WHITE PAPER

The benefits of end-to-end formulation and fill-finish of biologics

Internal tech transfers from R&D to clinical fill-finish mitigate risk, save time and reduce cost for large molecule production

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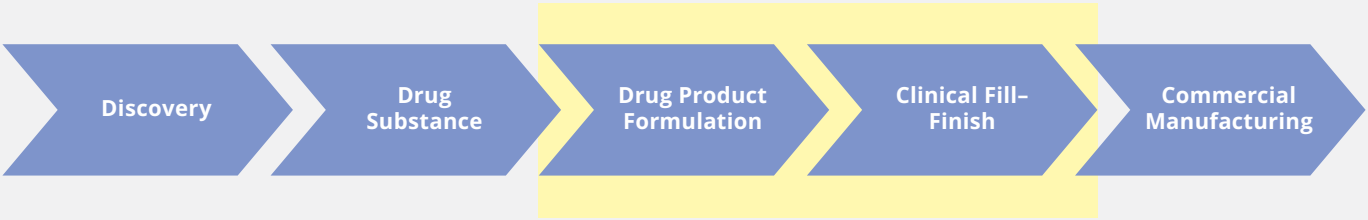
The clinical value of biologics for the treatment of many disease indications has been accompanied by phenomenal sales. By 2026, the global market for biologics is projected to increase to $537 billion, while the blockbuster Keytruda could be the top-selling drug with almost $25 billion in sales.[1]

However, getting a promising drug candidate from formulation development to clinical phase production and commercial manufacturing can be daunting. Proper formulation development has a huge impact on whether a technology transfer to clinical phase fill-finish is successful. This is especially true for biologics — high molecular weight molecules that are unstable and whose integrity is susceptible to upstream and downstream processes. Tech transfers from R&D to clinical fill-finish can encounter unforeseen issues — potentially leading to failures of GMP batches — unless the development team has an intimate knowledge of clinical phase manufacturing. This is a particular problem when a smaller-scale R&D-phase formulation process is transferred to an external company.

Ideally, biologics drug product formulation scientists will have a complete understanding of downstream processes of clinical fill-finish and how they affect development. Good communication between R&D and clinical fill-finish is crucial to help mitigate risk, save time and save money. When those working on formulation development and clinical fill-finish collaborate, tech transfers are smooth, problems are greatly reduced and improvements in speed, quality and safety occur.

The product development life cycle *Figure 1.*



The yellow box indicates the portion covered in this white paper, specifically the tech transfer between formulation development and early clinical phase manufacturing.

This white paper details how to optimize formulation development and tech transfer to ensure successful biologics production. Specifically, it deals with the transition from formulation development in R&D to early clinical phase manufacturing (**Figure 1**) and covers:

1. The need for intimate connection
2. The components of successful technology transfers
3. Case studies

Formulation development needs to be intimately connected with manufacturability

There are many points during formulation development that will impact future manufacturing success. This includes the control of drug substance, pH and excipients, as well as the choice of container and container closure system. How formulation components are combined and packaged — i.e., the manufacturing process — is as important to understand as the formulation itself, as it also impacts the performance of the formulation.

The goal of formulation development is to create a well-characterized biologic drug product. This requires a deep understanding of the behavior of the molecule of interest, including its critical quality attributes (CQAs) that impact quality, efficacy and safety. While assessing the CQAs is difficult enough for relatively stable small molecule APIs, biologics have an added layer of complexity since their fragility makes them susceptible to many stresses and degradation pathways. The manufacturing process affects CQAs and requires more than just a development scale formulation screening under ideal closed-system conditions.

UNDERSTANDING CQAs OF PROTEINS IS FUNDAMENTAL TO FORMULATION DEVELOPMENT

In an ideal world, API and excipients are the only ingredients that make it into the finished drug product. Unfortunately, there can also be impurities in the product, such as extractables and leachables, raw material-related impurities and degradation species of the API. Impurities fall into various categories, including unidentified, partially

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Critical quality attributes of proteins and changes that can result in impurities during biologics manufacturing

Table 1.

Critical quality attributes of proteins	
Product-related impurities	**Process-related impurities**
While each drug modality has unique challenges arising during development, formulation scientists have tools to mitigate the many common product-related impurities that may arise. **Physical changes** • Aggregation • Fragmentation • Denaturation • Subvisible/visible particulate formation **Physicochemical changes** • Oxidation • Deamidation • Disulfide-bond shuffling • Hydrolysis • Deglycosylation • Succinimidation • Maillard reaction (glycation) • C- or N-terminal modification • Isomerization	Impurities can be carried over from upstream processes, while during manufacture and fill-finish, other sources can affect performance or stability of the formulation. **Upstream drug substance processing** This includes potential carryovers from upstream processing, which should be resolved with a well-developed drug substance supply: • Residual host cell protein or DNA • Processing step carryover (e.g., elution buffer components) • Endotoxin • TSE/BSE, microbial contamination, mycoplasma, viral contamination • Cell culture media **Manufacturing** • Metal ion leaching • Extrinsic particulate • Raw material-related impurities • Microbial contamination

characterized or known structure. If present in sufficient quantity, these impurities should be characterized and their impact on the formulation performance, or even their own biological activity, should be understood. Some examples of potential product- and process-related impurities are listed in **Table 1**.

As is shown in **Table 1**, not all CQAs are related to the desired components of the drug product or the intrinsic degradation of the API; they can be connected in various ways to each other and also to upstream and downstream processes. An example of this occurred with a formulation Curia developed that was susceptible to oxidation. Small-scale formulation in the R&D lab, using dialysis and manual filling, resulted in negligible oxidation. However, when scaling up to a manufacturing process, oxidation was catalyzed by metal contaminants introduced via contact surfaces or pumping through filling needles. Robustness studies identified the downstream effects of this and, by adding chelators and antioxidants, oxidation was mitigated in the finalized formulation.

Manufacturing process stress testing during R&D

The goal of a formulation scientist is to hand over a successful formulation to the clinical fill-finish team with a scalable process that considers any equipment limitations, fits into GMP manufacturing limitations, uses compendial-grade raw materials, and has been tested to survive manufacturing process stresses.

The formulation is not in an ideal closed system; it will undergo a number of stresses that can be harsh, particularly for biologics. Screening for manufacturability of a promising formulation takes into account various process-related stresses.

Basic screening

During preliminary formulation characterization, the effects of a wide range of conditions such as surfactant selection, pH and ionic strength are screened and the following stresses are assessed:

- Storage temperature
- Agitation/shear stress
- Freeze/thaw cycles
- Photosensitivity (UV and visible light)
- Liquid stability of lyophilized formulations

Surfactants should be assessed as early as possible and samples should be exposed to both agitation and freeze/thaw stresses, as these stresses can elicit different behaviors depending on the surfactant.

UV testing

The ICH Q1B guidelines, which were designed for small molecules, require exposure to 1.2 million lux hours of visible light and 200 watt hours/m2 of UV light. These conditions will likely cause significant degradation for most proteins and can be too aggressive to ascertain useful information on more relevant photostability questions. For this reason, a UV test exposure of 8 watt hours/m2 is used, which is more in line with what would be encountered during a typical manufacturing run. Once a finalized formulation is determined, ICH Q1B exposure can be tested to generate necessary data, but for manufacturability assessment, a lesser stress is preferable.

Robustness testing

This is done once a formulation is nearly finalized to ensure a well-characterized drug product. There are countless robustness tests that may be performed depending on the eventual target product profile, manufacturing process and CQAs. Some common robustness tests include: silicone oil/tungsten compatibility for pre-filled syringes; material contact testing to isolate variables of potential

manufacturing contact surfaces; and pumping, filtration or UF/DF studies to bridge R&D scale processes to larger scale GMP processes.

SUCCESSFUL TECHNOLOGY TRANSFERS

Once a drug product formulation has been developed and deemed rugged enough for manufacturing, it can be passed on to the early clinical phase manufacturing team to progress through the clinical development life cycle. The development team provides the information needed to create a GMP manufacturing process, starting with a high-level view of CQAs. Some exploratory questions to be asked are:

- How is the formulation created?
- What excipients and raw materials are used?
- If there is a titration step, how is it titrated?
- Are there other major processing steps, such as tangential flow filtration (TFF) or lyophilization?
- Is solubility an issue?
- Does the formulation require heating or cooling or any other special equipment?
- Are there concentration concerns? High concentrations can lead to viscosity problems. Lower concentrations can have problems with analytical measurement.
- Are there material compatibility concerns?
- Are there any stability concerns at ambient temperatures? Manufacturing involves many ambient processing steps that can be long.

Answering these questions will determine the appropriate type of manufacturing facility for the formulation.

A MANUFACTURING APPROACH TO TECH TRANSFERS

Ensuring the R&D team understands what can and cannot be done in a GMP facility sets up the project for success. This includes knowledge about raw materials, components and scalability.

Compendial vs. research-grade excipients

It is necessary to choose raw materials suitable for GMP use, including excipients, buffers, water for injection (WFI), titrants and the API. Even though research-grade excipients may be used during development to reduce cost, the use of USP compendial-grade excipients in formulation development ensures your results will translate well to a final GMP-level process. To prevent lesser-grade materials being used in a GMP process following tech transfer, Curia provides its R&D teams with order numbers for raw materials that are compatible with many current compendiums.

Ensuring the R&D team understands what can and cannot be done in a GMP facility sets up the project for success.

Components

Components are all other materials used during production, including vessels, filters, vials, stoppers and seals. For example, R&D needs to select a container closure system — the vial stopper and seal — that has already been validated in the facility. This avoids incurring lost time to validate new change parts for manufacturing lines or performing R&D bridging studies to assess critical quality attributes in a new container closure.

Buffer exchange or concentration

While it is acceptable to use dialysis during development to exchange buffer systems, or

centrifugation to concentrate solutions, these processes are not used during GMP manufacturing. Instead, to exchange a buffer system or concentrate a drug substance, UF/DF systems are leveraged.

Scalable processes

The transition from small-scale, volume-based processing to large-scale, weight-based manufacturing means that almost every formulation needs to be reconstructed prior to transfer to a GMP facility. Weight-based processes are more precise, provide a reproducible and validated process, and allow the formulation to be scaled more easily.

DESIGNING A SUCCESSFUL TECH TRANSFER PROCESS

Designing a tech transfer process requires understanding many different attributes, including solubility, material compatibility and product concentration issues affecting the formulation.

Solubility

There might be a need for temperature control or specialized equipment for mixing to ensure the solubility of the products. Some processes require gentle mixing, using a magnetic stir bar, while others need a vigorous approach, using an overhead mixer or shear mixer. There are processes that require many hours of mixing at higher temperatures (e.g., at 50°C) to ensure solubility.

COMPATIBILITY

The move to single-use technology requires investigation about potential compatibility concerns with the product contact surfaces of current industry-standard disposable materials. This can include type one borosilicate glass containers, polypropylene plastic containers, proprietary films used in single-use technology bag systems, platinum silicone tubing and product filters.

While most tech transfers have no problems with sourced materials, R&D will identify any concerns with the materials used during formulation development.

- Some formulations or APIs are incompatible with glass and must be formulated in plastic containers and use cyclic olefin polymer (COP) plastic vials for the container closure system.
- Some common materials, such as platinum silicone tubing, are incompatible with today's manufacturing facilities, requiring special sourcing of non-silicone tubing to be used in all process steps.
- Polyethersulfone (PES) and polyvinylidene fluoride (PVDF) filters are typically used for biologics because of their low protein binding.

Concentrations

The majority of transferred processes are for drug products with low concentrations, which pose no significant challenge to the process. High-concentration formulations (>200 mg/mL) may be of concern due to high viscosity, which can lead to filtration problems (see **Case Study 1**). Peristaltic pumping of high-viscosity solutions can cause differential pressure in the tubing, which in turn causes the solution to continue to flow after the pump has stopped and leads to accuracy problems on the fill line. Also, high-viscosity solutions carry different surface tensions, and the filling needle inner diameter (ID) becomes an important variable in controlling dripping.

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CASE STUDY 1:
ENSURING FILLING ACCURACY OF A HIGH-VISCOSITY FORMULATION

The formulation of Product A, a peptide, required a high percentage of solubilized cyclodextrin, which created a formulation with high viscosity. During tech transfer, Curia's R&D team had concerns about filling accuracy.

We studied filling accuracy on the designated fill-finish line, using a surrogate material matching the characteristics of the formulation. By studying the components, such as tubing and filling needle IDs, in addition to peristaltic pumping parameters such as drawback and velocity, we were able to optimize the filling accuracy and set proper in-process controls (IPC) for the procedures.

This study established the correct bill of materials, pumping parameters and a solid in-process control that allowed accurate filling of this high-viscosity biologic.

CASE STUDY 2:
SOLVING A FILTRATION PROBLEM

While Product B, a peptide, was in a stable formulation, Curia's development team was concerned that filtration took 10 hours for a 50-mL sample, which was unacceptable to transfer into a GMP facility.

The scale of the process was increased to study a surrogate formulation with characteristics similar to Product B. We tested multiple filter types and materials to establish the ideal combination that would yield a reasonable filtration time. By applying a 0.45 micron filter in front of a sterilizing filter and ensuring there was enough surface area, filtration time was drastically reduced.

Product B was able to progress through clinical phase manufacturing as a GMP process.

CASE STUDY 3:
A LYOPHILIZATION TECH TRANSFER

This client had transferred its small-scale development lyophilization cycle of a protein to another contract manufacturing organization. When the process was scaled up, the mass transfer to the condenser was too fast and choked the condenser, which is known as choked flow or dryer overload. This created a failed lyo run that was insufficiently dried. At this point, the client transferred the project to Curia.

This is a situation when having both drug R&D and clinical phase manufacturing in the same organization benefits our clients. Our development team understands the performance specifications of our GMP larger-scale lyophilizers — including shelf-temperature ramp rate, chamber pressure limitations and mass transfer limitations, which are not as high performance as a smaller-scale R&D lyophilizer — and was able to design a successful cycle that fit within the capabilities of larger manufacturing lyophilizers.

An additional aspect of GMP production that is limiting, when compared to R&D, is the need to work within batch records. During development, for example, it may be possible to implement a hold step or a push-button step to monitor for the convergence of the Pirani gauge and capacitance manometer, which may also be feasible in earlier clinical manufacturing. However, in more concrete production processes for later clinical phases and commercial production, primary drying times are typically fixed and a push-button step is likely unacceptable.

SCALING UP TO GMP MANUFACTURING AT CURIA FACILITIES

To support flexible, efficient and phase appropriate tech transfers from R&D, Curia has two validated GMP fill-finish facilities. Each facility has its own preparation, formulation and filling suites. Both facilities leverage the latest single-use technology platforms from all major vendors.

Fill-Finish Facility 1: Liquid, lyophilization and automated syringe/cartridge filling

This facility, validated since 2008, is used for early-phase clinical manufacturing processes (**Figure 2**). Mainly a liquid and lyophilization line, and equipped with an automated syringe and cartridge filler, it supports many configurations that are either developed and tested by our R&D team or directly transferred from our clients. The facility offers flexibility in terms of batch sizes and capacities.

Production capabilities of Fill-Finish Facility 1 for liquid, lyophilization and automated syringe and cartridge filling

Figure 2.

EU Grade A environment

Automated filler for both liquid and lyophilized products
- M&O Perry Fill Line
- BOC Edwards Lyophilizer
- West Star PW500 Capper **Fully Disposable Components**

Vials Size: 2cc–20cc

Syringes: 1 mL–2.25 mL

Cartridges: 1.5 mL–3 mL

Max Batch Size:
10,000 liquid units (vials/PFS}

Lyophilizer Batch Size:
- 2cc = 5,000 vials
- 20cc = 1,200 vials

Fill-Finish Facility 2: Liquid RABS

This facility, validated in 2020, is equipped with a liquid-only restricted access barrier system (RABS) filler (**Figure 3**). The RABS has an in-line vial washing and depyrogenation tunnel attached, which allows for a more streamlined process. A RABS provides a better platform for late-phase manufacturing processes, as well as supporting tech transfers to commercial facilities since the updated technology is aligned with commercial production lines.

Production capabilities of Fill-Finish Facility 2 for liquid-only GMP manufacturing Formulation capabilities

Figure 3.

Bausch Fill Machine Type 515
- High speed, liquid only

Restricted Access Barrier System (RABS)

Integrated vial washing and depyrogenation tunnel

Fully disposable line

Vial size: 2R–30R

Fill volume:
0.2 mL to 35 mL

Max Batch Size:
20,000 vials

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Our GMP formulation capabilities are scaled-up versions of what is developed in our R&D labs, albeit with some changes in parts of the process. During development, for example, small batches are volume-based. While clinical phase fill-finish can use this approach, whenever possible, manufacturers will want to switch to a weight-based process to properly scale the formulation. Here are Curia's formulation capabilities:

- **Single-use formulation vessels** (1–200 L) – Disposable equipment — formulation vessels, transfer assemblies and final filtrate containers or bags — has the advantage of avoiding the time- and resource-heavy cleaning validation that is essential for stainless-steel equipment, which can add weeks or months to a project.
- **Weighing** (1 mg–250 kg).
- **Mixing** – The range of mixing, from gentle to aggressive using overhead shear mixers, provides the flexibility to work with all formulations, including those with solubility challenges.
- **Heating and cooling exchangers** – Connected to jacketed vessels, these give temperature control between 2–50°C. One formulation Curia worked with required mixing at 50°C for many hours to achieve full solubility while, at the other end of the range, high concentrations of poloxamer meant we needed to control the process temperature at 5°C to keep it from gelling.
- **Analytical support** – All facilities are equipped with pH and connectivity meters. For other in-process controls (IPCs), there is an onsite quality control laboratory that supports our manufacturing processes.
- **TFF unit operations** – Sometimes ultrafiltration/ with pH and connectivity meters. For other in-process controls (IPCs), there is an onsite quality control laboratory that supports our manufacturing processes.

Conclusion

Benefits of end-to-end formulation and fill-finish

Biopharmaceutical manufacturers looking for support during their drug product development life cycle will benefit from partnering with a company with end-to-end services from drug product formulation to clinical fill-finish. Having R&D and commercial manufacturing teams under the same roof mitigates risk, saves time and reduces costs:

- Tech transfers between different organizations are avoided, limiting problems that can lead to failures of GMP batches.
- Operational efficiency and excellent project management between tightly knit R&D and fill-finish groups improves efficiency and speed.
- Streamlined communication reduces risk and means teams are constantly available to lend support, answer questions and solve problems in real time.

Let Curia provide end-to-end support for the formulation of your next biologic. For more information, please visit https://curiaglobal.com/manufacturing/sterile-fill-finish/.

Reference

1 EvaluatePharma. World Preview 2020, Outlook to 2026. Accessed 4 Jan 22 at https://www.evaluate.com/thought-leadership/pharma/evaluatepharma-world-preview-2020-outlook-2026

ABOUT CURIA

Curia is a global contract research, development, and manufacturing organization (CDMO) with over 30 years of experience. With an integrated network of 20+ facilities worldwide and a team of 3,000+ dedicated professionals, we specialize in partnering with biopharmaceutical customers to bring life-changing therapies to market.

Our offerings in small molecules, generic APIs, and biologics span discovery through commercialization, with integrated regulatory, analytical, and sterile fill-finish capabilities. Our scientific and process experts, along with our regulatory-compliant facilities, deliver a best-in-class experience across drug substance and drug product manufacturing.
From curiosity to cure, we are your trusted ally in accelerating life-changing therapeutics.

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