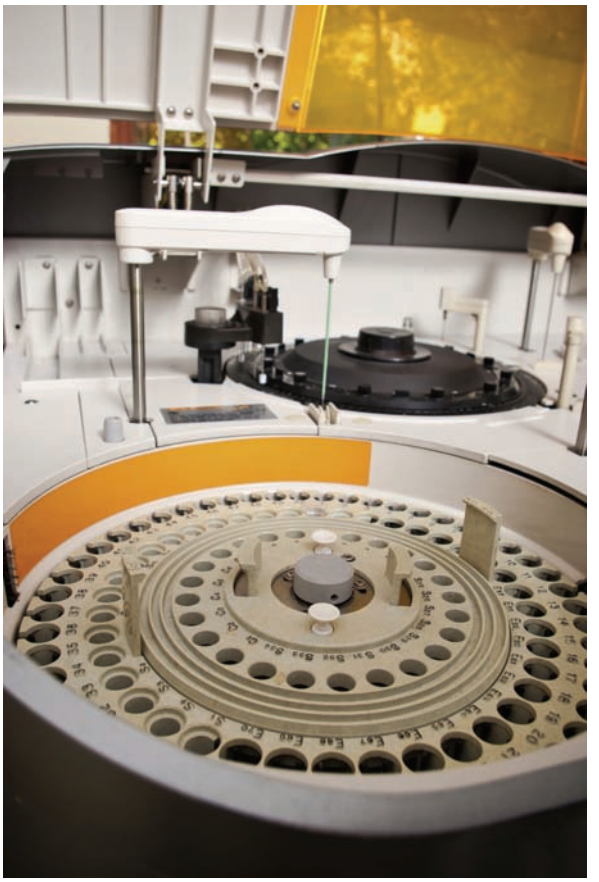
IVD TECHNOLOGY
FOR IN VITRO DIAGNOSTICS DEVELOPMENT & MANUFACTURING

PRODUCT DEVELOPMENT

Developing commercially successful diagnostic devices

Look beyond the assay—a parallel development approach that factors in the instrument, consumable and context of use will ensure optimal alignment of a technology with the target market. **BY PAUL WILKINS, Vice President Diagnostics Division, Sagentia. DR SUSAN WATSON, Associate, Sagentia**



When developing an IVD device, typically the first thing that comes to mind is the assay: what is the sample being tested for and how is the target detected? This is the central thinking of most companies, whether they are setting out to extend a product's lifespan or to bring a disruptive new technology to market. However, while the assay is core, focusing exclusively on this can significantly minimize the potential market scope and lead to commercial failure.

In this article we will evaluate a more comprehensive development approach that starts with the assay but also considers the instrument, the consumable and the context of use—an oft-neglected theme that warrants its own discussion. It will become clear that all of these themes are intricately linked and cannot be considered in isolation, requiring parallel development with regular input from all key stakeholders. To contextualize this discussion, we will start by evaluating two different usage scenarios.

Two usage scenarios: central laboratory system and portable handheld analyzer. The two system variants outlined below are intended to illustrate two distinct areas of IVD development.

- A high-throughput laboratory instrument for central lab use: MOLDX-5000.

Lab technicians would prepare samples from vacutainers and introduce them via pipette into either 96-well plates or integrated consumables containing standard pipettes and tubes.

- A handheld instrument intended for point of care use: MOLDX-LITE.

Nonskilled users would operate this device to process one sample at a time with minimum turnaround time and no external sample preparation.

We can imagine that these two system variants are based on the same assay/detection technology and both could be perfectly suitable paths to take the molecular technology to market. In both cases, an R&D team will need to have demonstrated the technology's feasibility often using a series of manual processes and off-the-shelf instruments. An R&D director will then need to work with the marketing team to evaluate the technology's commercial feasibility and to determine which product variant should be adopted. Even at this early stage of the process, the assay must be evaluated in the context of appropriate consumable, instrument and usage scenarios. Understanding these four areas will allow for more-informed decisions that can compare development plans, component costs, resource requirements and go-to-market timescales. Regardless of which product is chosen, the identical development approach needs to be followed to maximize the chosen market opportunity.

The Four Key Development Themes

Having agreed on the go-to-market strategy, the R&D director now has the task of resourcing a development team to bring the new test to market quickly. If the manual laboratory tests have demonstrated sufficient sensitivity and specificity for a world-leading product, some would assume that the development is halfway there. Whichever product variant has been chosen, shouldn't it now just be a case of handle-turning to build a "black box" around the assay

to replicate what has been successfully demonstrated in the lab?

Unfortunately not. We would argue that in terms of development timescale the team would only be at the halfway point when the intended assay is demonstrable within the intended prototype consumable and instrument. To minimize the time to get here and to drastically reduce the redevelopment effort required thereafter, it is crucial to have an integrated development team. This should include the engagement of all key technical and commercial stakeholders from the start, with representatives from usability engineering, consumable, instrument, assay development, marketing and regulatory experts.

Once the right team is in place, you can start understanding how the various streams are related.

The Assay

Having a laboratory assay with the required sensitivity and specificity is the first step. The test works in the lab, but this is a long way from a commercial product. Packaging up the assay from a multistep manual protocol carried out by a professional into a semi or fully automated process is complex. Deconstructing the assay workflow enables technology developers to determine the process step boundaries and categorically identifies the essential requirements versus those that are idiosyncrasies of the development scientist. It is not enough to take an existing protocol and map out the steps. If the R&D team is lucky, the protocol will work for anyone; however, most often scientists use the protocol as an aide mémoire, missing key actions, such as vortexing and shaking and not challenging redundant activities.

So how does an R&D team go about determining which steps are crucial and which can be challenged? Observation of the assay scientists by development engineers can extract valuable insights and contribute to piecing together the requirements of the device. This is usually where the process of making key development decisions starts:

- What is the most appropriate detection modality?
- What are the reagent requirements? Will they be stored dried down in a consumable or in liquid bulk?
- What impact will the usage scenarios have?
- What will this mean for the required assay steps?
- What impact will this have on the instrument's liquid handling requirements?
- What effect will this have on the consumable design?
- What does this mean for the reagent supply, stability, shelf life and packaging? For example, using lyophilization to improve shelf life may require the reformulation of enzymes, and, in turn, could impact the assay reliability, the manufacture of the consumable and the packaging.

And so the number of inextricable links grows and it becomes increasingly important that the assay scientists are able to work closely with others in the development team. Once these functional requirements are fully understood the process of translation and identification of technology and design solutions suitable for the target system and user can begin.

Successful assay development also depends upon the instrument and consumable development, and vice versa.

The Instrument

Defining the system architecture is a crucial task; the usage scenario and workflow require careful consideration:

- Who will use the system?
- How will they use it? What are the usage scenarios, such as throughput and turn-around-time, for single sample results?
- Will just one sample be tested at a time, will a number be tested as a batch or should the system provide an asynchronous capability?

Depending on the answers to these questions, the complexity of the device and the commercial constraints will differ. For example, a relatively simple instrument and consumable could be achieved if the user is asked to perform a number of complex steps but this would rule out a CLIA waiver. However, if a relatively complex instrument is acceptable, then the user steps may consist of simply inserting the sample into the instrument.

Some management teams will prefer to limit the discussions around these and other topics to input from a small number of trusted colleagues, but input should be sought from viewpoints including assay development, engineering, usability, design and marketing. There will be many available options and each of the potential system architectures will impact the development effort required to get the system to market. We would like to go back to our two different product examples to illustrate this.

The MOLDX-5000 system is a benchtop, mains-powered laboratory instrument to be used by skilled laboratory technicians, requiring the preparation of the sample and accurate metering prior to automated analysis and detection. Technicians will be asked to place an accurate volume of 100-µl whole blood into the instrument and then the system will automate the rest of the test process. This system will use the exact process developed by the R&D scientists and so the hope is that assay refinement will be relatively painless. Contamination control is essential here, meaning reagent containment and control of pipetting will be a key design consideration, and this will impact the process flow from the existing assay steps. The instrument size and complexity will be relatively large (weight is less of an issue but bench space is a key concern), but a degree of future-proofing can be incorporated, whereby thought is given now to additional bulk reagents or alternative analysis mechanisms. While the immediate focus may be to get an initial test to market, it is essential that this system development does not preclude additional tests or functionality from being added at a later date. This flexibility can either be built in now or left as a potential retrofit for the future. Either way, marketing will be happy that this can be a commercially successful product where all potential revenue streams have been considered.

Key instrumentation development tasks could require integration of off-the-shelf pipettors and robotic modules along with development of a sophisticated optics module. It is also important to carefully consider the requirement for sample tracking—above all else, in a central laboratory setting the data generated must be reliable and attributed to the correct patient! Instrument/consumable interfacing, data interpretation and transfer to a laboratory information management system (LIMS) should also be kept in mind.

The MOLDX-LITE, on the other hand, is a CLIA-waived battery-powered handheld analyzer for processing one blood sample at a time. For this system, the translation of requirements from assay into technology and system are more complex. Although the instrument itself may be less complex if it only has to perform one test at a time, this does not mean that system development is necessarily simpler. CLIA-waived devices should minimize manual metering by the user to reduce the risk-of-use error. Therefore the emphasis should be on the system to accurately meter both the sample and the reagents required for sample preparation. This often increases the internal complexity of the instrument, the required robustness of the assay and the stability of reagents. The consumable developed should be very well suited to the first test developed but also suitable for other assays that will be brought to market in the future. As such, the instrument must provide all of the functionality that could ever be required by this range of consumables.

To be well received by the market, the instrument's operation also must be clear and simple for the target user to understand in every aspect, including an easy-to-navigate graphical user interface. The development tasks required for this system place a far greater emphasis on consumable development and assay refinement, requiring input from assay R&D scientists, system development engineers, designers, and manufacturing experts.

Having defined the system architecture for either variant, the documentation required to build a complete Design History File (DHF) can start in earnest. Thorough, practical requirement specifications, agreed by all relevant stakeholders, should be established. This will, of course, be referred to during the eventual product validation.

A detailed system function diagram can be used to exhaustively list the functions that each aspect of the system will perform, as well as the interfaces between assay and consumable, instrument and consumable, user and instrument, and so forth. Inviting a core team representing all key functions to contribute will ensure this document maps out the entire problem space and will also help with effective management of the various interfaces that are essential for timely delivery to market.

Successful assay development **also depends upon the instrument and consumable development,** and vice versa.

The Consumable

The consumable will interface directly with the user, instrument, and assay. Whether you think the consumable is the most important aspect of system development, or simply the most constrained, it must be understood and its development managed carefully. For any diagnostic test, the handling of sample and assay reagents will differ significantly depending on how and where the assay is to be performed, throughput, and target cost.

Typically it is the consumable that drives profits and thought must be given from the outset to minimizing the cost of constituent parts, part count and simplifying the manufacturing processes required despite complexity. The consumable will be manufactured in high volume and so, as with the assay reagents, a company's manufacturing strategy and supply chain should be considered in parallel.

The consumable requirement for the MOLDX-5000 and MOLDX-LITE necessitates different approaches to sample metering, separation, mixing, and analysis, placing quite different constraints on the consumables developed.

The MOLDX-5000 should be able to use off-the-shelf components and therefore consumable development could be limited to optimization of manufacturing processes such as freeze drying and foil sealing.

For the MOLDX-LITE, significantly more design and development effort is required. Concepts for the various parts of the consumable should be sketched, modeled, prototyped, tested (both technical and user testing), and refined before combining them into an overall prototype. The consumable and assay development teams should work closely with each other as well as any key suppliers (such as moulders, makers of automated reagent deposition equipment and providers of production line assembly equipment). Ongoing testing should be carried out using consumables manufactured from the intended materials, using the intended assay reagents and blood sample as early as possible. At microfluidic scales, the intricate relationships between fluid and substrate mean that, although prototype models may look exactly the same, different materials and construction will have a significant impact on the reagent viability and assay performance.

Naturally, as the development progresses, testing migrates from individual components and subassemblies to tests using prototype instruments and consumables. There is no hard and fast rule as to when within the overall development program this should start, but it is helpful to have characterized a particular component or subassembly as much as possible before integrating it with the rest of the system. This will ensure that when assay, consumable and instrument are tested together, errors and variations will be tracked down and mitigated

more quickly, ultimately bringing the product to market faster.

A commercially successful product will mean the use of many consumables a day; therefore, the user experience of interacting with the consumable and the instrument interface—from opening the packaging and inserting it into the instrument to data interpretation—is key. These aspects are central to usability engineering and to the overall development process.

Usability

Some readers will question why usability should be considered in its own right. Surely good design includes consideration of the user experience? Absolutely. However, given that the consideration of usability is of increasing importance in medical device development in the wake of the IEC 62366 standard, it seems prudent to explicitly consider how we might aim to achieve an enhanced user experience while minimizing risks associated with using a device. We have deliberately envisaged two diagnostic systems with different users and significantly different user requirements. It goes without saying that both systems should be capable of using the assay to provide tests with high sensitivity and specificity, but throughout the process thought must be given to the user experience. A technically outstanding product with a poor user experience is unlikely to succeed commercially.

For both the system variants described, once the system architecture has been defined, a detailed task analysis can be provided to map out the user steps. This essentially starts with analysis of the assay steps performed at the outset of the development program and understanding the impact of the usage scenario on how the user will perform various steps and interact with the device.

As with more traditional technical development, the identification and mitigation of usability risks is now seen as an important part of the overall development. Several rounds of formative user studies, simulating use of the system ideally in its intended use scenario, should be used to accurately document and explore observed and potential user errors and issues.

One way of doing this is to generate a Usability Action Record. This is a live document that uses task analysis as its framework to generate and record goals, use errors (both potential and observed), risks and criticality, required actions, and mitigation status throughout the process. This supports adherence to IEC 62366, while also being an essential, efficient and effective way to manage the usability risk and performance exploration.

Conclusion

From the two system variants discussed, it is clear that there are different development considerations depending on what product an R&D team is pursuing. However, the comparisons also reveal common key success factors regardless of the type of product that is being developed.

First, it is important to recognize the significant overlap that exists between each of the four distinct development themes: assay, instrument, consumable and usability. Focusing solely on the assay, intricate relationships with other parts of the system will be overlooked. By considering all these themes throughout the development process, however, R&D teams can map out their go-to-market strategies more appropriately, develop the product more efficiently, and achieve greater commercial success.

> A technically outstanding product with a poor user experience is **unlikely to succeed commercially.**

Second, from this brief discussion it is clear that the overlap of each theme emphasizes the importance of having a fully integrated team working together early on to identify and channel valuable insights. Regardless of whether the technology comes out of the diagnostics division of a global medical device manufacturer or a start-up company borne out of successful postdoctorate research, R&D teams should include representatives from usability engineering; consumable, instrument, and assay development; and product management. This approach combined with careful management and regular communication can significantly reduce timescales, decrease development costs and produce a system that is more aligned with a company's target market. Ultimately, the chances of achieving real commercial success are very much improved. IVD

Are you faced with complex diagnostics development challenges?

Sagentia's work ranges from central laboratory instrumentation, through to Point of Care analysers and home use disposables, with applications in clinical chemistry, haematology, molecular diagnostics and genomics. For further information email us info@sagentia.com

Reprinted with permission from IVD TECHNOLOGY, July/August 2012. On the web at www.devicelink.com/mtprecision.
© A UBM Canon Publication. All rights reserved. Foster Printing Service: 866-879-9144, www.marketingreprints.com.

SAGENTIA

Telephone number UK +44 1223 875200 • Telephone number US +1 617 896 0213
info@sagentia.com • www.sagentia.com