Leading the way

What does a successful contract manufacturing organisation (CMO) look like? Bill Welch, chief technology officer at **Phillips-Medisize**, explains what the technical competencies and operating segments of a CMO for diagnostics consumables should be.

There is a clear trend in the diagnostics space towards higher-complexity consumable products. Various components in a diagnostic assay are now integrated entirely on a single consumable, with a corresponding system analyser often only responsible for simple mechanical actions. This increase in complexity drives more compact and efficient diagnostics systems but simultaneously raises new issues regarding manufacturing.

The intricacy of emerging diagnostic consumables necessitates manufacturing competencies that span a wide range of disciplines, thereby raising the standards for a contract manufacturing organisation (CMO) to be successful in this space. As diagnostic companies continue to develop these complex consumables, the need for a strong relationship with a consumable diagnostics CMO specialising in everything from early product design to final product manufacturing will become increasingly important.

Technical competencies and integration

Many firms can provide moulding and basic manufacturing services. However, only a few within this space meet the standards of a true consumable diagnostics CMO, providing the technology integration necessary for this area.

Replication (thermoplastic injection moulding)

Competency in injection moulding is crucial considering the high level of precision required by diagnostic products. For instance, the tolerance for manufacturing microfluidic products in the development stages is ±1µm. More extreme deviations would introduce the risk of bubble formation in the intersection of microfluidic channels, and render the test and product unusable.

Reagent handling and storage

Many consumables now have integrated components for all the necessary reagents to carry out a particular assay, effectively eliminating the need for external reagent addition. A CMO must be able to store and handle these reagents during the manufacturing process, including liquid and powder reagents for blister pouches or separated compartments.

Surface modification

Basic surface modification can include hydrophilic or hydrophobic coatings. Quite often, assays require more involved surface modifications, including antibody attachment. For instance, the surface modification necessary for a circulating tumour cell (CTC) assay requires a polycarbonate surface to go through UV light exposure and carboxylic acid treatment prior to the actual attachment of the antibodies.

Phillips-Medisize had the opportunity to manufacture a complex consumable in collaboration with a biopharmaceutical company.

Assembly technology

Diagnostic consumables are composed of many component parts, requiring sophisticated assembly technology. This includes the assembly of component parts, such as the consumable's plastic cartridge and spring system, as well as the binding of various materials through bonding or welding processes.

Automation design and implementation

Complementary to assembly technology, a CMO must have competency in automation processes. This not only includes knowing when to automate a process based on the volumes and consumable itself, but also how to implement an automation solution that is cost and time-optimised.

Sensor integration

Biosensor technology through the use of components such as electrodes is increasing in the diagnostics space as a more compact alternative to traditional optical target detection methods. Electrode integration in point-of-care cartridges creates a single consumable that can handle sample collection, sample preparation, reagent addition and target detection.

Supply chain

While a successful CMO does not need to manufacture all component parts in-house, it must be knowledgeable in the coordination and management of additional parts and activities.

Cleanroom and sterile manufacturing

Maintaining a clean and sterile environment is a crucial aspect of all medical device manufacturing. The contamination of drug-delivery devices could have severe consequences in terms of patient immunogenic response, and contamination of diagnostic products compromises validity of the results. Of particular note are the ubiquitous RNase and DNase enzyme contaminants that are present in the environment and many biological materials. These enzymes degrade RNA and DNA respectively, effectively threatening all molecular diagnostic assays that rely on the detection of fully intact RNA and DNA in samples. It is important for a consumable diagnostics CMO to have cleanroom and sterile-manufacturing knowledge, and capacities to protect against any form of contamination such as RNase and DNase.

Operations: end-to-end integrated service solutions

A diagnostic consumable's CMO is first and foremost well versed in the diagnostics market. A thorough understanding of the current technologies, emerging trends and market drivers is a crucial characteristic of an ideal consumable diagnostics CMO. The rationale behind this notion is best illustrated by analysing the overall manufacturing chain.

The cost-saving potential for manufacturing diagnostic consumables is almost entirely in back-end processing. Processes such as sealing, assembly, reagent storage and surface modifications all have a wide spectrum of potential costs. In other words, two cartridges performing the same assay could vary in cost of production due to processing discrepancies. The best practice for diagnostics companies and CMOs, therefore, is to collaborate at the design and development stage, and evaluate how design for manufacture and assembly (DFMA) practices can best be applied moving down the chain. Early collaboration at the design stage not only provides cost savings at the processing stage, but also provides a CMO with the opportunity to assess the potential for added value to a design. In this way, a diagnostic consumables CMO is truly an integral part at every stage of the manufacturing process chain, from design consultation to quality product manufacturing. This relationship and comprehensive service solution would, of course, not be possible without the CMO's thorough knowledge of the diagnostics market, including its emerging trends and current technologies.

Consumable project case study

In a recent project, Phillips-Medisize had the opportunity to manufacture a complex consumable in collaboration with a biopharmaceutical company. This consumable included dry reagent pellets and microfluidic components; the integration of dry reagents called for assembly in a dry chamber space and the microfluidic components required extremely tight tolerances.

Considering microfluidic device technology intersects multiple disciplines such as materials science, systems engineering, physics, chemistry and biology, the design and manufacturing of such products require a comprehensive array of abilities. These technologies, funnelled into compact devices, offer an exciting foundation for innovations. The manufacturing technologies for microfluidics are often broken into two different categories: mould-based and mould-free.

Mould-based techniques include casting, imprinting, hot embossing and injection moulding. Although these technologies are often less expensive at higher volume, they require significant cost to changes when a design needs to be altered. While a product is in development, it is natural for the development team to choose a manufacturing method that does not induce significant costs when a change is required. For this reason, most devices start with mould-free manufacturing.

Mould-free techniques include lamination, photolithography, stereo lithography/3D printing and machining. These technologies, although more expensive on a per-part price basis, offer an inexpensive cost to change designs at higher volumes. Mould-free manufacturing techniques are a much more advantageous and appealing route for early-stage developers.

Again, because microfluidics is such a multidisciplinary technology, it is important to develop all aspects in parallel so that there are no bottlenecks in later development. From the technical competency and technology-integration perspective, Phillips-Medisize was well positioned to develop this complex consumable. New air-handler systems were installed for the dry-chamber space requirement and the company's injection-moulding competencies with tight tolerances are well established.

There was limited flexibility in terms of implementing design suggestions and certain geometric changes that could improve the overall quality and structure of the final manufactured product. Because there was relatively little involvement from Phillips-Medisize during the initial design and development stages, there were ultimately more costly operations in the later manufacturing stages. In the end, few improvement suggestions from Phillips-Medisize could be implemented into the final product.

Other products the company realised for customers were titration plates with 1,536 bores for polymerase chain reaction (PCR) in DNA replication. Consistent fluorescence of the base material had to be guaranteed. Other important factors were the heatability of the plate at a high-stability rate, as well as an accuracy in the lower range of one hundreds of a millimetre.

"These characteristics, as sought by the customer, have been developed specifically for this product. That is what gives Phillips-Medisize its unique market positioning," says Welch.

The CMO has the appropriate in-house control facilities to check and test all products and also uses cytotoxicity tests, bioburden testing, LAL or risk analysis through FMEA. Validation of the processes follows DQ, IQ, OQ und PQ procedures.

Summary

The increase in complex consumable products translates to an increase in CMO opportunity. In order to be a successful diagnostic consumables CMO, there must be competency across all relevant technical disciplines and end-to-end integrated service solutions, all built on a solid understanding of the market. As illustrated by the case study, the model product development cycle cannot be fully achieved with technical competencies alone. Rather, these technical competencies must always be accompanied by end-to-end operations. A successful diagnostics consumable CMO can effectively apply these concepts for every manufacturing project. ■

Further information
Phillips-Medisize
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