Technology Transfer Tactics™

The monthly advisor on best practices in technology transfer

Consider outsourcing options when faced with production and scale-up challenges

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For discoveries made in university labs to reach the commercial marketplace, so many tasks must be completed, so many questions answered, and so many hurdles overcome. Is the invention truly novel and can it be protected? Are there competitors, and is there a market need? Can funding be obtained? And then, even if every challenge is successfully addressed, there's one more critical question that must be asked and answered: Can we actually produce the product, at scale and in a way that makes financial sense?

Although the actual physical making of the end product is not often the focus of research commercialization efforts, it is a critical challenge that must addressed. Can the product be produced at scale economically enough to be part of a viable start-up business or licensing plan? Depending on the technology, and researchers' or company goals, such a feasibility analysis might include:

1. Review and evaluation of the existing production process.
2. Production improvement strategies.
3. How to scale production of the technology.
4. How to cost effectively source the raw materials required for large-scale production.

What TTOs need, but may not always plan for, is an independent analysis of the chemical processes and engineering plans required to develop the new technology.

Phil Rufe, technology transfer coordinator at Eastern Michigan University, shares the challenges he faced: "Our partner provided Eastern Michigan University a Technology Assessment Report for a potential commercial process to manufacture a novel antibacterial fabric treatment. The technology assessment detailed and itemized scale-up costs, identified potential improvements for the manufacturing process, recommended alternate raw materials, and recommended several downstream process improvements for our technology. The technology assessment was an essential tool for our decision making process."

Chris Harris, PhD, director of licensing in the Center for Technology Transfer & Commercialization at Vanderbilt University, recounted a similar challenge. "Our external partner's technology assessment helped us make some important decisions about our current process assumptions and related costs. The technology assessment pointed out areas where we needed to reduce our cost as we prepared for larger scale production."

Depending on the technology, and/or the researcher's needs, technology assessment requirements will vary. Analysis might include the choices of reagents and intermediates for optimal performance, availability and cost. Or the assessment might need to evaluate impurities, by-products and yields in terms of alternative processes, regulatory concerns, or cost savings opportunities.

Many start-up companies select the virtual route of being "idea" firms that outsource their development and clinical pipelines because they know these activities are not their core competency. They know that obtaining help from external partners is necessary for commercialization and plays a huge part in the ultimate success or failure of the technology. For TTOs, it's an option that should be strongly considered.

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Scale-up challenges

Whether in industry or in university incubators, scale-up from the laboratory to commercial production scale can be a challenge for a variety of reasons. The early development stage of new technology is usually based on small scale batch synthesis. Drug development, for example, is often done virtually to minimize costs. A complicated and expensive laboratory process is often acceptable for producing gram scale quantities of a chemical product, but it may not be a scalable basis for commercial manufacturing.

At larger scales, obtaining raw materials and identifying appropriate and cost effective manufacturing partners represents a significant challenge, and the transition from the laboratory bench to large-scale production is a major step. Process modifications and raw material alternatives usually need to be evaluated in great detail.

Start-ups must find a production facility that is cost-effective, meets regulatory requirements, and in some cases, is geographically close. If the proper manufacturing facilities and/or raw material providers cannot be located in an efficient manner, unrecoverable time and money are lost. Because this is not their core competency, start-ups typically seek external partners to provide this service.

Companies that specialize in scale-up analysis can provide the expertise to scale the process to achieve successful manufacturing at the commercial level, as well as obtain the requisite raw materials with a significant cost savings on the commercial scale or help procure less expensive starting materials. Another option is to develop an alternative process technology.

We recently worked with a virtual firm that was looking to custom synthesize preclinical and clinical batches of its proprietary active pharmaceutical ingredient (API) under an aggressive timeline. The solution to scale-up challenges was to develop an alternative process technology. After initially working from a non-optimized process incompatible with scale-up objectives, the client was able to accelerate its commercialization timeline after the successful manufacture of its target API material.

Licensing challenges

It's not just start-ups that may be in need of help in the production end of the commercialization process. TTOs looking for licensees and investors must be ready to provide these potential partners with independent analyses of commercial viability.

Investors and potential licensees require proof-of-concept work, data collection, and analysis including synthesis, testing and formulation work. This is often one of the most expensive and difficult steps in the life of a start-up. While fledgling companies usually can confirm the bioactivity of a drug candidate on their own, their ability to prepare a comprehensive technical package suitable for licensing or transfer often remains beyond their internal capabilities.

In many cases, the most strategic approach is to outsource commercialization requirements to experienced specialists. In most cases this saves not only cost but precious time. The key drivers of cost savings are access to production capacity and facilities, access to expertise (regulatory, scale-up, etc.), reduced investment in capital assets and fixed costs, access to reasonably priced raw material supplies, and the ability to stay focused on core competencies.

Regulatory compliance challenges

Another common challenge is regulatory compliance. During the R&D phase, companies minimize expense by producing test quantities using non-compliant batch production methods. However, converting these processes to meet regulatory requirements for scaled-up commercial production can be extremely time-consuming and costly. Frequently a change in facilities is also needed, further complicating matters.

In the production of pharmaceutical products, cGMP regulations, for example, require that all commercially produced drugs and pharmaceutical products meet stringent assay, quality, and purity requirements. Facilities must have appropriate quality management systems in place that can detect, investigate, and correct product quality deviations. Investigational new drug (IND) submissions to the FDA can easily be delayed and rejected due to insufficient data, inadequate reporting or insufficient cGMP reference standards. This may necessitate rapid preparation of clinical trial batches and validation and/or production of GMP-grade material to serve as a reference standard itself.

Even if the custom compound is the active pharmaceutical ingredient (API), and therefore does not require cGMP certification, the supply of specialized intermediates and precursors for life science applications may necessitate specific ISO certification on the commercial scale. This is becoming increasingly rele-

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vant as medical device companies request custom synthesis services for new excipients and components for novel drug-device combinations.

A recent case history illustrates this challenge. A biotech start-up had an Investigational New Drug (IND) that had already been submitted to the FDA. There were several clinical trial candidates and the pre-clinical results were promising. However, the technical package contained vague data and there were no cGMP reference standards, resulting in poor FDA compliance. The start-up was up against the pressure of a critical timeline to save the project, and the potential for money to be lost and the project be abandoned was extreme. An external partner was called in. To address these issues, the partner conducted a comprehensive evaluation of the technical package and identified the weak links. Clinical trial batches were prepared with reference standards validation. Additional tests were performed for end formulation, concurrent with stability testing. A dialogue was established with therapeutic and delivery mechanism experts to ensure a product suitable for clinical trials. The result was a successful FDA review and a grant of fast-track status.

Finding the right external partner

An external partner will ideally have years of experience, proprietary knowledge and well-established industry relationships. They will be familiar with the capabilities and capacity at a wide variety of laboratories and manufacturing facilities including those facilities' technical competencies, scope of capabilities, track record, niche technologies, available equipment, manufacturing capacity, scalability and reliability.

There are various outsourcing models which can be utilized depending on specific need, company philosophy, and/or time and financial constraints. The Project Management Model is a good fit for many start-ups and TTOs.

In this model, a company is hired to provide project management services for the project being outsourced. The Project Manager (PM) does not conduct the actual physical manufacturing within its own facilities. Instead, the PM provides access to a specialized network of suppliers with whom it maintains established relationships. Enlisting the services of a PM effectively expands the potential sources for any company engaging in outsourcing. The PM provides industry vendors, such as contract research organizations (CROs) or contract manufacturing organizations (CMOs), with technical competencies, scope of capabilities, track record, available equipment, manufacturing capacity, scalability, and reliability. A PM functions as the client's *de facto* outsourcing department -- but without the internal cost.

The PM's technical and manufacturing experi-

Case studies illustrate benefits of outsourced project management

The following case histories are representative of the challenges that a start-up may face and how an experienced project manager such as Richman Chemical (RCI) can effectively help meet these challenges.

Case study 1: The TTO of a major East Coast university was working with three start-up biotechs in its chemistry and pharmacology departments. Each of the three was developing a unique product (medical devices and drug product), but all were based on the same chemical platform. While there was general knowledge amongst the three start-ups that their chemistry was similar, there was no realization that the core preparative chemistry was identical. RCI worked with each of the three to share the sourcing and preparation of the common chemical starting point. RCI developed a plan that allowed each start-up to benefit from the combined chemistry at an efficient scale and time. RCI's approach saved each start up thousands of dollars in development costs, optimizing their limited equity dollars. One of the companies is now successfully completing first-in-man studies on its medical device, and another is in Phase 1a clinical evaluations.

Case study 2: Richman Chemical was recently contacted by a virtual firm looking to custom synthesize preclinical and clinical batches of its proprietary API. The customer came to us with an aggressive timeline and academia-based technology offering significant scale-up challenges. In addition, the company was also experiencing employee turnover -- the head of manufacturing had been replaced twice within the previous 18 months. By combining our project management skill set and ability to identify the technological challenges essential for project success, we guided the customer through project development while its management team was reorganized internally. Further, an alternative process technology was proposed to aid with scale-up issues. Richman Chemical even went a step further and devised a contingency plan in case the new processing technology did not progress as quickly as anticipated. As a result, our customer gained a team of expert project managers who had broad knowledge of drug development and access to a network of cost-effective resources. After initially working from a non-optimized process incompatible with scale-up objectives, the client is now able to accelerate its commercialization timeline after the recent successful manufacture of its target API material. ▶

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ence leads to compressed timelines, lower costs and increased technical capabilities. Furthermore, PMs can facilitate the provision of auxiliary services as needed, including product development, raw material sourcing, and logistics coordination and regulatory support.

Within the parameters of the Project Management Model, the outsourcing client is significantly dependent upon the expertise of the PM to provide compatible service offerings. However, the model itself is based upon a cooperative, risk-sharing foundation between the client and the PM. It is not uncommon to invoice for services rendered only after the project has been successfully completed.

To summarize, the proliferation of start-ups within the life sciences market highlights the need for competent, highly skilled vendor partners capable of handling custom chemistry projects. Effective outsourcing to CROs/CMOs provides a significant opportunity to accelerate product development, maintain operating budgets, and use internal resources effectively.

A wider acceptance of the benefits of such a relationship can only be gained by fostering a greater understanding of the outsourcing process. Start-up organizations may find that, in many cases, the Project Management Model offers the greatest benefit when it comes to successfully commercializing technology within the shortest amount of time.

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