ThermoFisher SCIENTIFIC

STERILES DRUG DEVELOPMENT & MANUFACTURING

FLEXIBILITY AND OPTIMIZATION

- API
- BIOLOGICS
- VIRAL VECTOR SERVICES
- EARLY & LATE PHASE DEVELOPMENT
- CLINICAL TRIAL SOLUTIONS
- LOGISTICS SERVICES
- COMMERCIAL MANUFACTURING

patheon

Tony Pidgeon
Senior Product Manager
Pharma Services
Swindon, UK

HOW HALF THE BATCHES ACHIEVED TWICE THE RESULTS.

Sometimes, the future of a client's entire company is riding on the success of one trial. That was the case when a small client came to Tony looking for a formulation solution for a revolutionary treatment. The problem was, their clinical trial protocol, as originally written, required six blinded doses. But the client could only afford to produce three batches, not six. If they couldn't complete this trial milestone, the company was at risk of going out of business. When the client presented Tony with the issue, he recommended an adjustment to the trial protocol that would ensure they could gather the clinical data they needed with just three batches. By changing the clinical protocol, the trial the client thought was beyond their reach, suddenly became possible. And now this small company could move forward to make a big impact.

TABLE OF CONTENTS

5 **Integrated offering with a global network**

6 **Formulation development**

Pre-clinical, Phase I, Phase II, and Phase III

8 **Product contact material & component selection**

Pre-clinical and Phase I

9 **Clinical trial materials**

Pre-clinical, Phase I, Phase II, and Phase III

10 **Analytical method development & phase appropriate validation**

Pre-clinical, Phase I, Phase II, and Phase III

Solve complex challenges throughout your product lifecycle

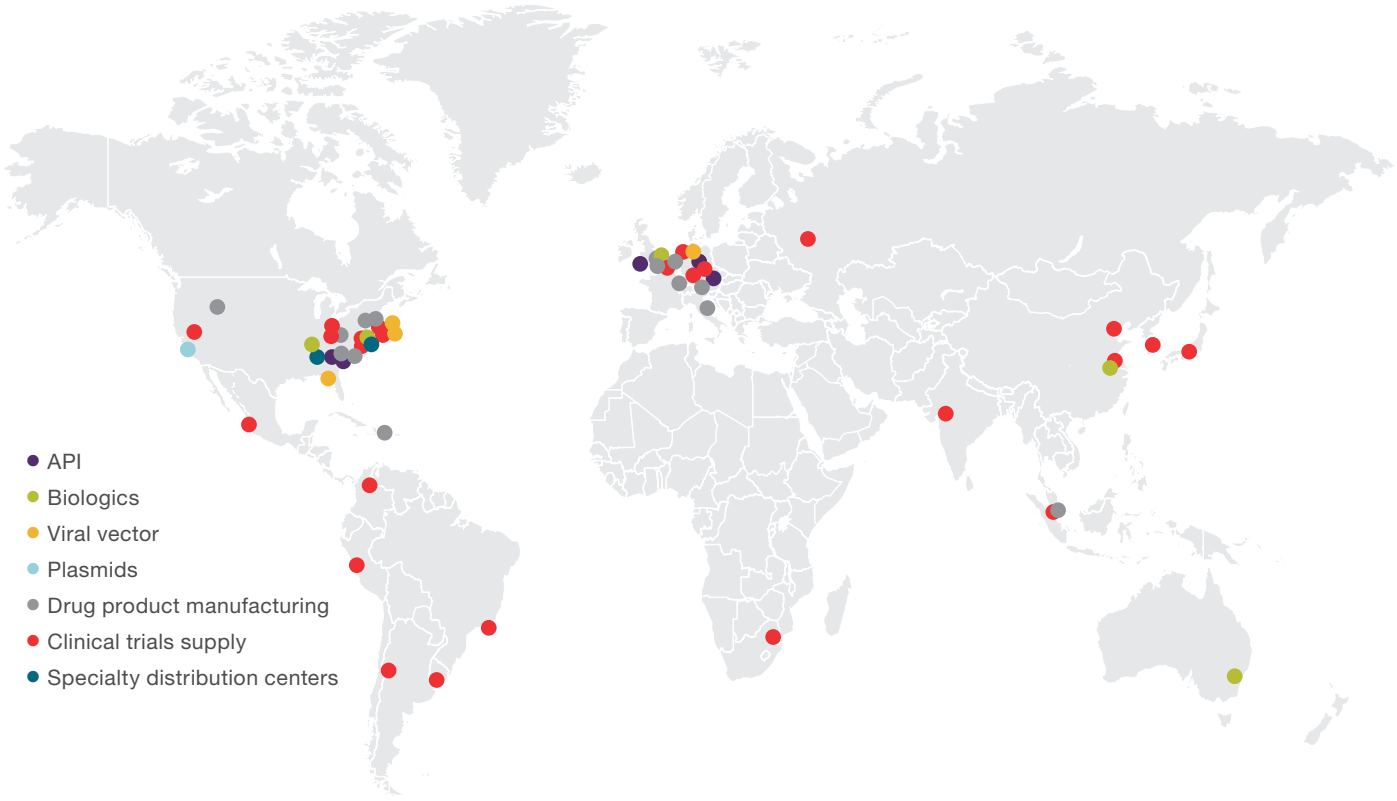
The rapid 10 percent growth of sterile drug product over the past five years has resulted in the need for capacity and innovative solutions within development and manufacturing. Navigating a complex regulatory environment, analytical data, process development and optimization, and on-time delivery are all vital to the success of your sterile drug product. Our flexible offering of solutions and strategies for your large molecule's unique needs and challenges will enable success in early development, as well as lay the foundation for success in commercial development.

We work with over 600 emerging biopharmaceutical and biotech companies in addition to working with all top 20 global pharma companies—17 of which are among the top 20 biotech companies.

Integrated offering with a global network

Thermo Fisher Scientific has an integrated global network of over 55 sites across five continents compromised of technical, quality, and customer engagement teams—each team can help support and solve the complex challenges of your drug product's lifecycle. Our robust large molecule offerings provide robust drug substance, drug product, and clinical trials supply solutions that support early development into commercial launch.

Integrated global network of technical, quality and customer engagement teams to support the drug development journey



~17,000
colleagues in 55+ sites

~3,500
scientists, technicians and engineers with deep technical expertise

~3,000
quality specialists

Our Quick to Care™ solution delivers a streamlined drug development program for your large molecule. This program combines your drug substance and drug product development, clinical manufacturing, forecasting, demand planning, and clinical trial supply execution into a single solution to help accelerate your discovery through clinical development.

Formulation development

Pre-clinical, Phase I, Phase II, and Phase III

Avoid rework and costly delays by getting formulation right from the start

Getting formulation right from the start of early development can help save time and money as you advance through each phase and on to commercialization. Our early development formulation experts and scientists are here to support every step of your project. Gain access to an integrated drug formulation program that is tailored to your large molecule and your process can help you overcome many formulation challenges in the following areas:

- Small and large molecules—whether it's a liquid and lyophilized formulation
- Lyophilization cycle optimization
- Temperature and shear-sensitive compounds
- Poorly soluble compounds
- Highly potent compounds
- Container closure system selection

From 2010-2019—within small and large molecule—we have manufactured over 109 products that have received NDA approval. In the past 10 years, we have received as many NDA approvals as the next four CDMOs combined, and more than third of our commercial manufacturing product launches originate from our formulation and development programs.

Proven expertise in formulation development

1 Pre-Formulation

Identify the optimal pH, ionic strength, degradation pathways and stability indicating methods

2 Surfactant Screening

Select and define optimal levels of surfactants using OFaT approach

3 Formulation Development

Select and define optimal levels for all excipients using OFaT and/or DoE approaches

4 Formulation Confirmation

Confirm stability in the selected final formulation buffer

1 Screening

Evaluate platform formulations to select a phase appropriate formulation for IgGs

- **For biologics:** Susceptibility to physical stress conditions such as agitation, freeze-thaw
- **For lyo products**
  - Evaluation of cryoprotectants and bulking agents
  - QbD applied to lyophilization cycle and to solution formulation

"The formulation team made sure that the robustness study was done on time."

— Small biotech focused on antibiotics, USA

DOSAGE FORMS

Gain access to a broad range of dosage forms to meet your molecule's unique needs

In 2019 alone, we produced 132 million sterile liquid and lyo vials. We also developed and manufactured 40 different pharmaceutical dosage forms, addressing 72 percent of all dosage forms approved. With traditional or niche indications in drug development for steriles, Thermo Fisher understands the unique set of challenges that arise—we offer a broad range of dosage forms to meet your large molecule's needs:

- Small and large volume parenterals
- Liquid filled vials
- Lyophilized vials
- Extensive range of vial sizes including ISO standard
- Pre-filled syringes and cartridges

Product contact material & component selection
Pre-clinical and Phase I

Reduce costs and assure quality with pre-qualified processes and systems

From a quality and cost management standpoint, ensuring consistency across your processes in early development is critical. Access to pre-qualified components and standard processes allows you to have consistency across your project as you move from phase to phase. Thermo Fisher's product contact material and component selection enables shorter timelines, reduced capital expenditure, and the elimination of cleaning validation, media fills, and CCI (container closure integrity).

- ISO standard vials are utilized, which are type 1 glass with fluorotech coated stoppers
- Vials in the range of 2R-20R are qualified across the network with 50R in some locations
- A fully disposable product pathway is utilized that compromises of all USP Class VI materials

LYOPHILIZATION DEVELOPMENT/OPTMIZATION
Preclinical and Phase I

Simplify your process and produce stability within your drug product

Leveraging lyophilization development and optimization within your early development allows you to reap a variety of different benefits from a quality and manufacturing standpoint.

Lyophilization: Quality impacts

- Maintains potency of the product during a process that can induce degradation
- Ensures a product's pharmaceutical properties are acceptable for use
- Enables stability and a manageable shelf life for the duration of clinical trials and for the marketed product

Lyophilization: Manufacturing impacts

- Provides foundations for a consistent, reproducible manufacturing process
- Ensures a cycle that is transferable to—and compatible with—GMP production-scale equipment
- Minimizes rejection rate—i.e., minimizes the number of vials within a batch
- Reduces the likelihood of batch rejection—i.e., reduces the impact on timelines of pharmaceutical development program and market supply
- Reduces production costs, by minimizing lyo cycle duration

NON-GMP LAB BATCHES
Preclinical and Phase I

Lengthy timelines in early development increase costs

In pre-clinical and Phase I, lengthy development timelines are common. To help shorten timelines for accelerated development, we offer non-GMP suites that ensure scalable equipment. The setup of our non-GMP lines mimic our GMP lines—it's the same material without the aseptic processing and costs associated with GMP spaces. As a result, our non-GMP lab batches ensure:

- Shortened timelines
- Stability
- Filterability
- Compatibility

Clinical trial materials

Pre-clinical, Phase I, Phase II, and Phase III

Deliver high-quality clinical trial materials at any phase for regulatory approval

As you look to achieve regulatory approval, you will have access to high-quality clinical trial material that is tailored to fit your needs and scope of work. Our exemplary inspection record and reliability will ensure on-time and right-the-first-time delivery. In 2019 alone, our average on-time delivery rate was approximately 90 percent and our right-the-first-time rate was approximately 91 percent.

> ***"Team has been very helpful in working with us to move production schedules to align with moving regulatory milestones."***
>
> — Pharmaceutical company focused on antibiotics, USA

By providing reliable, tailored, and flexible clinical trial material solutions, we are able to:

- Minimize the loss of expensive product
- Reduce variability and risk through a quality driven, global, and automated processes
- Minimize the "time out of environment" (TOE)
- Eliminate costly bottlenecks and deliver efficiency

Get Phase I clinical materials in as little as 14 months

Our Quick to Clinic™ for steriles can expedite your product with high-quality Phase I clinical materials in as little as 14 months. That's approximately six months faster than most standard timelines and includes a minimum of one month of stability data. Designed with speed and flexibility, Quick to Clinic™ for steriles allows you to meet key milestones to reach patients faster. This program includes:

- Cell line development—optional but not required
- Cell culture and purification processes
- Liquid-filled vial drug product formulation
- Analytical methods
- Early non-GMP material for toxicology studies
- Released GMP drug substance
- Released GMP drug product
- Viral clearance and stability study data

> ***"Both very good technical capabilities and effective project management resulting in on-time delivery."***
>
> — Biotech focused on immunotherapy, UK

Analytical method development & phase appropriate validation

Pre-clinical, Phase I, Phase II, and Phase III

Access scientific data for strategic decision making

Whether you are in early development or commercial drug manufacturing, access to your drug product's high-quality scientific data is critical. When it comes to regulatory submission, this scientific data can help with drug product efficiencies and strategic decisions. It also is valuable with each part of the process and aids in strategic decisions because it helps back up the quality of the product and processes you built. With fully equipped cGMP labs, Thermo Fisher provides comprehensive analytical solutions to help transform your discovery into a drug product with the best chance for approval by leveraging:

- Physical and chemical characterization
- Pre-formulation studies
- Method transfers—both analytical method risk and method validation gap analysis
- Raw material release testing
- Drug product release testing
- Component compatibility testing
- Product contact part compatibility testing
- Container-closure integrity studies
- Method development and validation
- In-process drug product testing
- Clinical trial material stability testing
- Cleaning method development and validation
- Microbiological method development and validation
- ICH stability testing

We have cGMP labs staffed by highly experienced teams within each of our manufacturing and development sites. From a small quantity of your drug substance or drug product, you can gain the scientifically sound data you need for regulatory submissions and to guide your next steps. We provide through analytical data for high-quality products, processes, and business decisions, such as:

- Chromatography: GC, HPLC, and UPLC
- Spectroscopic: UV, FTIR, ICP, and AA
- Moisture analysis
- Rheology
- Particle size analysis
- Thermal analysis
- TOC
- Dissolution analysis
- Thin layer chromatography

STABILITY STUDIES/EXTENDED STABILITY
Pre-clinical, Phase I, Phase II, and Phase III

Stability insight of your large molecule

Stability studies are vital to early development phases. Our solutions allow you to store samples and ship off for testing or test in-house, as well as vial and syringe stability. Our stability study solutions include:

- Standard ICH conditions
- Inverted, upright, and random positioning
- Stability protocol design
- Supporting analytical and microbiological testing
- Specialized temperatures available

PROCESS OPTMIZATION, SCALE-UP
Phase II and Phase III

Building out an optimal and flexible process design

To achieve high-quality results and sustainability within your product's lifecycle, building out a robust process with agility and flexibility will set you up for long-term success as you scale. Our industry experts have the experience to develop an optimal process that is tailored to your unique challenges and needs, which will include:

- Formulation development
- Lyo-cycle process development and optimization
- Manufacturing process development
- Mixing and pump-shearing studies
- Holding time studies
- Freeze-thaw studies
- Cleaning validation
- Product contact part compatibility studies
- Sterilization cycle development and validation
- Scalability studies

COMMERCIAL PRODUCTION

Tech transfers: Short-term strategic investment for long-term cost savings

Whether it's for scaling-up or moving to another facility, technology transfers are part of the normal course of business. In 2019, we successfully completed 119 technology transfers—44 commercial, 60 drug substance, and 15 development.

Our dedicated global experts ensure:

- Process validation is in accordance with regulatory and cGMP guidelines
- Your project remains on track and product supply is preserved
- Seamless execution for right-the-first-time delivery
- You have access to a robust system to manage the product lifecycle
- You have insight to all stage gates required for each phase
- You have access to stability studies, analytical data, release testing, and other regulatory documentation

"Excellent technical performance, responsiveness, flexibility, positive attitudes, collegial and friendly atmosphere."

— Pharmaceutical company focused on oncology, USA

“Excellent collaboration between sites; quick batch turn-around times.”

— Large pharma, USA

CASE STUDY

SITUATION: The clinical batches were successfully completed at another in-network site at a small scale and the customer was looking to scale-up batch size. There were a variety of technical challenges that needed to be addressed.

Sensitivities	Hold Times	Batch Processing
• Oxygen • Stainless Steel • Heat • Hygroscopic API	• 6 hours from API addition to completion of pH adjustment • 20 hours from API addition to Lyo start w/IPC • Filling line hold time of 30 hours from SIIP to end of fill	• Nitrogen sparging in disposables • DO measurements • Localized high pH • Active cooling

SOLUTION: We implemented the following keys to successful registration and validation.

- Constant updates and good communication between operations and QC labs
- Customer on site during production allowed for expedited decision making
- Very specific batch record instructions and operator training for highly technical batch

OUTCOME:

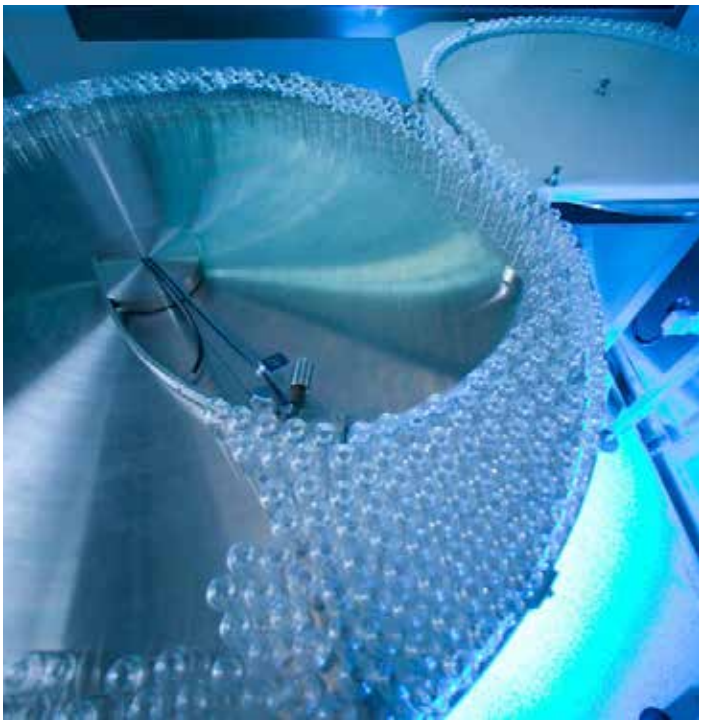
- Three registration batches were successfully completed
- Commercial launch from an additional network site
- Process improvements were made along the way, with a robust process designed and executed prior to PV batch production

Optimize your chances for approval

Thermo Fisher Scientific offers experience, reliability, and a broad range of sterile fill/finish commercial capabilities. We have an unrivaled record of sterile drug product commercialization success for our clients.

Leveraging our commercial production and clinical trials solutions will give you extensive access to global technical experts, scale, capability, global regulatory insights, and transportation. Global network and solutions span across:

- Global clinical trial packaging and storage
- Clinical supply optimization
- Clinical label
- Cold chain storage and logistics
- Distribution and logistics
- Global clinical ancillary management



Contact us now to learn about our flexible steriles solutions

+1 919 226 3200 ● thermofisher.com/patheon ● pharmaservices@thermofisher.com

Published 03/21

ThermoFisher SCIENTIFIC