Article

Steriles

# Three decision domains shaping sterile program success

## How development, manufacturing, and stability decisions shape outcomes across the product lifecycle

Sterile development is often discussed as a sequence of activities: formulation development, process development, fill-finish manufacturing, analytical testing, technology transfer, and commercial scale-up.

In practice, successful programs are shaped less by individual activities than by the decisions that connect them.

For example, a concentration selected during formulation development may influence manufacturability years later. A container closure system chosen to support an early clinical study may affect stability, delivery strategy, and commercial flexibility. Decisions made to accelerate a near-term milestone can create constraints that only become visible during technology transfer, scale-up, or commercialization.

As sterile products become more complex and development timelines remain compressed, organizations must balance the need to move quickly with the need to make decisions that remain viable as programs advance.

Many of the delays, redesigns, and manufacturing challenges that emerge later in development can often be traced back to decisions made much earlier.

The cost of those decisions is not always measured in dollars. It is often measured in time lost to additional studies, reformulation work, manufacturing investigations, technology transfer delays, and changes to presentation or stability strategy. Each consumes time that organizations often cannot afford to lose.

Three decision domains have an outsized influence on whether sterile programs maintain momentum as they progress:

- **Development decisions** that influence future manufacturing readiness
- **Manufacturing decisions** that determine execution success
- **Stability decisions** that shape long-term lifecycle flexibility

While these domains are often managed by different teams, their impact is interconnected. Understanding those connections can help organizations identify risk earlier, preserve future options, and reduce the likelihood of costly rework later in development.

### Three questions for evaluating sterile program readiness

1. Are development activities generating the knowledge needed to support future manufacturing and commercialization decisions?
2. Are manufacturing activities reducing uncertainty and building readiness, or simply producing supply?
3. Have stability, delivery, patient, and lifecycle requirements been evaluated early enough to preserve future flexibility?

## Development decisions influence manufacturing readiness

Development activities have traditionally focused on demonstrating technical feasibility and generating material for clinical studies. Today, development is expected to do more. Organizations rely on development activities to generate the product and process understanding needed to support manufacturing, regulatory submissions, technology transfer, and future scale-up.

The reason is straightforward. The earlier a risk is identified, the easier it is to address. Formulation issues discovered late in development often require additional studies, process changes, stability work, or manufacturing assessments. Each can introduce delays at a stage when timelines become increasingly difficult to recover.

A formulation that performs adequately at laboratory scale may not necessarily support future manufacturing requirements. Factors such as concentration, viscosity, filterability, stability, and process robustness often influence manufacturing performance long after development activities are complete.

This is particularly relevant as development programs involve more complex biologics, antibody-drug conjugates, highly potent compounds, and other specialized products where material availability may be limited and manufacturing requirements more demanding.

Consider high-concentration biologic formulations intended for subcutaneous administration. A formulation that appears stable during development may become increasingly difficult to process as concentration increases because viscosity can rise significantly. That can affect filtration performance, pumping efficiency, filling operations, and overall manufacturing scalability.

Viewed solely through the lens of formulation performance, the program may appear to be progressing successfully. Viewed through the lens of manufacturing readiness, additional questions emerge:

- Can the formulation be filtered efficiently at manufacturing scale?
- How will viscosity affect mixing, pumping, and filling operations?
- Will the formulation remain stable throughout compounding, hold times, and fill-finish processing?
- Are there concentration limits that could affect future presentation or delivery options?
- Can the process be transferred and reproduced consistently across manufacturing environments?
- Will the formulation continue to perform as batch sizes increase?

These questions often determine whether future development stages proceed efficiently or require additional work. A formulation adjustment made during development may take days or weeks. The same adjustment discovered during technology transfer or scale-up can introduce months of additional studies, manufacturing work, and regulatory activity.

The same principle applies to development efficiency. Drug substance is often among the most valuable resources available during development. Material limitations can constrain experimentation, delay decision-making, and reduce the ability to evaluate alternative pathways.

**The most effective development programs generate more than data. They generate the knowledge needed to support future decisions.**

Development strategies increasingly focus on maximizing learning while minimizing material consumption. Design of Experiments (DoE) methodologies, high-throughput screening technologies, platform formulation approaches, and phase-appropriate development strategies help teams generate meaningful product and process understanding while preserving material for future development and manufacturing activities.

Development complexity can also increase when activities are distributed across multiple organizations. Differences in analytical methods, process assumptions, data packages, and documentation approaches may not create issues during early development but can introduce challenges during technology transfer, scale-up, and regulatory preparation if critical information cannot be easily compared or reproduced.

Container closure decisions provide another example of how early choices influence future outcomes. Selecting between a vial, prefilled syringe, or cartridge affects far more than packaging. Presentation decisions influence formulation requirements, manufacturing processes, delivery strategies, packaging considerations, and future commercialization pathways.

As more therapies move toward self-administration and home-based care, those decisions often remain in place long after the clinical study that initially drove them.

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## Manufacturing decisions that determine execution success

Manufacturing is often where the consequences of earlier decisions become visible.

Technology transfer provides a useful example. Transfer activities are frequently viewed as a handoff between development and manufacturing. In practice, transfer success depends heavily on the quality of information generated long before transfer begins.

Product understanding, process characterization, analytical readiness, and cross-functional alignment all influence transfer success. When gaps exist in any of those areas, organizations may encounter delays, increased costs, additional studies, or operational complexity that affects future timelines.

Many transfer challenges originate from assumptions that were never fully evaluated, process parameters that were never fully characterized, or manufacturing requirements that were not considered early enough.

Scale introduces another layer of complexity. Parameters that are manageable in a development environment may behave differently at larger batch sizes. Critical hold times can become more difficult to maintain. Process variability that appears insignificant during early manufacturing may become more consequential during scale-up and validation.

The result is often additional work at precisely the point when programs are attempting to accelerate. What appears as a technology transfer delay is often the consequence of information that was never generated, assumptions that were never challenged, or manufacturing requirements that were never evaluated earlier in development.

Organizations that invest in process characterization, manufacturing readiness, and cross-functional planning earlier are often better positioned to reduce transfer risk later.

This same shift in thinking is changing how organizations view clinical manufacturing, which has traditionally been viewed as a means of supplying material for a study. Today, it also serves as an opportunity to generate operational knowledge that supports future manufacturing success.

Development-scale manufacturing environments that closely mirror commercial operations, including equipment, process design, and operating approaches, can help establish manufacturing readiness earlier, reduce scale-up risk, and create greater continuity as programs advance.

Process characterization studies, engineering runs, scalability assessments, and platform manufacturing approaches all contribute to a deeper understanding of how a product is likely to perform in future manufacturing environments. That knowledge can help identify potential challenges earlier, reduce uncertainty during scale-up, and support more effective decision-making as programs advance.

Manufacturing activities can also generate insights into material flow, component availability, cold-chain requirements, and other supply chain considerations that become increasingly important as programs move toward larger-scale manufacturing and commercialization.

Manufacturing readiness also extends beyond process performance. As sterile products become more specialized and valuable, manufacturing efficiency and material utilization take on greater importance.

Product recovery, line loss, hold-up volume, and process variability all affect the amount of usable product generated during manufacturing. While losses at any individual step may appear modest, their cumulative impact can affect supply availability, development timelines, and overall program economics. This is particularly relevant for biologics, ADCs, and programs operating with limited drug substance availability.

Manufacturing performance is therefore evaluated through multiple lenses: quality, compliance, material utilization, operational flexibility, and readiness for future scale-up.

Execution remains important. The ability to execute without creating avoidable delays is becoming a competitive advantage.

## Putting accountability behind execution

As development timelines become increasingly important, sponsors are looking beyond technical expertise and manufacturing capacity alone. They want confidence that development and manufacturing commitments can be achieved.

This shift is contributing to greater interest in performance-based partnership models, where execution against agreed milestones becomes a shared responsibility rather than solely a service-provider obligation.

For qualifying programs, Thermo Fisher's risk-sharing approach links a portion of project fees to on-time delivery. When delays occur due to our execution, we share in the financial impact, reinforcing accountability for the timelines we commit to and aligning our success with our customers' success.

## Stability decisions that shape lifecycle flexibility

Stability decisions affect far more than shelf life. They influence manufacturing strategies, supply chains, patient delivery options, distribution models, and commercial flexibility. As products become more complex, stability planning has become closely connected to broader lifecycle planning.

Lyophilization illustrates this shift. Freeze-drying is often associated with product stability. In reality, lyophilization decisions frequently influence formulation strategy, analytical methods, manufacturing efficiency, storage requirements, distribution models, dosing flexibility, scale-up activities, and future commercialization strategies.

Few sterile development decisions illustrate interconnected decision-making more clearly. Successful lyophilization programs require coordination across formulation development, thermal characterization, analytical method development, cycle optimization, scale-up planning, and commercial transfer activities. Decisions made in one area influence outcomes in the others.

Cycle development introduces its own set of tradeoffs. A cycle that performs well at development scale may affect manufacturing efficiency, throughput, product variability, or cost differently at commercial scale. Decisions about cycle design therefore influence more than product quality; they can also affect long-term manufacturing performance.

Those tradeoffs help explain why lyophilization decisions are rarely driven by stability considerations alone.

For some products, lyophilization is necessary because acceptable stability cannot be achieved in liquid form. For others, the decision may be influenced by future supply chain requirements, clinical dosing flexibility, storage constraints, or delivery objectives. The downstream implications can be significant.

A stability strategy that supports early clinical development may not support future commercial requirements without modification. Likewise, a decision that simplifies manufacturing today may create constraints around storage, distribution, or patient delivery later.

Evaluating these considerations early helps preserve future options and reduce the likelihood of costly changes as programs progress. Stability-related changes introduced late in development often affect far more than the formulation itself. Manufacturing processes, packaging configurations, supply chain plans, and regulatory documentation may all need to be revisited.

This broader perspective also applies to delivery strategy. Patient expectations continue to evolve as more therapies move toward self-administration and home-based care. Prefilled syringes, cartridges, autoinjector-compatible presentations, and other patient-centric delivery options now influence development and manufacturing decisions much earlier in the product lifecycle.

Organizations are often balancing multiple considerations simultaneously:

- Product stability
- Manufacturing efficiency
- Product recovery
- Supply chain requirements
- Patient convenience
- Commercial viability

These priorities are not always aligned, and tradeoffs are often unavoidable.

Programs that evaluate those tradeoffs early are often better positioned to avoid delays, preserve flexibility, and adapt as requirements evolve.

### The hidden cost of late decisions

Many sterile development challenges emerge during late-phase clinical manufacturing, scale-up, or technology transfer to commercialization. The decisions that created them often occurred much earlier. The cost of these issues is often measured in time rather than direct expense. **Examples include:**

| Decision | Potential downstream consequence |
|---|---|
| Formulation concentration | Manufacturing and scalability challenges |
| Container closure selection | Stability, delivery, or commercialization constraints |
| Limited process characterization | Technology transfer delays |
| Late stability strategy changes | Additional studies and regulatory work |
| Presentation changes | Packaging, manufacturing, and supply chain rework |

## Bringing the domains together

Development, manufacturing, and stability decisions are often made by different teams at different stages of a program. Yet their impact rarely remains confined to a single stage of development.

Formulation decisions influence manufacturability, delivery options, and commercialization pathways. Manufacturing decisions influence scalability, supply chain readiness, and execution risk. Stability decisions influence future delivery, distribution, and commercial flexibility.

Many of the challenges that emerge later in development are not created there. They are the result of decisions whose downstream consequences were not fully understood at the time they were made.

Organizations that recognize those relationships earlier are often better positioned to reduce rework, preserve flexibility, and move more efficiently from development through commercialization.

## Related resources

### Development decisions and manufacturing readiness

Explore strategies for formulation development, material-sparing approaches, and generating the product knowledge needed to support future manufacturing and scale-up.

**Resource:** Early-phase injectable formulation development: Proven strategies for success

### Manufacturing decisions and execution readiness

Technology transfer often reveals the downstream impact of earlier development decisions. Understanding transfer readiness can help reduce risk, improve execution, and support scale-up.

**Resource:** Technology transfer: Best practices for optimizing success and mitigating risk in sterile drug manufacturing

### Stability decisions and lifecycle flexibility

Explore how formulation strategy, cycle development, scale-up planning, and commercial considerations influence successful lyophilization programs.

**Resource:** Lyophilization excellence: Partnering for sterile fill-finish success

Learn more at thermofisher.com/patheon