PAPER

Creating novel medical diagnostics with a design for manufacturing

Translational Materials Research

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Abstract

When research is undertaken with the aim of creating a product to address real-world problems, incorporating considerations for manufacturing early in the creative process is important to reduce the barriers to translation later in development. A general description of the product development process is provided within the context of design for manufacturing. Building technologies on existing infrastructure for manufacturing can dramatically reduce the cost and time to create a product. The trade off of such an approach is that the work may not be deemed novel and may, thus, be harder to publish. A brief overview of recent work by several groups to develop a point-of-care test for Zika virus illustrates the repercussions of different approaches to novelty versus manufacturability. Actionable guidance is given for both researchers and those that support the research endeavor, such as funders and editors of peer-reviewed journals, on how to incorporate manufacturing into early research.

1. Introduction

The field of point-of-care diagnostics, which includes medical diagnostic tests designed for use at home, at the bedside of a patient, at primary care clinics, or in remote settings, has seen tremendous activity in academic research over the past decade [1–3]. Only a handful of these newly invented techniques and materials, however, have found their way into products that are available today. A lack of early testing in the intended end-use setting is one reason that has been identified for the disconnect between research and product [4]. Equally important, and equally lagging, is the gap between the invention of new tests and the demonstration of methods to manufacture them at scale (figure 1). On average, from 2011 to 2016, only about 1 in 77 publications on point-of-care diagnostics deals with manufacturing, while 1 in 49 dealt with clinical trials or field work.

By understanding and incorporating the views and voices of manufacturers early in the process of invention, innovators in point-of-care diagnostics can lower the barriers of cost and time to translate their idea into a product. As inventors, it is tempting to think of manufacturing and supply chain as someone else's problem; a matter for 'engineering' and 'development'. In reality, decisions made at the point of invention often set the trajectory of the final product and have a greater impact on the cost and configuration of a device than almost any other stage of product development.

Having moved from research in academia to research and product development in industry, I have seen the disconnect between invention and manufacturing first hand. It poses a significant challenge to getting a product to market. There are, fortunately, many opportunities to improve the efficiency of translational research. This perspective (1) describes the gap between invention and manufacturing in point-of-care diagnostics, (2) highlights approaches to reduce the gap, (3) identifies structural and systematic barriers to closing the gap, and (4) proposes actions for both researchers and the broader system of funders and academic research. This article is not intended to be an exhaustive review of manufacturing for point-of-care diagnostics. Recent reviews on manufacturing of paper diagnostics [5], microfluidics [6], and lateral flow tests [7] provide detailed coverage of the field.

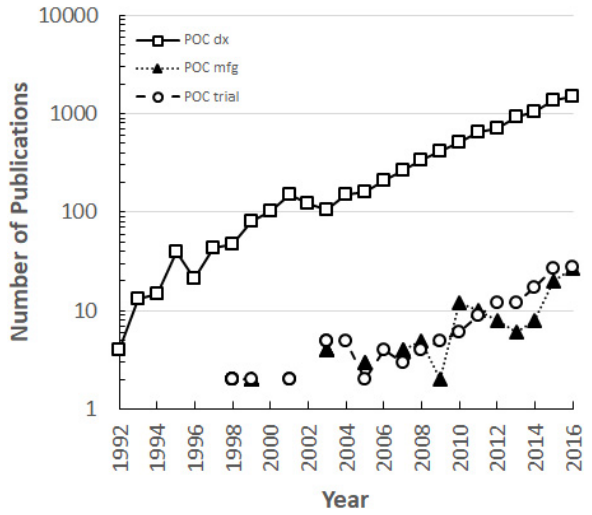

Figure 1. Publications on point-of-care diagnostics that include manufacturing (POC mfg) are even rarer than publications on point-of-care diagnostics that include field trials or clinical trials (POC trial). Both are orders of magnitude less frequent than publications on point-of-care diagnostics in general (POC dx). On average, from 2012 to 2016, only about 1 in 77 publications on point-of-care diagnostics deals with manufacturing while 1 in 49 dealt with clinical trials or field work. Web of Science (Thomas Reuters) was used to generate results by searching for (point-of-care AND (diagnostic OR test)) for POC dx, ((point-of-care AND (diagnostic OR test)) AND ('field trial' OR 'field evaluation' OR 'clinical trial' OR 'clinical evaluation')) for POC trial, and ((point-of-care AND (diagnostic OR test)) AND manufacturing) for POC mfg.

2. The gap between invention and manufacturing in product development prevents translation

For an idea to become a product, it must successfully proceed through the product development process (table 1). Incorporating considerations for manufacturing throughout the entire process enables a more efficient transition from idea to product. During *Phase 1: Concept*, the majority of work is done on paper: understanding the background and prior art, defining the problem and end-user, and identifying key innovations. Some experiments may be done to demonstrate proof of concept and demonstrate key inventions. For a successful commercial venture, this stage also includes market research to check whether there is a true need for a new product based on the concept developed. Designs at this stage should incorporate knowledge of common manufacturing practices.

If the concept checks out in these early experiments and a real need exists, the project moves to *Phase 2: Feasibility*. At this point, 'looks-like' and 'works-like' prototypes are built. Individual concepts from Phase 1 should be assembled together. For example, blood separation methods should be connected to the assay in a prototype device for a blood test for a serum protein. Ideally, work should be done with the sample matrix relevant to the final product. In addition to the bench work to determine if performance specifications can be met, the team developing the product begins assembling a bill of materials for the product to determine whether the market specifications of the product can be met. In addition to the per test cost, the team can get an idea of the fixed costs needed to get manufacturing up and running. By drawing on experience of veterans in the field and manufacturing partners, the team can identify parts or processes that will require specialized manufacturing techniques and begin planning for them.

Once a successful prototype is demonstrated and specifications are met, the team can progress to *Phase 3: Verification*, where a low- to medium-volume (hundreds to low thousands) build of devices is done and tested more rigorously to determine characteristics such as shelf life, stability, failure modes, and interferences.

Going from Phase 2 to Phase 3 requires either setting up a manufacturing line internally or transferring the technology to a contract manufacturer. Depending on decisions made in R&D and how the prototypes were built, the cost of this transition, whether internal or external, can be significant. If existing manufacturing infrastructure can be used or repurposed, the costs could be as low as $50,000 (depending on the complexity of the product) at this stage. If custom machinery is required and must be validated the costs can easily exceed $1 million.

With the manufacturing design verified, the product moves to *Phase 4: Validation*, in which multiple lots (usually three) of the diagnostic device are built where at least one lot is commensurate with the volume expected for scaled production (generally on the order of tens of thousands to hundreds of thousands). The tests built in these runs are then used for rigorous testing for building technical files for regulatory approvals. Because the build quality at this stage must be up to the required specification for the final product to be sold, once required

Table 1. Manufacturing considerations in the product development process.

Phase	Key activities	Scale (devices)[a]	Manufacturing activity
1. Concept	• Perform background research • Identify needs and do stakeholder analysis • Define target technical specifications • Identify potential solutions • Show proof of concept	0–1	Choice of materials and designs that are amenable to manufacturing infrastructure
2. Feasibility	• Make prototypes • Achieve key technical specifications • Gather feedback from intended users • Develop a bill of materials	10–100	Identify specific processes or parts that require specialized manufacturing
3. Verification	• Test key performance characteristics such as limit of detection and precision • Begin assessing shelf life and stability • Achieve desired performance with intended use	100–1,000	Transfer to scalable manufacturing process
4. Validation	• Demonstrate that fully manufactured product performs at specifications • Begin clinical and analytical studies for regulatory submissions • Finish all packaging and supporting materials	10,000–100,000	Production of 3 lots following final manufacturing processes
5. Launch	• Scale up production • Develop and deploy marketing strategy • Provide technical support to customers • Perform post-market surveillance • Feed learnings into new concepts	100,000+	Fully implemented manufacturing process

[a] Exact numbers will vary depending on specific cases. Estimates are given to signal order of magnitude changes.

regulatory approvals are in place for a particular country, tests from these lots can be sold. More often, scale up and commercial launch comes as *Phase 5: Launch*. At this phase manufacturing is fully in place and both in-process controls and post-market surveillance are used to ensure the product maintains performance and is being used correctly. Learnings from post-market surveillance can be fed into new concepts to restart the cycle and either improve an existing product or develop a new one.

Often in academic research, and even occasionally in industrial R&D, scientists and engineers are concerned only with Phases 1 and 2 to get a prototype that works well enough for a proof-of-concept or a publication. Neglecting thoughts for manufacturing at these early stages can be disastrous for translating the concept into a product. A prototype that satisfies the feasibility requirements but is not easily manufactured may inadvertently signal to others that less work remains to be done than is really the case. This situation makes it harder for R&D to secure the resources (whether grants or internal funding) to make significant redesigns to make a prototype manufacturable.

The final cost of goods sold (COGS) of the product are also dependent on how the transition from Phase 2 to Phase 3 occurs. The COGS include costs that in addition to the bill of materials (BOM) that is often cited as evidence of a low cost product in early publications. The BOM is an important consideration, especially if the ultimate aim is to build a low-cost diagnostic test, but focusing exclusively on minimizing the BOM may not minimize the COGS. For example, for a specific diagnostics application that require uniform flow, a cellulose-based string may be a very low cost material but may require several steps of dipping and drying in various solutions to improve the uniformity in flow over the string. Alternatively, a string woven from polymers that is highly uniform and requires no further treatments could have a higher materials cost than the cellulose-based string, but the final product will have a lower COGS because of the reduction in labor and processing.

3. Leveraging existing manufacturing processes enables speed

The recent outbreak of Zika virus and the ensuing rush to develop rapid diagnostics for Zika provides an illustration of the importance of considering manufacturability early. Several academics and companies jumped at the opportunity to create a rapid test for Zika.

At the 2016 meeting of the American Association of Clinical Chemistry (AACC), Elizabeth Holmes, CEO of Theranos (Palo Alto, CA, USA), announced that her company's MiniLab platform had a test for Zika virus

that would soon be available [8]. The MiniLab platform is a complex system that would require a fairly high end manufacturing system and process controls to ensure adequate performance. It's unclear how the per test pricing of the test would be. In late 2016, the company voluntarily withdrew their FDA application [9]. As of late 2017, no product for Zika is on the market from Theranos.

In early 2016, a novel diagnostic for Zika virus was published in Cell [10] that used a combination of isothermal amplification, toe-hold switch RNA sensors, and CRISPR-Cas9. While the authors spent some discussion on manufacturing and stability, they did not demonstrate a clear way to manufacture tests at scale. The method requires lyophilization, which could be used in a batch style manufacturing process, but would be difficult to implement in a roll-to-roll system. Many of the authors were involved in subsequent work using CRISPR-Cas13a as a diagnostic platform [11]. Again, lyophilization is used and much work remains to take this promising work from proof-of-principle to scale as a diagnostic platform. In time these technologies could have a major impact on POC diagnostics, but there are no products currently on the market using them.

The company Nanobiosym (Cambridge, MA, USA) has been developing a platform technology for POC diagnostics called Gene-RADAR for several years. In early 2017, they received emergency authorization from the FDA for a test for Zika virus on their system. Nanobiosym was able to take advantage of the general platform they have built to add a new test quite rapidly. Before the test can launch at scale, work is required to expand production [12]. The challenge with a radically new platform is that manufacturing often requires the development and validation of entirely new processes to ensure quality at scale.

Chembio (Medford, NY, USA) has developed a rapid test for Zika antibody detection. Rather than developing a new platform, they built on a tried-and-true technology, lateral flow immunoassays. They introduced novelty to their design using their Dual Path Platform technology, but the fundamentals of the test rely on rectangular strips that can be assembled from cards or rolls, and injection molded plastic parts that can be assembled by hand or by a pick and place machine. As a result of leveraging existing infrastructure, Chembio was able to attain emergency use authorization from the FDA in late 2017 and their product is currently available for authorized laboratories in the US [13]. They also have a Zika antibody test with CE mark that is commercially available in Europe.

4. How do we close the gap between research and manufacturing?

Just as materials and technology research is constantly evolving, manufacturing continues to evolve as well. Taking advantage of well-established manufacturing while keeping an eye on new trends in manufacturing may provide the best mix of novelty and scalability for researchers looking to create a new diagnostic test.

In the area of paper diagnostics, advances have been made by looking to technologies from the printing industry [14]. These methods can be useful for both patterning barriers in paper as well as for spotting or striping reagents. It is important, however, to note the difference in scale between an office printer and an industrial dispenser from companies like BioDot (Irvine, CA, USA), Imagene Technology (Hanover, NH, USA) or Kinematic Automation (Sonora, CA, USA). Designing tests to use the industrial scale printers can save time down the line since many contract manufacturers are already familiar with these machines.

In the area of open channel microfluidics, PDMS is often the go-to material for researchers [15]. It is, however, anathema to manufacturers. As a result, companies that have successfully made microfluidic products almost never have PDMS in the final product [16]. Etched glass or injection molded plastic parts are more common in products. For small scale production, the cost of molds may be prohibitive. Alternative methods that allow researchers to work in materials more similar to moldable materials can aid in the transition. Hot embossing is one method to make microfluidics channels and other features in plastics [17–19]. Advances in 3D printing also allow users to rapidly iterate over designs in a variety of resins [6, 20].

One way to ensure research decisions are made with manufacturing properly considered is to include the voice of manufacturers early on in the research endeavor. Talking with molders, strip manufacturers, and companies that make dispensers and automated systems can be illuminating. Often they are happy to provide feedback without a significant obligation. Manufacturers want your design to succeed because they have an interest in your final product actually being manufacturable.

5. Structural and systemic changes can create incentives to incorporate manufacturing into R&D

In addition to changing practices of researchers, there are systematic changes that could encourage consideration of manufacturability and improve the translation of new technologies to products. In publications, there is significant pressure to create something new; work that builds on existing technologies or methods are sometimes criticized as being derivative. While some of this criticism is merited, it also discourages researchers to think about how to innovate with existing manufacturing processes. When researchers make a specific choice to build something new by leveraging existing manufacturing technology, it should be applauded by editors and

peer reviewers. Conversely, peer reviewers should evaluate whether researchers have adequately thought of the manufacturing challenges for new methods or devices that claim to have practical applications.

Research fundings similarly does not provide incentives for manufacturing. Grants often focus on proof of concept and fund work through Phase 1 or Phase 2 of the product development path. Foundations and agencies often assume that manufacturing and scale up will be covered by investors. Investors, however, often have little appetite for risk and they want to see regulatory approvals or early market traction. These milestones require some degree of manufacturing. The US Small Business Innovation Research (SBIR) program offers some support for transfer to manufacturing through its Phase II and Bridge awards. If more agencies and foundations could offer such programs, it would promote design for manufacturing.

6. Incorporate manufacturing considerations early ensures that research translates to products

Researchers that want to see their ideas for low-cost diagnostics become real products, should build relationships with manufacturers early and include them in the design process every step of the way. When trying to create a disruptive new product, understanding the manufacturing paradigm of the incumbent technologies can help inventors avoid running into costly translational expenditures further down the line. If new manufacturing methods are needed, the earlier they can be identified, the sooner they can be de-risked through manufacturing method innovation or design changes. Whenever possible, build on existing infrastructure to save time and money.

Leveraging existing manufacturing may mean that an invention is less flashy than a more novel approach. As a result, such work may be harder to publish in a high-profile journal or the IP around it may not get investors to through large sums of cash at it. Actually making a product, however, may require less cash than would otherwise be necessary if manufacturing has been carefully considered at the earliest stages of research.

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