Patheon
A HEALTHIER WORLD. DELIVERED.

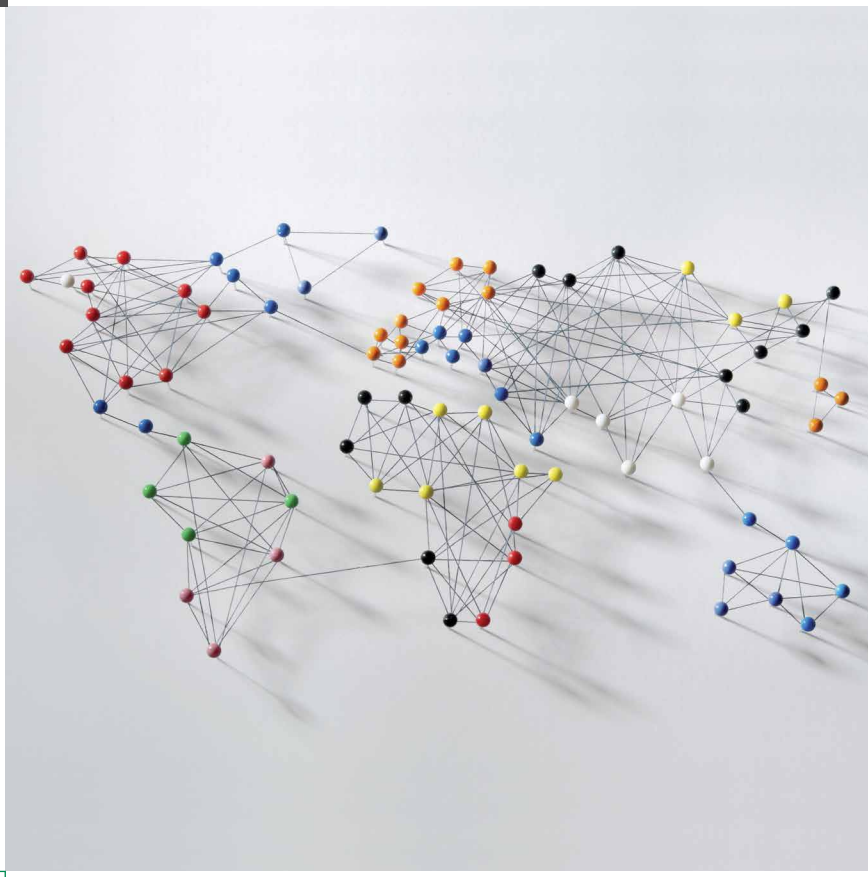
OneSource™

Simplicity and speed. Delivered.

A Cure for Pharmaceutical Supply Chain Complexity

The pharmaceutical industry lags in the sophistication and performance of its supply chains when they are compared with best-in-class companies in other industries. This is due to the complexity that has come with new drugs, more complex production technologies and evolving regulatory requirements. In this environment, integrating and aligning the supply chain makes it more flexible, bolstering operational performance and financial competitiveness.

By **Lukas Utiger**, President Drug Substance at Patheon, and **Mike Mencer**, Vice President PDS Operations & Global Integrated Offering



The complexity of drug product supply chains has increased in recent years thanks mainly to the development of more complex chemical molecules (with more synthesis steps), more suppliers and geographies in the chain, and reduced average production volumes. Preparing for commercial release, the time from raw material to finished drug product can be as long as two years, and those months are fraught with hazards that can cause delays and rework, leading to extra costs, stock-outs and poor capacity utilization.

According to a 2014 survey of pharma companies by A.T. Kearney, many pharmaceutical firms have significant room to improve supply chain performance and efficiency. For example;

- Customer service levels of 90% at the best pharma companies are world-class, and equivalent to the best consumer goods companies. Average customer service levels, however, are five percent lower. A service-level improvement of just two percentage points can translate into 80 percent fewer stock-outs at non-generic prescription drug firms.
- Forecast accuracy, which is important for keeping inventories low as possible, and production stable, is about 90% at the best companies, but only 61% on average.

The single biggest barrier to improving performance, according to the survey's respondents, is supply chain complexity. And while 92% of respondents see simplifying their supply chains as a strategic priority, nearly 40% of surveyed firms are not yet doing anything about it.

While 92% of respondents see simplifying their supply chains as a strategic priority, nearly 40% of surveyed firms are not yet doing anything about it.

The roots of complexity

Drug manufacturing is challenged by long investment horizons and uncertain demand forecasts. The need to minimize capital intensity for new assets works against the option of using excess capacity as a hedge against – or solution to – uncertain demand.

As organizations move from clinical to commercialization, a cost effective, responsive supply chain can only be achieved by tightly integrating drug substance (DS) and drug product (DP) supply chains. That's difficult because their time horizons are very different. Two months' lead time, and two weeks' batch production time are typical for DP. Machine changeover times are two to three days, so DP time horizons are quite manageable. For DS, however, the total elapsed time is typically one to two years. Manufacturers tend to run big production campaigns because cleaning and changeover takes two to three weeks, and raw material lead times can be several months to a year, depending on the complexity of the materials and where they're coming from. There is a similar horizon for biologics production, due to lengthy media lead times, long production times, and the six to eight weeks needed for the quality release of the active pharmaceutical ingredient (API).

So while the fundamental roots of pharma supply chain complexity are the long lead and manufacturing times of DS, there are several factors which further complicate matters:

- Regulations have become more demanding. For example, the November 2013 Drug Supply Chain Security Act requires that within 10 years, pharmaceutical companies should be able to track products at the individual package level at every point in the supply chain.
- Compliance with VAT and duty regulations has become more complex in recent years, and can be costly to comply with, especially where the supply chain cuts across multiple geographies.
- The definitions of starting materials, and registered intermediates, have become more elaborate, and in general have increased the number of production steps that must be validated.
- Drug molecules have become more complex, requiring more chemical production steps, or specialized downstream processing for biologics.
- Many new drugs target smaller indications, in general are more potent, and therefore require smaller production volumes – typically two to five tons per year instead of several hundred.
- There may be many parties involved in the production of a molecule, and they may not have been chosen with long-term coordination in mind. There can be considerable cost and effort involved in managing them.

These challenges are especially acute just before or during a product launch, where unpredicted demand can cause havoc. In the past, the industry managed uncertain demand with excess production capacity and surplus inventories of both DS and DP. But today's pressures to better use capital and assets demand a smarter solution.

A big part of the solution is to simplify the supply chain, which can be achieved with end-to-end integration that improves visibility and reduces hand-offs, and optimized inventory levels that enable flexible production capacity.

A case study in supply chain integration

To illustrate the connection between integration and flexibility, consider a real-world case study of a newly launched product that involves three dispersed raw material suppliers, and DS and DP production.

Three key raw materials are ordered from Asia and shipped by sea to the U.S. The critical lead time is 7-1/2 months, without any safety margins. DS manufacturing takes place in the U.S. Five chemical steps are required to produce the API. Intermediates are produced in campaigns. Quality release is carried out at the DS manufacturer, and testing is repeated at the DP manufacturer. DP is manufactured in the U.S as well, reducing transportation time. In this case, no extra time is needed for drug packaging.

Some of the process time inefficiencies can be seen in Figure 1. Supply chain planning adds safety buffers to the raw materials lead times to ensure

Value of optimization savings:

3-5 month of total time reduction

$185K in QA cost savings per year

$100-$200K saving per API on QC method transfers & validation work

on-time startup of DS and DP manufacturing. Average buffers are one-to-two months (pink on the diagram) depending on the shipping route, and the company's experience with the supplier. Some of the API manufacturing steps are inflexible, because of specialized plant, high asset utilization and other constraints, so buffers of up to 13% are needed to de-risk the API production. In addition, a safety buffer between DS & DP adds month or so to the timeline. QA/QC release (green) is repeated at several points as different manufacturers with different quality systems are involved.

The bottom half of figure 2 shows the supply chain after simplification.

In the simplified and integrated supply chain, buffers and QA time are substantially reduced. The total time is reduced by about three to five months, or 13% to 22%. By replacing incoming QA steps with certificates of analysis, four releases of nine are saved for each batch of final API: one for each raw material received into API production, and one receiving into DP. Per batch of API, QA cost savings are $2,000-$5,000. For a campaign with 20 API batches, and 40 first intermediate batches, savings add up to $180,000 per year. In addition, fewer QC method transfers and less validation work has to be done, saving at least another $100,000-to-$200,000 per API. Processing fewer samples also reduces operational and technical errors, cutting the number of expensive out-of-specification (OOS) investigations.

With more stringent supply chain management, down times in production are reduced and inventory levels can be reduced. This typically translates to a total supply chain cost avoidance. And with less (but better distributed) inventory, and fewer repeated QC steps, the supply chain can better accommodate unanticipated surges in volume.

Figure 1: The campaign timeline

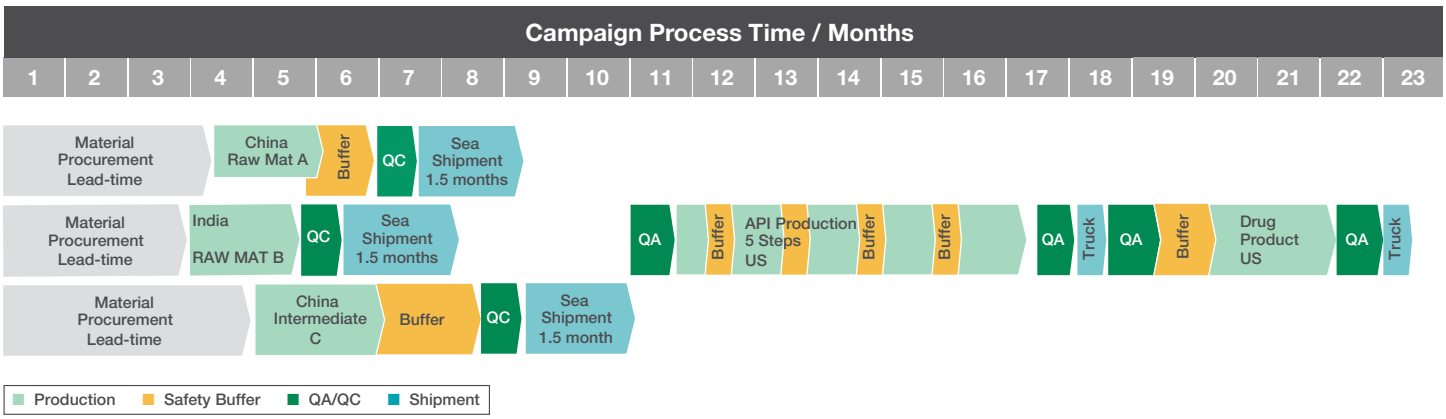
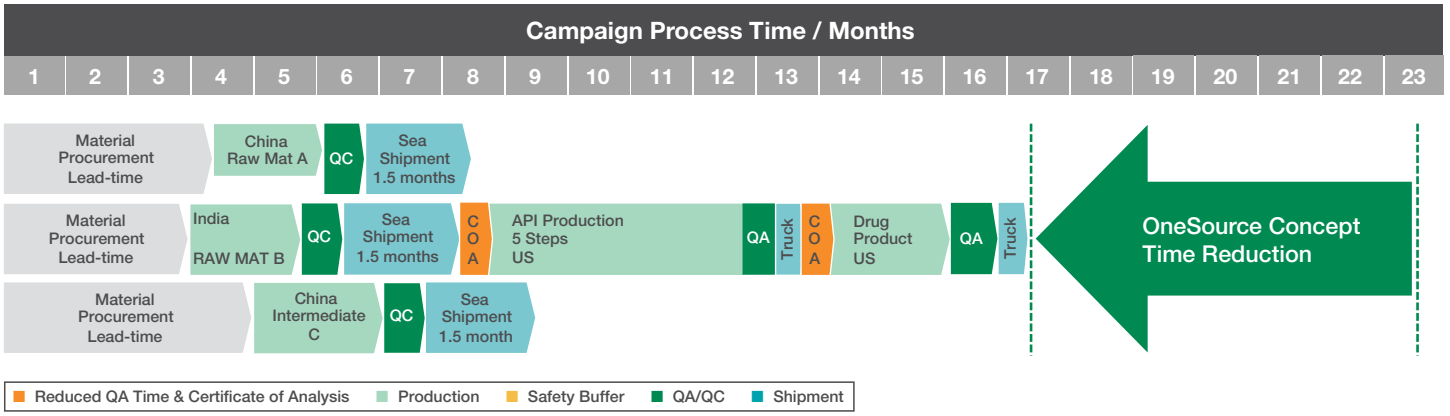


Figure 2: The simplified campaign timeline



Four steps to a better supply chain

To create a harmonized and integrated supply chain, it's critical to:

1. Implement a strong and uniform quality system. Apply it, too, with regular audits at your suppliers. Measure performance with strict KPIs such as right first time (RFT). With a small, stable network of quality suppliers, a harmonized system can be achieved with several measurable benefits:

- **Safety margins in ordering lead times can be substantially reduced or eliminated.** As soon as the network is qualified, and regular auditing established, there will be no returns for re-work. This will create stability in the supply chain. In our example, at least two months were recaptured.
- **The manufacturing process becomes transparent.** A strong quality management process with quality leaders at the raw material suppliers allows for quality agreements that can be enforced. With such a system, suppliers' certificates of analysis (COAs) can be trusted, and time savings achieved. In our example, this removed at least a month from the timeline.
- **Network partners can provide capacity flexibility.** With harmonized process validation for chemical APIs, a network partner can serve as an extension of internal manufacturing to accommodate unforeseen demand. A strong and enforced quality system is the foundation of this capability.

2. Reduce the number of interfaces, and standardize operational models. Standardize project management internally, and with suppliers, to allow for direct and clear communication. Share data with a collaboration tool such as SharePoint. With such a system:

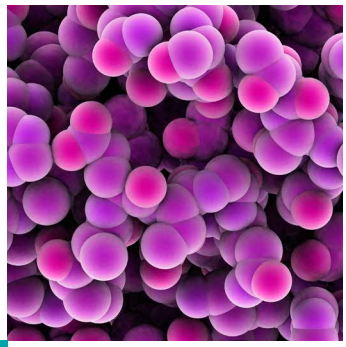
- **Important information can be communicated quickly and reliably.** For example, toxicology classifications of raw materials can be exchanged immediately and special handling requirements consistently conveyed. This will prevent lengthy reworks of intermediates or DS, or last minute changes to plant configurations.
- **Supply chain breakdowns can be avoided.** Real time and transparent information means fewer disruptions due to miscommunication. Also, where a problem needs to be addressed by changes to the upstream system, it can be recognized and the changes initiated without delay.

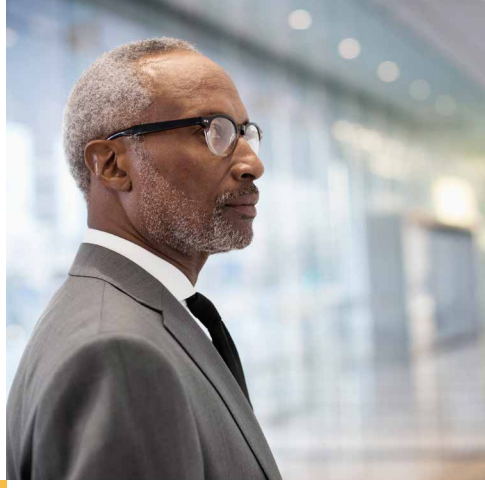
3. Optimize intermediate inventories. Identify the bottlenecks and add safety stocks on the downstream side. Bottlenecks usually appear in API production rather than DP due to the latter's shorter manufacturing cycles and faster change-over times. You can add safety stock appropriately if you have a view of demand and of the whole supply chain, and if suppliers and API manufacturers collaborate. With safety stocks rationalized:

- **Large and expensive API safety stocks may be eliminated.** Safety stocks of precursors or starting materials may obviate the need to hold stocks of API. In our example, a stockpile of one intermediate significantly reduces lead time.
- **Demand responsiveness may be increased without holding excess DP.** Inventories of intermediates for API synthesis can provide flexibility to demand changes without the need to hold expensive excess stocks of DP.

4. Validate more than one production site. Validate two production sites, ideally within the same company network, and file for them both during the initial set-up. Harmonized quality systems, manufacturing, and QC setups will simplify such an approach. For biologic APIs, it is also possible to cross-validate two production sites. Harmonized operations and quality systems will make this substantially simpler. With more than one production site, a company has the flexibility to respond to unanticipated demand. With biologics, for instance, single use fermenters can be quickly added to expand capacity if enough downstream process capacity is available.

Focusing on these four steps will drive down inventory costs, and shorten the timeline from raw materials to finished product. Adopting standardized processes and common metrics will improve end-to-end transparency, accommodate unforeseen variations in demand, and lower the risks associated with complexity.





Why change is your only option

Historically, the pharmaceutical industry has deployed cruder tools than we've discussed to manage problems in the supply chain, such as using air freight, amassing huge safety stocks, and contracting for dual or triple supply. But these solutions are expensive and, today, ever less sustainable.

Of course, integrating a supply chain is enormously challenging, and if the drug substance and product manufacturing are owned by different parties, it becomes even harder. Before there can be strong collaboration, a great deal of work will have to be done to establish standards and processes.

But, as we have shown, the benefits of supply chain simplification and integration, measured in time, cost, and improved responsiveness to demand, are substantial. These benefits cannot, however, be retrieved overnight, in one giant leap. Integration must be accomplished over a period of time, in many small steps. Clearly, it's time to start.

Patheon
4815 Emperor Blvd, Suite 300
Durham NC 27703-8470 USA
P: +1 919 226 3200
F: +1 919 474 2269
www.patheon.com

Patheon
Kingfisher Drive
Covingham, Swindon
Wiltshire SN3 5BZ UK
P: +44 1793 524411
F: +44 1793 487053
www.patheon.com

Patheon
7F Wakamatsu Building, 3-3-6
Nihonbashi Hon-cho, Chuo-ku,
Tokyo 103-0023
Japan
P: +81 3 6202 7666
F: +81 3 6202 7676
www.patheon.jp

Patheon®
A HEALTHIER WORLD. DELIVERED.

Published 1/16 PATHXXXXXX