Launch excellence: Everything depends on flawless operations

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Launch is a critical capability in biopharma and its success hinges not only on good clinical data and a savvy marketing strategy but also on operational excellence. Yet biopharma operations—including production process development and the transfer of such processes to commercial facilities—are very complex and time consuming. By understanding the complexities and managing them better than rivals do, biopharmaco players can boost the odds of a successful launch—product after product. The result is that they position themselves at the front of the pack by meeting four increasingly critical imperatives: speed to market, flexible response to volatile demand, quality and compliance, and regulatory compliance.

The right product, at the right time: Why biopharma operations matter

With new biological entities (NBEs) flooding the biopharmaceutical industry pipeline, a huge number of products are likely to reach the market in the coming decade. To stack the odds in favor of successful launch, biopharmaco players need to achieve new levels of excellence in their operations. Sharply honed operations not only further strengthen the drivers of launch excellence but can also enable companies to meet four imperatives that have grown increasingly critical to launch success:

- **Speed to market.** As more NBEs are developed to treat the same indication, competition heats up. Companies that get their product to market faster than rivals do, stand the best chance of claiming the bulk of the market.
- **Flexibility.** Stiffening competition, the emergence of new markets, and the uncertain outcomes of late-stage clinical trials are all leading to unpredictable demand for biopharmaceuticals. To deliver the type and amount of product needed to satisfy unpredictable demand, companies will have to infuse flexibility into their operations.
- **Quality and compliance.** NBEs must meet current good manufacturing practice (cGMP) standards and product quality specifications—and, in the case of biosimilars, interchangeability

criteria. To comply with quality and manufacturing standards, launch and commercial supply material has to be very similar to the material that was used for clinical trials, even though earlier-stage efforts are often carried out in different locations, with different equipment, and on a smaller scale. Finally, to get biologics license applications approved, manufacturing sites need the green light from health authorities around the world. A company that gets approval to launch an NBE won't necessarily get approval to manufacture the product at a particular site if that site has received a warning letter.

- **Regulatory compliance.** To comply with government regulations, companies must understand and tightly control input parameters (such as pH) and output parameters (including cell density, viability, and yield) if they want to provide a strong validation of the production process and a solid chemistry, manufacturing, and control (CMC) package to regulators.

To meet all these imperatives, it helps to quickly examine the unique complexities that characterize biopharma operations.

Molecule development: A science and an art

In the biopharmaceutical industry, development of a new molecule is a highly technical, multistep process that entails long lead and cycle times and requires biopharma experts in specialty areas as diverse as quality assurance, quality control, engineering, and manufacturing. The process centers on the use of genetically modified living organisms. Consider the development of a recombinant monoclonal antibody from a mammalian cell culture. Typically, over as many as 15 months, a company prepares a production cell line, which is accomplished by cell biologists using transfection to insert the DNA developed by molecular biologists into living cells. The company also applies sophisticated methods to select clones for high product quality and process productivity.

After one or two years—depending on the availability of platform technologies—cell culture technologists develop a production process that can be industrialized. That is, the process will deliver consistently robust growth, high titer, high yield, and reliable product quality. The cells are cultivated in media. Previously, media were blood or serum; today, they are highly complex, chemically defined materials that mimic the properties of the older media. And because protein molecules are sensitive to heat, pH, and organic solvents such as acetone, companies must deploy complicated and expensive purification technologies to control the molecules' environment.

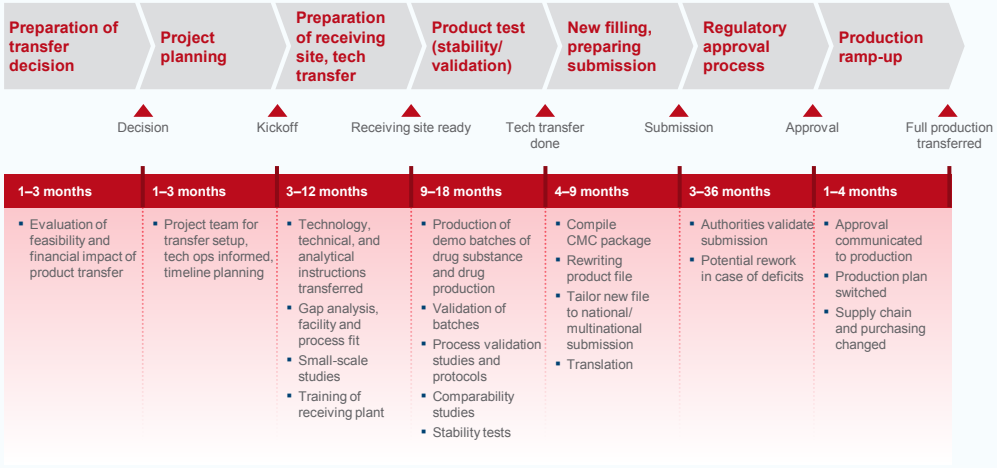
Production process transfer: Complex and time consuming

Often, in the early stages of clinical trials, molecule supply is produced in GMP pilot facilities with capacity of up to 2,000-liter bioreactors or even disposables up to 1,000 liter (internal or external at a contract manufacturing organization [CMO]). For Phase III and final launch, production process formats must be locked in, and the production process needs to be transferred to a launch/commercial facility.

The choice of facility where the production process will be transferred requires careful thought and close attention. That's because the production process will remain at the selected site for multiple years, owing to regulations and the risks inherent in making repeated transfers. In deciding on production sites, companies need to weigh numerous considerations, such as whether to use an internal or external site, whether a potential site has the capacity to meet anticipated demand as well as respond flexibly to volatile demand forecasts, and whether multiple sites should be selected, to serve as backup if problems arise at a particular site (Exhibit 1).

Exhibit 1

Steps to successful production process transfer



Source: McKinsey

From vial crack to formulated bulk, hundreds of input and output parameters must be considered during decisions about production process transfer. More than 50 key operational parameters (KOPs) affect yield and process duration, and about 10 critical operational parameters (COPs) influence drug substance product quality. Companies must understand and clearly describe the ramifications of each KOP and COP, including potential risks to the production process and to product quality. Moreover, companies must characterize parameters using small-scale batches. The number of batches depends on the parameters to be investigated and their links, which can easily translate into the need for as many as a hundred batches. KOPs and COPs are then validated at large scale, which (depending on the validation strategy) can translate into as many as seven costly engineering and validation batches for each. Finally, the validation strategy must be described in a master validation plan and validation protocols. The results of the validation become a key part of the CMC package for regulatory authorization and provide the frame for production indefinitely, if parameters are not changed.

Tackling the complexity: Best practices for operational excellence

To establish the levels of operational excellence needed to manage the complexity inherent in biopharma development and production process transfer, companies must focus on three areas: governance, process control, and performance management. The following practices can help:

Governance

- Set up a cross-functional team comprising individuals from quality assurance, quality control, drug regulatory affairs, manufacturing, process sciences, manufacturing sciences and technology, supply chain management, and engineering and technology. Assign an experienced, full-time project manager to lead the team.

- Establish a strong governance body to which the team can escalate complications and that will make decisions as quickly as possible. Such bodies may include joint steering committees if the NBE donor and receiving sites differ or if production processes will be transferred from an internal to an external site or vice versa.

- Install a physical “launch room” for operations. Ensure that the operational launch room team interacts closely with launch room teams associated with R&D and with marketing. Only by fostering collaboration among the three launch rooms can a company coordinate schedule and supply expectations for molecule development and production process transfer.

Process control

- Define and follow a procedure for new-product introduction covering the risks associated with the product (such as poor process fit, compliance uncertainty, and poor facility fit) and risks associated with the site (including impact on employees, environmental pollution, or the presence of other products produced in the same facility).
- Provide quality oversight for the production process transfer or launch activities.
- Develop and use checklists to assess the readiness of product transfer or validation. Checklists should cover content such as production process transfer documents, gap and risk analysis, batch records, standard operating procedures, change controls, validation protocols, training documents, and facility fit (equipment) of the sending or receiving production site.

Performance management

- Ensure the transparency of the progress toward launch preparation and execution so that management can respond swiftly to deviations from plan.
- Use maturity-level tracking to preview progress toward the launch at major milestones, such as successful execution of conformance runs, completion of validation, and readiness of the CMC package. Have a cross-functional team measure project maturity for each project milestone using criteria such as success rates and on-time deliverables.
- Create a “launch cockpit” for operational progress tracking. To establish the cockpit, analyze existing reporting formats, adapt them to reflect best practice, and roll them out in a standardized format for all launches. Use the cockpit to provide an overview of launch progress based on KPIs. For all major deviations from the plan, describe the problems in detail and propose solutions.

Best-practice companies have achieved launches in 15 to 24 months by adopting these practices. Boehringer Ingelheim is an excellent example of that based on the vast experience from the 22 molecules it has sent to market since entering the CMO market. The company developed what it calls “Smart-to-Launch” processes that can shorten the timelines from kickoff to drug substance availability and completion of the CMC regulatory package to just 8 months and 15 months, respectively—without compromising quality.[1] By contrast, the industry average is 30 months.

Biopharmaco players that understand and manage the unique complexities inherent in their operations coming along with production process transfer and launch can sharpen their competitive edge on all the fronts characterizing successful NBE launches—including speed to market, flexibility, quality and compliance, and regulatory compliance. Setting up the required governance structures, process controls, and performance management systems takes time and effort, but the investment can pay big dividends.

1 Boehringer Ingelheim, press release, October 1, 2012, https://www.boehringer-ingelheim.com/news/news_releases/press_releases/2012/01_october_2012_smarttolaunch.html; Dr. Markus Wollenberg (Boehringer Ingelheim), “Smart and flexible manufacturing solutions in Multi-Product Facilities,” BioProcess International Conference 2012, October 9, 2012.

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