling equipment manufacturers and with installation specialists, opening the potential for savings to be made in the line build and fit-out.

In addition, the modular approach allows the functionality of the cleanrooms, process equipment and RABs to be tested by each supplier prior to it being transported to the site, instead of waiting until final assembly. This streamlines the validation process and can help ensure new lines are prepared more quickly for compliance with future legislative changes, such as the upcoming Annex 1.

On top of all these benefits, prefabricated sterile fill and finish lines deliver the same high-quality end products as lines built using traditional methods.

BUILDING THE NEW LINES

The decision to build a modular line was taken in June 2021, following investment by

the French government* designed to support the expansion of sterile filling capacity within France to optimise the roll-out of COVID-19 vaccines in the EU.

Recipharm engaged a specialist prefabricated module supplier in Spain to construct the modular units, which were then transported to France by truck in around 30 deliveries. For the process equipment and RABS environment, we identified a supplier from China that was able to ship all process equipment in less than 6 months. Transport to France is scheduled by mid-February 2022 by aeroplane to further streamline the delivery time for the finished capacity.

The outsourcing of the development of the cleanroom modules allowed Recipharm to decouple the creation and installation of the equipment and cleanrooms from the construction of the new buildings to house the lines. This meant that the three projects could run concurrently, instead of consecutively, saving even more time.

The project was designed in a way that would allow the continued use of the existing production lines at Monts during the build, meaning that the site remains fully operational throughout, allowing it to continue serving customers.

COMPLETE AND READY FOR OPERATION

The new capacity at Monts will be fully operational in summer 2022 already delivering batches of COVID-19 vaccines to support vaccination programmes across the EU and around the world.

The new line features 16 fill heads, which allows for faster production than ever before. This enables Monts to deliver more than 500,000 units per day, helping us not only support more clients than ever before, but to deliver larger batches than previously possible.

The additional capacity is flexible too, allowing easy and rapid changeover for new projects. This means that Monts is now able to respond quickly to a wide range of client sterile fill and finish requests, regardless of the specific nature of the drug formulation they need to fill.

LOOKING AHEAD

Thanks to the use of prefabricated modular technology, the Monts expansion project has been so successful that we are now considering its use in the construction of our new facility in Morocco to speed up the delivery of new capacity in the region. We plan to even go one step further and implement most of the process equipment into the cleanroom modules prior to deliver to our new site, further speeding up the construction process.

The interest in the new capacity at Monts from large multinational clients is such that we are also imagining a future second expansion project at the facility, building out further modular sterile filling lines.

Looking further ahead, we are also exploring potential future technologies capable of even greater enhancement of productivity and line flexibility. Currently, filling systems are based on traditional conveyor belts, with a combination of automation and manual handling for certain processes. There is also potential for robotics to be utilised in the filling procedure. This can not only eliminate any remaining requirements for manual handling, but also allow a line to be easily adapted for new and even more complex drug presentations, enabling it to support an even wider array of complex drug projects. In addition, there is potential for specific tools to be manufactured on site, leveraging 3D printing, rather than having to order them with long lead times, which can help streamline our supply chain.

There are a growing number of innovative Biotech companies developing revolutionary new large molecule drugs that have features distinct from many treatments currently on the market. These will require specialist processing, manufacturing, and filling support. A new generation of flexible sterile production lines like those at Monts will be crucial to support the commercialisation of these products.

LESSONS TO LEARN

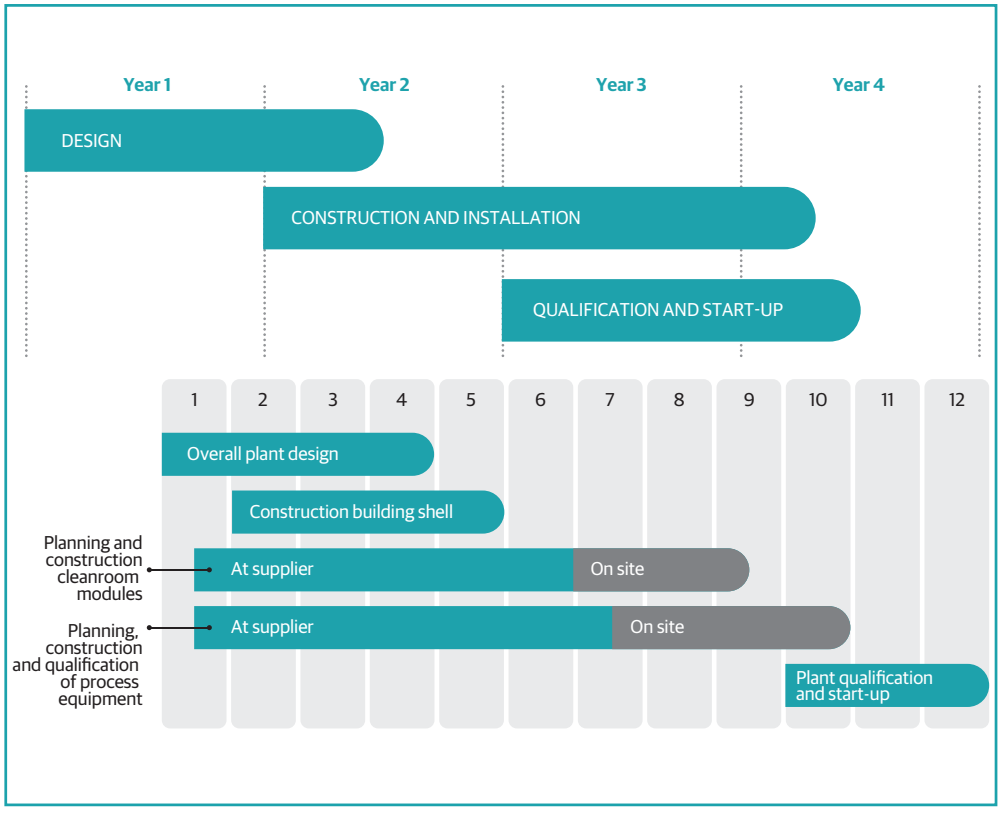
Our experience expanding capacity at Monts offers several lessons that can be heeded by others in the pharmaceutical industry. Whether responding to present demands for new capacity, or anticipating increases in the

future, companies need to be confident that they can build and put into operation additional lines as rapidly as possible. As demonstrated, prefabrication can enable this rapid roll-out.

To ensure the resulting lines are suitable for your needs, there are a few considerations to bear in mind:

- **Flexibility is key** - when working with your supplier to design your preferred production line, make sure that the finished design is as flexible as possible, facilitating easy and straightforward product changeovers and simple upgrades. This can help future-proof your line, ensuring it remains compliant with future legislation and can be easily repurposed for new projects, whatever they may be.
- **Don't forget the other pieces in the project jigsaw** - your own team and your line supplier are not the only moving parts in your expansion project. You also need to bear in mind the logistics partners responsible for transporting your finished line to site, the company installing it, as well as the companies responsible for constructing the new facilities to house it. It is imperative that you are confident in the ability of all these companies to deliver on time, otherwise you may find that deadlines are missed.
- **Be prepared for the unexpected** - even in the best planned projects, there is potential for unexpected issues to occur that can push back deadlines. Make sure that your plans build in contingency to cope with these challenges, through spare budget or time - this will help minimise impact and ensure your project continues to run on deadline. Your prefabricated line supplier should also be able to advise and support on unforeseen challenges unique to the installation of modular lines to further reduce the likelihood of delays.

COMPRESSED TIMELINES REQUIRE A NEW APPROACH TO PLANNING



Source: Recipharm

About the author

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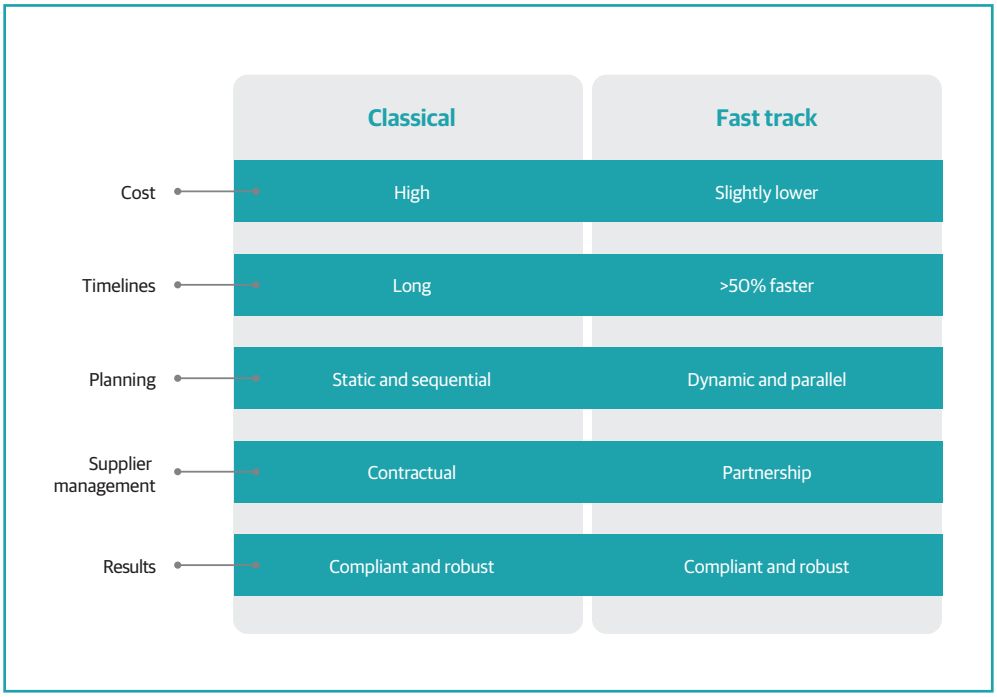
COMPARISON OF CLASSICAL AND FAST TRACK APPROACH



Source: Recipharm

- **Build on the right talent** - your project team needs to be diverse, creative, strong, and resilient. Following the rulebook will not deliver the required speed. You need to believe in what can be achieved - not everything will work out as planned, and the team needs to be aligned around the will to find solutions to remain on track.

FINAL THOUGHTS

With the rapid rise of the biopharmaceutical segment and the likely continued need for vaccines to tackle COVID-19 for the foreseeable future, it is likely we will continue to see high demand for drug products in parenteral presentations. To meet this demand, sterile fill and finish capacity will be required.

Investing in novel line construction solutions like prefabrication can help deliver effective, high-quality and high-efficiency sterile fill and finish capacity faster than ever before. As a result, the pharmaceutical industry can be confident that the extra capacity is there to ensure we can continue to bring innovations to market quickly and effectively when and wherever it is needed. ■