EXECUTIVE SUMMARY

# Transitioning from using RUO to cGMP chemicals for clinical trials

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ThermoFisher SCIENTIFIC

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## Global biologics pipeline analysis

The global biologics market is expected to grow at a CAGR of 8.7% and reach $664.7 billion by 2030.[1] However, the regulatory demands, time and costs of bringing a new drug to market are also growing, with one study reporting a 27% increase in the number of endpoints for typical Phase II and Phase III trials since 2009. For new and emerging biopharma companies who want to be first to market with their molecule, the pressure of balancing budgetary and regulatory requirements while accelerating the pace from lab to clinic can be challenging.

### Common biopharma challenges going into preclinical and early phase trials

Thousands of compounds are screened, tested and optimized in the search for new drug candidates. As the drug development journey progresses, fewer and fewer compounds advance. Only a small fraction is granted FDA approval. The entire process, from discovery to market, requires an estimated 10 to 15 years and can cost over $2.6 billion, while FDA approval will be granted to around 12% of the compounds that enter clinical trials.[2] Mitigating risks and avoiding delays related to raw material sourcing and supply chain management can help new and emerging biopharma companies maintain a competitive edge.

### Common material risks

In biopharmaceutical manufacturing, sourcing and applying regulatory guidance confidently and correctly to raw materials and products is not always straightforward. A thorough understanding of the material, including its role in the overall process, quality level and risks regarding safety and performance is fundamental. For example, source or starting materials that will become an essential part of the active substance will require different assessments and controls than other raw materials used during the manufacturing process. Additionally, the quality requirements of all materials and processes escalate upon entering human clinical trials.

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# Navigating the unknown: What to expect when transitioning from RUO to cGMP

## What is cGMP

Current Good Manufacturing Practices (cGMP) are globally recognized guidelines for ensuring the safety, quality and traceability of manufactured products. The guidance emphasizes the continual improvement of industry best practices. The methods for maintaining compliance are integrated throughout the organization by way of quality systems, policies, procedures, material choices and training. In biopharma, adhering to these guidelines helps assure the safety, quality and consistency of drugs and other therapeutics manufactured for use in humans.

Regulatory guidance, though broadly similar on a worldwide level, do vary by country or region. The formation of global organizations, such as the International Council for Harmonisation (ICH) and the International Organization for Standardization (ISO), helps reconcile diverse guidelines to maintain compatibility across regulatory bodies and streamline the compliance requirements for multi-regional projects. In global manufacturing, companies must comply with both general ICH and regional cGMP guidelines.

## Why is cGMP important?

cGMP manufacturing is intended to produce safe, high-quality products that consistently meet regulatory and patient expectations. Integrating robust quality controls and monitoring throughout the manufacturing process can reduce non-conformances caused by human error, equipment malfunction and other failures, thereby minimizing the production of non-compliant products and the risks of causing serious harm to consumers. By providing a set of foundational standards for organizations to build and improve upon, companies from diverse regions can create products that meet the same final safety and quality specifications today and in the future.

## RUO vs. cGMP starting materials

From sourcing raw materials to implementing quality systems, cGMP demands a greater organizational commitment than the research use only (RUO) approach; however, both have a role in the drug discovery process, as well as preclinical and clinical trials, respectively. Companies with limited manufacturing experience may expect that determining raw material quality is a straightforward task rather than a multi-layered endeavor that will affect all stages of bringing a biologic to clinic and to market.

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### *Upstream and downstream considerations*

RUO materials are not produced to the same quality standards as their cGMP counterparts and are not intended for manufacturing products for use in humans; however, due to their lower costs and wider availability, RUO materials are generally used in the research and discovery phases of the process. GMP-quality materials are required once the project transitions to clinical trials and the focus becomes testing in humans for safety, dose range and efficacy.

While timing the introduction of cGMP materials and processes will vary in response to an organization's risk sensitivity, cost, and the specific needs of the project, adopting cGMP materials as early as possible may actually save valuable time and resources by reducing inevitable manufacturing process adjustments and retraining when additional controls, systems and documentation are integrated. Typically, biopharmaceutical companies developing a therapeutic or vaccine should transition from RUO to cGMP materials no later than Phase I clinical trials.

## Producing cGMP-compliant biologics

Manufacturing reliable cGMP-compliant biologics, like monoclonal antibody therapies, requires expertise, advanced technology and diligence. In addition to the general cGMP guidelines, products derived from biological sources require additional controls and must adhere to specific regulations due to the inherent variability of source materials. These biological sources, as defined by the World Health Organization (WHO) include:

- Non-transgenic animal or plant sources
- Transgenic animal, plant, or bacterial sources
- Virus or bacterial cell cultures
- Human sources[3]

## The tech transfer: Working with suppliers and partners when transitioning processes

Developing strong relationships with suppliers is essential to effectively transition from RUO to cGMP-compliant materials. Trusted suppliers will add their expertise to the planning and management of the RUO to cGMP transition. Identifying and effectively collaborating with reliable suppliers will make the transition shorter and simpler, thus reducing the potential for significant delays.

Early cGMP compliance lays the groundwork for a simpler and more comprehensive tech transfer that can save valuable time and resources. The additional level of preparation offers potential advantages that include effective planning and project management, the ability to share robust information and analytical methods, allowing you to smoothly conduct pre-GMP engineering runs and GMP runs.

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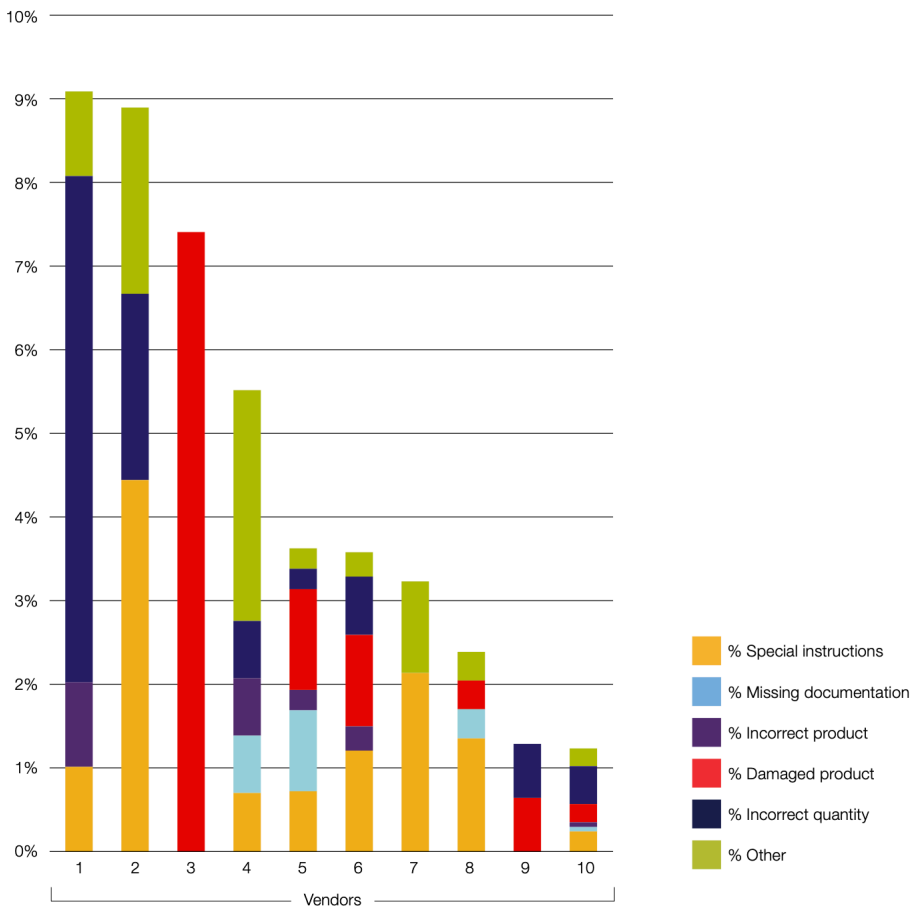
## Mitigating risks: The importance of quality

In the first quarter of 2021, non-conformances affected 4.5% of chemicals received by the Thermo Fisher Scientific Production Chemicals and Services team.[4] These errors consisted of mixed or incorrect lot numbers (27%), damaged materials (20%) and shipments not meeting customer specifications (19%).[4] Figure 1 shows the most prevalent errors Thermo Fisher observed from cGMP chemical vendors in a three-month timeframe. Partnering with a quality-conscious distribution and service provider can help protect organizations from the complications and costs of poor quality (COPQ) resulting from supply and material errors. Monitoring disruptions in supply chain availability and intercepting and resolving shipment errors before the items reach the client go a long way to avoiding production slow-downs due to a lack of supplies or the inadvertent use of an out-of-spec material in the manufacturing process.

**FIGURE 1**

**Raw material errors from cGMP chemical vendors**

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### Access to chemical documentation and dossiers

Identifying reliable supply chain partners is based on quality management essentials that include:

- **QMS system:** A QMS (quality management system) identifies, monitors and manages processes and resources to ensure that customer needs and requirements are met.
- **Order and supply chain management:** Effective order and supply chain management helps ensure compliance with customer requirements at every turn, from order and storage through delivery.
- **Material receipt:** A documented, multistep material inspection is needed to verify the condition and compliance of materials upon receipt. If non-conformances are identified, documentation and resolution steps are taken in collaboration with the vendor before non-conforming material is delivered to the customer.
- **Handling and storage:** Raw materials are stored according to product and customer requirements in a cGMP warehouse under controlled conditions to prevent commingling with non-conforming or chemically incompatible products.
- **Picking and shipping:** A documented process using state-of-the-art scanning technology ensures picking accuracy and compliance with customer requirements.

## Secondary sourcing and supplier selection

### Multiple suppliers as back-ups

Supply chain disruptions can create chaos for biopharma manufacturers, especially when budgets and timelines are tight. Disruptions caused by supply shortages or spikes in demand dramatically increase manufacturing and sourcing costs and affect the ability to meet milestones. Identifying and maintaining multiple trusted suppliers along with employing a primary and secondary sourcing strategy creates a resilient supply chain by providing the depth needed to successfully weather fluctuations in the availability of supplies.

### Case study

A recent experience by a CDMO client of Thermo Fisher emphasizes the importance of a comprehensive supply chain strategy that includes secondary sourcing, communication and transparency. The CDMO was facing a possible facility shutdown due to the supply disruption of a high-volume raw material. The upsurge in global demand increased the lead

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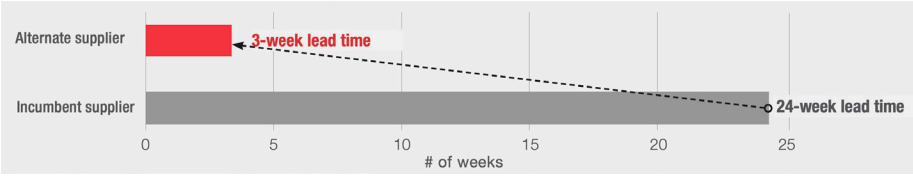
time from three to 24 weeks and made predictable sourcing problematic. The CDMO's only stop-gap was to hold excessive safety stock in their warehouse; however, this had additional drawbacks and was not a permanent solution.

The Thermo Fisher team worked with the CDMO's Directors of Materials Management and Operations to evaluate the extent of the supply disruption and its impact on the company. The results identified several key areas for improvement, including supply chain planning and transparency, supplier communication, a lack of multiple qualified material sources, and inadequate warehouse capacity due to the reliance on excessive safety stock.

Through the expertise and access to a global network of qualified suppliers from Thermo Fisher, the CDMO was connected with an alternate provider within days and a stronger sourcing strategy based on contingent suppliers was developed and implemented. This second sourcing strategy allowed the CDMO to avoid $3M in lost revenue by maintaining their original production schedule.[5] Additionally, the CDMO now enjoys $30K in annual savings and an 87% reduction in lead time due to improved raw material sourcing with an alternate supplier, as shown in Figure 2.[5]

**FIGURE 2**

**Reduction in lead time by sourcing from an alternate supplier**




## Resource allocation and planning

Careful resource allocation and planning are critical to the success of small and medium biomanufacturers.

### Pool of qualified staff

Manufacturing biopharmaceutical products is complex and highly regulated, requiring specialized systems, equipment, materials, technology and staff. Any adjustments made to the manufacturing process will require some level of technology transfer that will include additional training, documentation and validation. To maintain speed to market while minimizing operational expenses, working with a manufacturing team with a solid grasp of cGMP regulations and experience with different product and technology platforms will help maintain compliance and prevent non-conformances.

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### Supply Chain Consolidation - Making the most out of existing investments

The total cost of ownership of cGMP chemicals can rise dramatically due to the hidden costs associated with inefficient supply chain management. Resource-intensive activities are wide-ranging and include the management of multiple supplier relationships as well as the coordination of ordering, receiving and sampling for large numbers of supplier shipments. The resulting complexity creates a myriad of potential points where inefficiencies can occur. Consolidating your supply chain by partnering with a well-established supply chain management company will help simplify processes and free-up resources while reducing operational expenses and ownership costs, particularly those costs that tend to get lost in the complexity of improperly managed systems.

## Economics of strategic sourcing

Strong supply chain and sourcing strategies align with your production schedule and include contingency planning for cGMP chemical supplies, increase material delivery accuracy and streamline inbound receipt and quality inspection processes. Effective strategies will help small and medium-sized biomanufacturers create cost-effective alternatives to in-house material and supply chain management.

### Minimizing new investments

Any strong supply chain strategy will include partnering with well-established supply companies and leveraging their expertise and resources to expand the material sourcing capabilities of biopharma companies while avoiding extra costs from unnecessary on-site storage and management. By outsourcing supply chain activities, biopharma manufacturers in Phase I and Phase II clinical trials will experience a projected annual savings of $207K in operating expenses.[6]

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## Conclusion

Bringing a new biologic to market involves meeting an assortment of regulatory requirements and clinical milestones while adhering to budget and time constraints. Avoiding time-consuming and costly pitfalls such as non-conformances, sourcing, and manufacturing delays are essential to maintaining momentum in the drug development process.

Partnering with a qualified supply chain management company like Thermo Fisher can help small and medium-sized biomanufacturers maximize limited resources by implementing robust systems and mitigating material and supply risks early in the process. A reliable supply company values transparency and proactive communication and will minimize risks and inefficiencies during the RUO to cGMP transition by providing consistent support and management of supply availability, interruptions, and lead times issues.

ThermoFisher SCIENTIFIC

Thermo Fisher Scientific Production Chemicals and Services team brings over 30 years of experience delivering cGMP chemicals and direct material supply chain solutions. With their global network of qualified suppliers, they can help biopharmaceutical companies mitigate risks, streamline processes, and maintain regulatory compliance so they can focus on what they do best—innovating and producing life-changing biologics.

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