

Building Your Biotech Company: The Basic Building Blocks

Chapter Three: Operations

“Virtual to Literal Construction.”

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Even at the kitchen table stage, a company must operate with a practical and pragmatic system that wastes little and accomplishes much in proportion to its size.

Organization into needed activities and functions form the underlying support, but no amount of planning can substitute for managing the ongoing action of physical operations as the company and its activities constantly scale up. For this chapter, numerous experts address the following three areas in separate sections:

- **Siting/Building**
- **R&D/Manufacturing/Supply Chain**
- **Outsourcing**

Here is a short summary of the major questions addressed by the expert panel:

Renting or buying company structures, from office to lab space, soon becomes a necessity in a new company. Our panel lists the best practices and first principles of matching building space to a company's growing needs, including key criteria in selecting proper sites, financing construction/remodeling, and planning for future growth. They also address real estate and tax issues, as well as staffing issues associated with site selection, construction, and management.

Starting at research-level production, a company must anticipate and plan for needed quantities, time delivery, and resources to ensure efficient supply and processing of raw materials into finished product. Our experts offer advice on how to plan for increasing volume and changing technologies in scaling up manufacturing from product development to marketing and distribution.

Outsourcing has always been a mainstay for biotech start-ups, especially in manufacturing and research operations. Our panel addresses the typical types of and timespans for outsourcing key operational functions. They assess the degree to which a company should be “virtual” at each stage in its growth. They examine the stakes involved with in-house versus outsourcing strategies. And they offer informed guidance on selecting, contracting with, and managing external operational resources.

SITING/BUILDING

If you start a biotech company, no end of economic development clusters, contractors, and site owners will stampede to your door offering you a place to set up business. Objectively, however, you must make basic decisions about sites and building space that may have nothing to do with the sales points in such pitches. Though no size fits all, our expert discussion here answers the most common questions that arise as companies evaluate and accommodate their need for physical workspace.

What are the best practices and first principles of matching building space to a company's growing needs?

It is important at this juncture that your business plan is clear and your funders and managers share the same vision. If your ultimate goal is to be a megacorporation in your own right, the decisions you make at this point may be different than if you see partnering or M&A as your eventual exit strategy.

According to Tim Noffke of Integrated Project Management, “If you intend to out-license or sell the product you're developing, the acquirer will be interested only in your

THE BASICS OF LIFE SCIENCE BUILDINGS

Generic Lab Space
100% outside air, 6+ air changes per hour
Lab benches, fume hoods, biosafety cabinets
Lab utility support area to include redundant power, tanks (oxygen, CO ₂ , N ₂ ,) etc.
Build out could include: tissue culture, cold/warm rooms, autoclaves, vivarium, chemistry labs, dark rooms, freezer boxes, deionized water, glass wash, vacuum
Biosafety Space
BSL 1—similar to a high school biology environment. No agents that are harmful to lab personnel and no special containment necessary
BSL 2—lab designed to enhance containment (100% outside air, fume hoods, biosafety cabinets). Agents moderately harmful to lab personnel/environment
BSL 3—required lab environment when working with infectious diseases (20 air changes per hour, hepafiltered, full redundancy in mechanical/electrical, gowning procedure prior to entry into BSL 3 contained area)
Manufacturing Space
Designed, constructed and validated to meet Good Manufacturing Practices (GMP) guidelines
BSL 2 / BSL 3 with class 10,000 clean room environment
Significant redundancy
Downtime can cost a company millions of dollars in lost production
Vivarium Space
Animal Husbandry Space
Accredited by Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)

technology: how robust it is, how well-protected from an intellectual property standpoint, and so forth.”

Noffke adds, “Bricks and sticks” are not the usual assets of a startup biotech. Put your money into getting the space you need to support the evolution of your technology (for example, lab space) and to foster collaboration and communication among your team.”

Your business plan will inform your decisions. The amount of space you’ll need down the road may be hard to estimate, but leasing or building too much property too early is unnecessarily expensive. On the other hand, do plan for expansion. Noffke says, “Try not to pay for space that may remain empty for 12 months or more.”

It is important to consider whether the space you are moving into will facilitate and enable growth. If your company outgrows the facility too soon, you will be looking at either moving, or separating functions, which does not create the best possible working conditions. Space in an existing laboratory or an incubator building are

logical candidates for a fledgling company. Repeatable, modular lab space is a viable option. (See also “The Basics of Life Science Buildings.”)

William Ju of PTC Therapeutics points out, “There is a fine balance between not taking on too much space and wasting resources on overcapacity on one hand, but on the other hand, having enough to grow and meet the ever-changing needs of research, development, and eventually commercialization in a timely fashion.” It is important to establish milestones early on so that you know when it is time to add space or equipment.

Put your plan on paper, know when the time is right to make adjustments, and expand as necessary to accommodate the need.

Ju suggests developing a plan based on anticipated head count. He says, “Then the assumptions and plan need to be reviewed regularly so adjustments can be made to meet changes, which can be driven internally (such as progress in the science) and/or externally (such as business development opportunities). Such planning requires a vision of where the company will be,

how many employees will be required to meet the needs of the operations, which projects will be in the pipeline, and what strategic alliances that may develop. It is often more art than science.”

What are the key criteria in selecting proper sites, financing construction/remodeling, and planning for future growth?

When planning where to locate your company, there are myriad things to consider. Proximity to what Tim Noffke calls “intellectual horsepower” as well as financial backing is important. If you hope to gain angel or VC backing, it is wise to locate in an area near your intended source. Active early-stage investors often want to participate in the day-to-day management of the companies they fund, and will therefore value proximity.

Urs E. Aeberli of FFF Enterprises reminds us of some of the basics. Facilities, he points out, should be located close to traffic corridors, airports and shipping hubs. You also need to evaluate tax implications, tax abatements, property tax exemptions, sales

tax and use tax exemptions as well as the local labor pool and economy.

“Try to take advantage of incubator space offered by academic centers or funded by state or federal dollars,” advises Noffke. “Incubators provide startup companies with some of the basics, such as access to laboratory facilities and equipment, and help to write grants or determine IP strategy. You can identify local incubators through major universities, or by contacting a local chapter of the Biotechnology Industry Organization (BIO).”

Noffke also advises, “When leasing space, you can often negotiate that the owner build out your space according to your specific requirements with the cost of the build-outs amortized over the life of your lease. Why would owners front potentially tens of thousands of dollars of their own money to renovate space for you? Because their building becomes more marketable when it sports a high-quality build-out, and when space is occupied, rather than left vacant. You have more bargaining power than you think, but may have to sign a longer-term lease.”

Bill Ju goes beyond geographical siting. “After proper site selection, especially for laboratory operations, it is important to allow for the changes that take place in the infrastructure required,” he advises. “Once a general area for the site is selected, the key points to look for are enough clear space between the finished floor elevation and the steel superstructure, the ability of the superstructure to handle the load of the infrastructure (ductwork, pipes, electrical, air handlers, exhaust, chillers, and so on) and the growth potential. Because lab space is so infrastructure intensive compared to office space, the above-ceiling space fills up quickly when ductwork, pipe racks, electrical and other utilities are installed, so it is important to have enough room to fit it all in and be able to maintain it over the life of the facility with minimal impact to the laboratory operations.”

Ju continues, “The intensity of the infrastructure also requires a good structural analysis to ensure that the

building can support the heavy equipment that it will need to operate such as air handlers, ductwork, pipes, electrical equipment exhaust fans, chillers etc. This may also require some additional reinforcement of the building steel or adding steel to accommodate the equipment. Finally, it is important to select a location that will grow with a company. Since it takes a long time for a project to go from inception to design to occupation, the plan has to be flexible to allow for the growth in the future. Additional space may be warranted to be left shelled out until it is ready to be fit out.”

What staffing and organization do site selection, construction, and management require?

Construction of a dedicated facility is arguably a company’s most time, energy and resource-intensive endeavor and the skills sets necessary for its accomplishment rarely reside within the start up management team. Reputable professionals should be hired to manage the project from the drawing board to ribbon-cutting. As Noffke warns, “Because of the big money involved in building facilities, missteps in this process can cost a bundle.”

Ju lists a few of the resources his company found useful at this stage. “Our real estate broker has the knowledge of the market, pricing, and what else might be available to quickly occupy. An architect can plan and understand codes and zoning requirements for an area. A construction project manager can help establish accurate budgets and schedules and keep costs down and timeframes short. The in-house maintenance staff can provide input on how the design should incorporate long term equipment maintenance how the systems should be managed and monitored. Typically, small biotechnology companies run on a lean staff with people who wear many hats, so a strong facilities manager who has some project management skills is helpful to oversee the project and lead all aspects.”

Noffke gets more specific, “You’ll want to outsource construction project

SUPPLY-CHAIN GURUS

Tim Noffke of Integrated Project Management offers this advice on where to get help with setting up your supply-chain operations. Enlist the support of the appropriate experts to develop your plan:

- Chemistry-manufacturing-controls (CMC) input – A CMC expert (find someone who knows your specific technology) can offer insight on potential issues (if any) and timelines for scaling up production.
- Clinical development input – Your clinical development strategy will drive clinical protocols, which will in turn drive how much material you need for trials.
- Regulatory input – Your regulatory strategy will help define timing of needed clinical and commercial supply.
- Commercial input – What is the market potential and launch plan? How much finished product will you need and when?

management to a trusted partner—many are readily available. You’ll need to understand and be able to articulate your facility and infrastructure requirements to your outsource partners. For example, ‘I need an 800 square-foot lab with two hoods and vents and a ten-liter reactor, which will need purified water and compressed air.... And three office cubes with high-speed internet connections and phone systems....’ Avoid conflicts of interest between the project- or construction-management company and contractors that will bid on the job.”

R&D/MANUFACTURING/SUPPLY CHAIN

More businesses, by far, have failed for inability to deliver product than for inability to sell it in the first place. Typically, small businesses drown in unforecasted orders because they have filed to think about their supply chain: the continuum of production and distribution for R&D and the market. For biotech companies in particular, the supply crunch often hits earlier than the market—in clinical trails, which reflect all of the same demands except

total volume. Our panel takes on the most basic (also the toughest) questions about setting up an operating chain of supply.

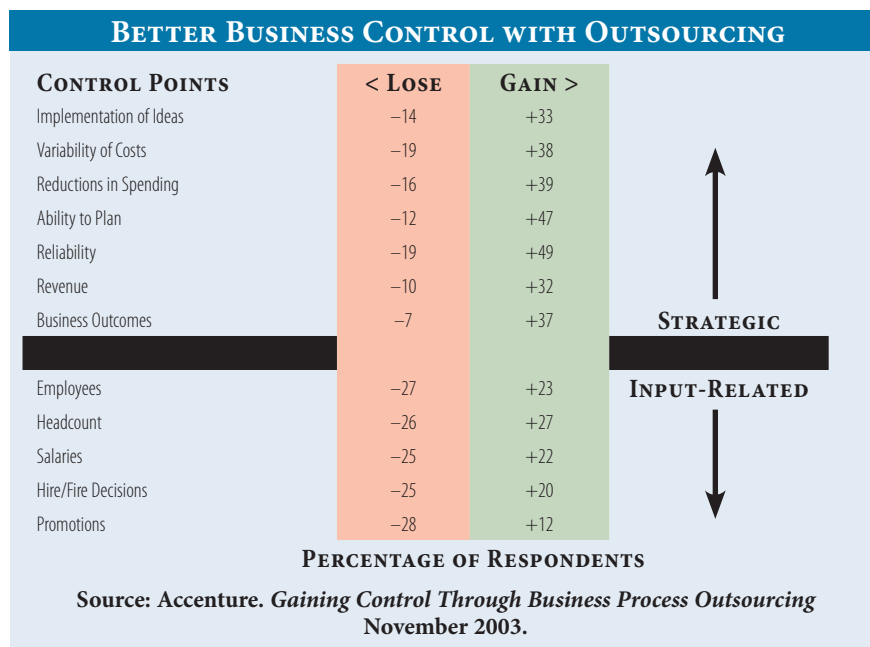
Starting at research-level production, how can a company anticipate needed quantities, time delivery, and allocate resources to ensure efficient supply and processing of raw materials into finished product?

Tim Noffke responds in depth:

Projecting demand. First, you need to be able to project your demand: How much material do you need for preclinical testing; once you're further along, for clinical development; and, ideally, for the commercial market? Once you know that, you can fabricate a supply-demand model to show how much you're going to need and when, and how your technology will need to scale up to meet that demand.

Planning for the supply. Now you're ready to map out the supply chain, which will include such critical elements as when you need to order raw materials and the supplier relationships you'll need to establish. Because you've forecast your demand, you'll be able to pursue whether your vendors can provide not only research-level production, but ultimately scale up to the commercial-level quantities you anticipate, preventing the need for technology transfer to another manufacturer (the ideal scenario, but not always possible).

Mapping the supply chain. Project managers literally create a graphic sequence of interrelationships among material sourcing, material acquisition, analytical testing, quality assurance, production, inventory management, data acquisition and so on. Rigorous fact-finding interviews with personnel at each link in the chain determine who does what and when; what materials are involved; how long it takes to complete specific tasks; and (critically) at what points they depend on others, across functions or across companies, for input to get their own jobs done on time and on target. Such detailed mapping not only enables each party to understand how they interrelate, but enables you to anticipate where



constraints may occur, so you can act proactively when needed.

Bill Ju of PTC offers examples of early supply-chain planning from his own company:

Research. We estimate that approximately 50-500g quantities of active compound will be required before a compound can enter early development. Production at that scale generally does not require significant investment in supply chain management. Many CROs are capable of producing compounds at this scale.

Early development. Initial estimates of compound requirements for toxicology and early clinical studies are developed. Based on those estimates, the CMC team identifies appropriate drug substance and drug product manufacturers. A project plan is constructed by the project team to align drug supply requirements, manufacturing and development timelines. At this stage of development, raw material suppliers are identified by the CRO.

Late development. Based on development timelines, phase 2-3 drug substance and product manufacturers are identified. The required quantities of drug substance and drug product are determined by long-term toxicology studies and clinical needs. Manufacturing at this stage of develop-

ment is performed at a similar scale to that of commercial production.

How can the company plan for increasing volume and changing technologies as it scales up during product development, marketing, and distribution?

Noffke says, "You are faced with huge risks throughout the development and commercialization process. How do you manage that? The key is not to get overwhelmed by all of the uncertainties—just develop a baseline plan of your most likely scenario. Do it early. You'll be able to handle problems proactively and much more effectively if you have a fairly robust plan than if you just 'wing it.' You can use your plan to identify potential risks, determine how to prevent or mitigate those risks, and map out how you would manage issues that do arise." (See "Supply-Chain Gurus.")

Before a product is fully developed and approved, it is essential to conduct market research to drive the commercial forecast. A successful and timely launch requires proactive, focused planning, good communication and flawless execution. You must coordinate the development of required documentation; start of volume production with suppliers and manufacturers; planning and execution

Supply Chain Partnership Selection Network



of marketing activities; training of sales and support personnel (internal and external); filling of channels; and customer support preparedness.

OUTSOURCING

“The whole question of make-versus-build for a company with resources as limited as a small biotech, using our business model, is the thing that keeps you up at night the most, besides the science,” says Kenneth C. Carter, of Avalon Pharmaceuticals. (CTW Live! *BioExecutive International*, March 2006.)

It could hardly be said any better: for most new biotechs, outsourcing decisions largely define their companies. Our panel tackles this complex subject with advice tested by experience. (See also “Better Business Control with Outsourcing.”)

When and for how long in its growth period should a biotech company outsource key operational functions? What functions lend themselves best to outsourcing, and under what ideal circumstances?

“You really need to be objective and assess your core competencies,” advises Noffke. “Those strengths should remain internal, such as your scientific or technology core competency, which is the heart of the company; and

a small executive-level management team to steer the ship. Everything else can be outsourced essentially right away. That’s often the most strategic way to operate, so you can stay in large part ‘virtual’ and flexible, and only pay for what you need as you go along.”

Bill Ju specifically outlines some good outsourcing targets.

Research:

- High cost, need for unique expertise to build in-house or infrequent need.
- Increasing capacity of internal functions for the short or intermediate term.

Development:

- Work that is regulated by the health authorities (GLP, GMP, GCP) has special needs, making it attractive to outsource large parts of such activities to companies that have established systems and successful track records with the agencies. Note, however, that capable internal staff is needed to project manage and monitor such work, and that external consultants may be critical for strategic and tactical direction and for auditing.

Overall:

The goal is to play to your immediate strengths, but outsource whatever is expected to be used infrequently or that has a high cost to build. The other situation is to outsource to expand

existing internal capabilities, either because it takes time to build in-house and the capacity is needed immediately, or it is an activity with a defined short or intermediate duration.

Noffke further elaborates, “When should you consider internalizing outsourced functions? One juncture may be when you achieve proof of concept. At that point, you’re more confident that your business will be viable going forward, and the risk of adding headcount drops slightly. Another time to consider adding expertise may be when you have a flurry of activity focused to a particular event, such as clinical trials. A financial ‘make-buy’ analysis may also be helpful, for example, if you find that the level of work has reached a point where there are cost advantages to hiring staff rather than continuing to outsource.”

How “virtual” should a company be at each stage of its development?

Tim Noffke states, “How ‘virtual’ a company should remain depends upon the company’s end game.” He continues, “Are you trying to develop a fully integrated pharmaceutical company? Then you should probably try to start internalizing functions as soon as you can afford to do so.

“If your goal is to reach phase 2a and then license out your technology, partner with another company, or try

to get absorbed by another organization, then you'll probably want to stay virtual longer. A virtual company probably is more attractive as an acquisition target because your suitor will pay only for the real asset of the company—the IP and technology—and not for unnecessary overhead or headcount they may have to shed later.”

What are the stakes involved with in-house versus outsourcing strategies?

“The stakes are financial,” Noffke points out. “If you bring too many functions in-house, you could amass too much overhead too quickly and accelerate your cash burn unsustainably. With an outsource model, you pay for what you need—both in materials and expertise—when and where you need it.”

He further explains, “Some companies are afraid that their institutional knowledge will disappear with the departure of their outsourced partners. But by properly transferring the knowledge by capturing it through detailed documentation, well before your resources leave, you can easily internalize knowledge of history, science, facts, processes and any other information vital to your business.”

What are the essentials of choosing, contracting with, and managing an operational outsource?

Cynthia Robbins-Roth of BioVenture Consultants says, “You can do everything through outsourced partners/collaborators/contractors. You just need the strategic decision-maker in house!” When selecting partners, Noffke advises, “Seeking referrals through your personal network is often a good way to start. Who do they recommend? Who do they say to avoid? Another good resource is an industry organization, such as the Biotechnology Industry Organization (BIO), which often offers lists of pre-screened, qualified vendors.”

Noffke breaks down the process of partner selection into components:

Commitment. Choose a company that has as much stake in your success as you do in theirs. If you get the sense

you'll be their tenth priority because they need to tend to their giant customers first, then maybe they're not the best partner for you. Choose a company with a reputation for delivering on commitments and being customer-friendly. They don't have to be one of the “big names.” Contract with people you can feel you can trust.

Communication. Ensure that your partner will be transparent regarding communications—especially when problems arise. Ask how they relay and document information in general, and how they've handled communicating issues with their clients in specific. You need a partner that will be open and honest, so that if issues arise, both sides are aware of what's happening and can resolve problems most effectively.

Contracting with and managing partners. You need to ensure even-handed negotiations. No one party can dictate terms, no matter the differential in size. Ensure that you know the processes the partner has in place to ensure quality and meet timelines. They should have and be willing to share some form of documented process, so you have a level of comfort that they can deliver what you need to meet your goals. Then, speak with their other clients.

(See also “Supply Chain Partnership Selection Network.”)

Measuring the performance of all operations demands application of the best technologies, involving IT systems, to monitor and test the process outcomes. In that area, a wealth of information exists from other companies and industries in the public literature. Hire managers that are knowledgeable, and able to apply those systems to performance measurement. (See “Biopharma Operations Excellence Consortium.”)

BOTTOM LINE

It is fitting that the chapter on operations ends with a mention of communications as essential to that area. Once again, the overlap of all four chapter topics gets a nod. Establishing

~ BIOPHARMA OPERATIONS EXCELLENCE CONSORTIUM: ~

For four years, the BioPharma Operations Excellence consortium has been a leading, global forum for industry benchmarking and networking.

Meeting quarterly, the group tackles issues important to driving excellence within the industry—OE program design, cultural change, quality management, and supply chain excellence, to name a few.

This group was founded to create a forum for biopharma leaders to share experiences and challenges facing the industry and to leverage the group's collective knowledge and insight to drive each member company, and the industry as a whole, to world-class levels of operational effectiveness and efficiency.

Member companies include eight of the top 10 biopharma companies, including Amgen, Genentech, Biogen IDEC, and Serono.

Each meeting is hosted by a member company, with the most recent sessions being held at Baxter in Thousand Oaks, California, Medimmune in Gaithersburg, Maryland, and Lonza in Slough, United Kingdom. Each quarterly meeting has been an important mechanism for driving OE programs within all the participating companies. For information on previous or future meetings, please contact excellence@tefen.com.

physical movement of goods through the supply chain not only requires good communications, but is also an embodiment of communications in itself.

As materials flow, so does information. Companies will benefit from looking at the supply chain as a two-way street, a conversation requiring anticipation and feedback. It is also, to reflect the other chapters, an organizing force for management, strategy, and finance. ~