Application Note

Considerations When Developing Diagnostic Assays Using Leading-Edge Technologies

The breadth of foundational technologies used in development of *in vitro* diagnostic (IVD) assays continues to expand and diversify beyond conventional lateral flow and immunoassays. From molecular diagnostics based on polymerase chain reaction (PCR) and next generation sequencing (NGS), to those incorporating CRISPR-based gene editing, strategies used in the design of these tests increasingly take advantage of novel and potentially disruptive technologies at the forefront of innovation.

Given the power and potential of molecular IVDs, it is not surprising that in recent years clinical laboratories have seen significant growth in the available menu of tests based upon DNA and RNA analysis[1]. Similarly, the rapidly evolving set of applications based on CRISPR now encompasses point-of-care diagnostics for routine clinical care which take advantage of the specificity, programmability, and ease-of-use of this versatile technique.

Advanced diagnostics are suitable for analyzing biological markers across the genome, proteome, and transcriptome and offer the potential of greater accuracy, sensitivity, and specificity. Given this broad potential, these tests are being developed and used to identify and characterize infectious agents, diagnose disease, identify risk, monitor the progression of disease and the impact of treatment, and predict response to therapy.

Undoubtedly, the recent pandemic emphasized the true value of molecular diagnostics and accelerated and expanded research and development efforts.

"By brutally exposing the shortcomings of existing diagnostic technologies and clinical testing infrastructure, COVID-19 is supercharging R&D efforts to establish novel testing approaches that are faster, simpler, cheaper, and more scalable than existing methods, and just as accurate."[2]

As with all diagnostic assays, the performance of novel technologies used to assess health at the cellular and molecular level must be validated and is a requirement for regulatory approval and commercial success.

Development and manufacturing of these disruptive technologies into validated IVD assays can, however, require strategies and resources that differ from those needed for traditional approaches. Below, we highlight key considerations for emerging and established companies as they advance novel molecular diagnostics from the bench to commercial production and distribution and how a contract manufacturing (CMO) partner can help.

- **Validate and ensure supply of bench-to-production material.** Emerging technology-based assays sometimes require more types of raw materials, intermediate solutions, and conditions. Working with an established contract manufacturing partner can help ensure a comprehensive, globally sourced portfolio, a stable and secure supply chain, and broad assay development expertise for scaling protocols from bench to manufacturing with transparency and compliance. By leveraging a global sourcing network, the partner can also help ensure competitive pricing of raw materials. When it comes to manufacturing, a partner with multiple sites and a common quality system can help ensure timely production, deliver products at the correct time and temperature, manage subunit kits requiring different temperatures.
- **Ensure raw material integrity.** With a robust process to ensure the integrity of raw materials, specifications can be controlled, as well as batch-to-batch accuracy and reproducibility. This is especially important with highly sensitive molecular diagnostic assays that can amplify errors caused by raw material instability or handling variability. Because of this, assay components such as the viral transport medium must be carefully formulated and controlled. PCR is particularly prone to raw material variability. Proteases and natural inhibitory elements can impact the PCR reaction and lead to false negatives. In addition, the process used to produce oligos and probes used for code detection is vulnerable and could also introduce variation, for example, if exposed to aerosol-based or handling contaminants.

- **Maintain flexibility.** Using novel technologies in diagnostic assays may require longer and reoccurring optimization periods that result in late-stage changes to the bills of material (BOM) as well as bench to manufacturing scale production. In addition, QC parameters for kit components and intermediate solutions are not fixed in late development and may need to evolve as the process is finalized. A CMO partner with a global network of suppliers is more agile and can more rapidly and seamlessly pivot as needed.
- **Confirm access to the necessary intellectual property.** With novel technologies evolving so rapidly, it is critical to define a clear path for licensing or royalties, if incorporating raw materials or technology from a third party. When considering the kit itself, confirm that the intellectual property remains with the innovator, even if the manufacturing technology resides with the CMO.
- **Know the necessary ISO certification level.** Raw materials, components, and intermediates may require an ISO certification from 9001 to 13485. Select a CMO partner that has the flexibility to source materials at any level. The 9001 certification reflects a research use only product; pilot development can start at this level and move to 13485 for FDA approval or a CE Mark. Regulatory agencies set specific rules on how many lots must be performed and validated.
- **Understand that scale-up is not always linear.** Scaling from bench to commercial production with novel technologies can be particularly challenging. In addition to not being linear, manufacturing may not have the same success rate. The quality team needs to be involved if there are changes and a new validation is required. An accurate long-term forecast is essential as it will determine the appropriate batch size and validation requirements. Limitations imposed by availability of capital or physical infrastructure can be overcome by partnering with a CMO with expertise in scaling processes and the ability to implement the necessary resources.
- **Understand regulatory requirements for both raw materials and the final product.** Consider partnering with a well-known, established CMO that has experience successfully navigating the regulatory landscape as the requirements and paperwork can seem overwhelming and are constantly evolving. This type of partnership can also help alleviate concerns on behalf of regulators about a novel assay development and help build the credibility of early-stage companies for investors and other stakeholders as well. The right CMO partner can keep a novel assay commercialization project on a firm foundation with a solid risk mitigation strategy.
- **Ensure universality.** If the innovator is developing a kit for use on existing platforms, it is essential that the assay be compatible with and reproducible across platform instruments typically found in the clinical laboratory. This approach creates the foundation for reaching as many testing locations as possible.
- **Be realistic about timelines and anticipate changes.** A savvy CMO can offer creative, alternative ways to meet project launch deadlines such as releasing initial pilot batches as research use only (RUO) to allow more time for final 510(k) and CE mark approvals. In addition, the global connectivity of an established partner can give more options for changing timelines, securing materials, or reacting to commercialization challenges.
- **Prepare for commercial success.** A regulatory approval may result in significant demand, which can strain internal manufacturing and distribution. This pressure can be offloaded to a CMO partner with the dedicated resources to accommodate rapid increases in demand and create seamless distribution channels.

1. https://asm.org/Articles/2021/July/Molecular-Diagnostics-in-the-Medical-Laboratory-in
2. Sheridan, C. COVID-19 spurs wave of innovative diagnostics. Nat Biotechnol 38, 769–772 (2020). https://doi.org/10.1038/s41587-020-0597-x

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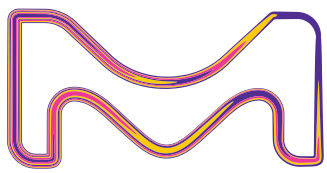

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03/2022