

SYSTEMATIC APPROACH TO EARLY PHASE STERILE DRUG PRODUCT TECHNOLOGY TRANSFER

Source: Singota Solutions

Singota® Solutions is a CDMO located in Bloomington, Indiana, USA that specializes in Parenteral, Early Phase Drug Development and Aseptic Filling projects.



Initial scale-up of a sterile drug product manufacturing process can present significant challenges and pose risks to new drug development timelines, budgets, product quality, and even patient safety if not properly managed. It is difficult to anticipate every potential issue but experienced pharmaceutical formulation and manufacturing specialists familiar with these challenges can minimize overall risk and ensure successful production of the first plant-scale batches.

During the initial phases of parenteral dosage form development, formulation scientists strive to generate a drug product formulation that facilitates delivery of the drug substance to patients in a safe and convenient manner. The fact that a drug must be delivered by a parenteral route is often an indication that the active ingredient may possess properties that present challenges to finished dosage form manufacture. It is these potential challenges that must be addressed by a technology transfer team in order to ensure manufacturing success.

How should a manufacturer go about preparing for the initial transfer of a lab-scale process to the manufacturing plant? Experience demonstrates that while it would be convenient to simply apply a scale factor to formulation ingredients and prepare a manufacturing batch record on this basis, this is rarely the case. More often than not, there are factors that a tech transfer team must carefully evaluate and, where necessary, take measures to overcome potential problems in order to avoid a failure in the manufacturing setting.

The more systematic the approach to preparing for initial plant-scale production and the more coordinated such effort is between formulation scientists and manufacturing personnel, the more likely it is that the transfer will be successful.

Assessing Potential Manufacturing Risks

Any injectable drug formulation will likely have undergone extensive development in order to generate product to support animal studies. Therefore, when the time comes to produce drug product to support “first in human” studies, the formulation is usually well defined. It is likely that in the production of initial in vivo animal study supplies, drug product has been produced at a modest scale, most likely in a GLP laboratory. These supplies are frequently prepared by formulation scientists who have a good deal of flexibility in how they operate.

The transition from this non-GMP production mode to GMP plant scale where batch sizes are often significantly larger and the strictures imposed by GMP guidelines can present certain challenges.

Issues that may be encountered at this stage may be grouped into six general categories:

- **Safety:** Does the product/process entail any health/safety risks for operators when handling larger quantities of API and excipients?
- **Scale:** How will a process vary depending on the volume of materials processed?
- **Materials:** Are there differences between lab-scale and manufacturing-scale materials (e.g. excipients, API, container closures) that would affect process performance or product quality?
- **Equipment:** How will differences between lab-scale equipment and plant equipment affect process performance?
- **Environment:** How will the attributes of the manufacturing environment (e.g. presence of sterilant gas, air flow, time out of refrigeration (TOR) impact the formulation or product efficacy/stability?
- **GMP Considerations:** How will the need to collect and analyze in-process control samples and various record keeping requirements impact process performance?

It is important that the team tasked with the initial scale-up and GMP manufacture of a new parenteral formulation systematically assess these factors and, where they note risk, devise strategies to address such risks. Key to this initial assessment is a thorough understanding of both the formulation's particular properties and the characteristics of the manufacturing facility where the scale-up will be carried out.

Many organizations conducting technology transfers utilize formalized procedures for risk assessment which may include such tools as technology transfer checklists and risk assessment scoring systems. Whatever method is used, the outcome of a pre-production assessment should be a list of process parameters that require evaluation in the formulation development laboratory prior to initiation of production activities.

Process Evaluation and Development

Once an initial assessment has been completed and any knowledge gaps or high-risk areas identified, the tech transfer team should prepare and execute a formal development plan. Since it is an expectation of regulatory authorities that a history of a product's process development be available at the time of a regulatory submission, it is advisable to carry out all lab work under written protocols and to document results according to applicable internal guidelines.

Of course, some products present unique challenges that should also be addressed prior to scale-up. Complex formulations such as liposomes, nanoparticles or lyophilized powders merit extra attention and may require extensive pre-production laboratory development programs.

While a laboratory scale evaluation will often yield most of the information required to ensure a successful first-in-plant production run, there are a number of variables that are often quite challenging to address in the laboratory. Some factors that on the surface may seem straightforward, can actually be difficult to model in the laboratory.

For example:

- **Mixing** – Mixing rates can be difficult to model in the laboratory due to the size and geometry of plant-scale agitators compared to lab equipment. Formulators must determine whether components present any challenges to dissolving or dispersing solids such that formulation homogeneity is difficult to achieve. Part of the development effort should be to establish appropriate in-process control check points to ensure formulation homogeneity.
- **Heat Transfer** – Laboratory heating/cooling units often have different relative capacities compared to those available in the plant. The laboratory should ensure that these differences are taken into account in establishing heating and cooling instructions in master batch record and allow adequate leeway to account for scale effects.

Besides scale related challenges, the differences between laboratory conditions and the manufacturing environment should be considered.

- **Environment:** Common sanitization agents such as hydrogen peroxide can pose a serious threat to active ingredients sensitive to oxidation. Especially in the case of isolator-based manufacturing lines, peroxide residues can be present in the manufacturing atmosphere and expose drug product solutions to oxidative conditions. It is imperative that a manufacturer understand the performance of its sanitation systems and ensure that residual oxidant levels are at or below the maximum acceptable levels for any given formulation.

In extremely oxidation-sensitive formulations, even the oxygen present in the filling suite can pose a risk to product quality. In these cases, it may be necessary to introduce inert gas such as nitrogen or argon in order to minimize oxygen contact with the formulation both during production and in the headspace of sealed finished product containers.

- **Formulation Components:** Sources and grades of API and excipients used in the formulating process can differ between the lab scale and manufacturing scale. Every effort should be made to ensure that sources used in the development of a new formulation are of the same grade as those that can be sourced at the larger manufacturing scale. Where this is not possible, for instance due to lack of representative API, every effort should be made to understand the physical properties of such materials and be alert for potential changes in such attributes during scale-up. An example would be particle size of an API that may have been produced in a laboratory as opposed to a plant-scale process. Having the ability to analyze API prior to initiation of manufacture may help alert the operations team to a potential change in that API's behavior during formulation.



- **Materials of Construction:** Formulation scientists should be aware of the type of equipment and supplies that will be used during manufacturing activities and be prepared to conduct compatibility studies to ensure that such materials will not adversely impact the finished product. If there are any doubts as to compatibility, it is usually a simple matter to conduct experiments to rule out any such issues. When using a sterilizing filter in a drug product process, it is common practice to subject a lab-scale batch of product to the sterilizing filter type to be used to ensure that filtration does not alter the potency of the batch nor impart any extraneous substances (e.g. extractable compounds) to the final product. Similarly, when little or no information as to the compatibility of formulation components with other product-contact materials such as formulating vessels, transfer tubing or connectors, it is usually advisable to conduct small-scale experiments to assess compatibility with these materials.

Knowing the specifics of plant-scale equipment and procedures, it is possible to systematically address potential risks as shown in Table 1 below.

**Table 1 –
Manufacturing
Risks
Associated
with
Technology
Transfer &**

Scale-up
*H₂O₂ only
necessary if
manufacturing
facility utilizes
peroxide as a
decontamination
agent. Could also
include other
sanitizing
vapors/gasses as
appropriate.

Where possible, it may be advantageous for manufacturing personnel to participate side by side with formulation scientists as a process is developed in the laboratory so that they may become familiar with a procedure before it is transferred to the plant. This is particularly important when a process differs significantly from a plant's "standard" process. For example, a simple aqueous solution consisting of API and water for injection may present few, if any, challenges, while a process that involves numerous excipients and relatively exotic processing such as homogenization, may be well outside the experience of a manufacturing organization. Producing a batch at an intermediate scale in a kilo lab using the definitive manufacturing process is often a good opportunity to confirm that a process is ready for the plant and also affords operations staff a chance to see the process in action.

Ideally, a new process should be run at plant scale for the first time as an engineering batch under non-GMP conditions. An organization may elect to forego this "dress rehearsal" if the risk assessment revealed no significant challenges. In such cases, it may be reasonable to proceed directly from the laboratory to GMP production without incurring undue risk of a batch failure. A more difficult situation may arise where for any number of reasons including lack of sufficient API or a highly compressed timeline may preclude the execution of a non-GMP engineering batch.

An organization must weigh the risks and rewards associated with skipping any of the intermediate steps along the way from the lab to GMP production. In cases where it is deemed necessary to proceed to GMP production without the benefit of a thorough tech transfer process, including production of at least one engineering batch, it is advisable to ensure that all stakeholders are aware of the risks being taken prior to proceeding. While it may be tempting to take shortcuts in the tech transfer process, the downside associated with a failed batch can be dramatic especially when API supply is in short supply or timelines are compressed.

While all process scale-ups entail risk, it is possible through the careful application of risk assessment principles and targeted laboratory development to anticipate challenges that may be present in a new drug's production process. Coordination between formulation development staff can play an important role in anticipating challenges and developing effective strategies to limit challenges that may exist in the initial scale-up of a new manufacturing process. With proper documentation, the combined efforts of the formulation development laboratory and operations team can add important data to the development history for any new product and demonstrate to regulatory authorities the rationale for decisions made in the production process.



Singota Solutions is a US based CDMO in Bloomington, Indiana. Singota specializes in formulation development and aseptic fill finish for injectable projects. Once a formulation is established, Singota utilizes state of the art robotic filling technology and focuses on smaller batch size requirements. For more information, visit Singota.com to explore how Singota has established itself as a one-stop solution for all your developmental needs.

Contact solutions@singota.com to schedule a meeting with our business development team to further discuss your current or future projects.