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From IND To NDA: The Role Of The Kilo Lab In A Seamless Scale-up

By Robert Hughes, R&D Fellow, and James Springer, R&D Director

Pharmaceutical process development and scale-up can sometimes feel like a balancing act between speed-to-market and mitigating risks, resulting in sacrificing one to secure the other. The fact is that scaling up rapidly typically requires drug sponsors to accept more risk. However, by partnering with an experienced CDMO, you can deftly navigate this crossroads by driving efficient scale-up and risk mitigation simultaneously via specialized expertise and advanced technologies like the kilo lab.

A vital step in securing your operation at scale, the kilo lab serves as a transitional stage at which you can assess your manufacturing process and address any issues prior to manufacturing at larger production scale. Though most CDMOs have them, not all kilo labs are created equal. As you determine whether a potential partner's kilo lab is designed to accommodate the needs of your project, consider the following.

What Is A Kilo Lab?

The kilo lab is where processes are run for the first time at kilogram scale; it's an intermediate scale between research and production. Kilo labs serve to support tech transfer from lab to pilot plant to commercial scale and to generate product for early development programs, including toxicology (tox) material and small quantities for Phase 1 clinical trials. At this intermediate scale, a CDMO will execute a client's manufacturing protocol to identify potential challenges prior to moving to the next phase of production.

Though less common, a kilo lab can also be used in scale-down scenarios. For example, if a process incurs difficulties at production scale, the kilo lab can serve as a platform to evaluate process changes and remediate the difficulties. This allows researchers to test potential solutions at a much lower cost than at the production plant and ensure a higher level of confidence that their findings will translate back into the production scale process; ultimately, this approach can provide significant savings to the program compared to planned changes at the larger production scale.

How Does The Kilo Lab Enable Better Tech Transfers?

On the path from Investigational New Drug Application (IND) to New Drug Application (NDA), a CDMO must provide the drug substance as well as comprehensive data about a compound and its manufacturing process to ensure its quality, safety, and scalability for clinical trials and commercial production. Kilo labs provide a facility where a CDMO can demonstrate the process at an intermediate scale and identify potential challenges prior to moving to the pilot plant, enabling critical troubleshooting without significant added costs.

The kilo lab also provides an opportunity for better modeling than what is accessible at lab scale. Some techniques are difficult to model in an R&D lab but easier to accommodate in the kilo lab, where the CDMO can verify its ability to control process-related impurities. Though taking the time to conduct testing in the kilo lab may slightly extend your timeline in the short term, it offers significant benefits in the long term by reducing risks later during clinical and commercial production, streamlining your path to market.

Where Do CDMOs Differ In Their Kilo Lab Approaches?

Different CDMOs have distinct strategies for kilo lab design based on the goals of their clients and the projects they want to take on. Some CDMOs opt to set the space up similarly to an R&D lab; for example, this type of setup often includes large round bottomed reactors and large rotary evaporators (rotovaps) that are used for running a process that has not been fully developed. In these types of kilo labs, you will find reactors and equipment that accommodate the needs of R&D rather than large-scale production, and as a result, operators will run a different version of the process that will need to be redeveloped for scale-up to a pilot plant setting.

CDMOs that want to prioritize seamless scale-up for clinical and commercial processes will strive to design a kilo lab that is a scaled-down version of the pilot plant. This allows their teams to evaluate the workflow with equipment that is functionally identical but smaller than what will be used during commercial manufacturing. At Grace Fine Chemical Manufacturing Services, we opted for the latter approach: our kilo lab was built with scaled-down versions of our pilot plant equipment and designed to run processes in the same way they would be

with our larger equipment. As a result, a process developed in our lab can be demonstrated in the kilo lab, then move directly into the pilot plant and then to commercial production. Though there may be small tweaks, this largely eliminates the need for major downstream development efforts and supports downstream timeline savings.

Another major distinction between our kilo lab and many other CDMOs is the use of chromatography. Because the kilo lab is frequently used in early development to generate active pharmaceutical ingredients (APIs) for tox studies when process chemistry is not yet well developed, some companies use chromatography to isolate the product. However, a kilo lab process that leverages chromatography would likely generate material that is not representative of the material that would be produced at a larger scale, particularly when it comes to impurities. Furthermore, conducting chromatography at a larger production scale requires large volumes of solvent, resulting in greater process waste. At Grace, we opt not to use chromatography in our kilo lab.

To ensure accurate levels of impurities are qualified in toxicological studies, it is in a sponsor's best interest to perform the study using an API that was manufactured with a representative process. Having typical process impurities qualified during the tox studies allows flexibility when going into Phase 1 and Phase 2 studies – which becomes very valuable if the dose needs to be increased. Failure to conduct the tox study with representative material may result in having to conduct a bridging tox study, which can delay the progress of the program and incur additional costs in the future.

At Grace, we aim to form long-term partnerships, preparing to accommodate customers across every stage of the journey to new drug approval, from IND to NDA. A critical component of this commitment is our project team. Maintaining the continuity of the project team, from the kilo lab to the pilot plant, ensures subject matter expertise and familiarity at each transition. With standard operating procedures accompanying each process, a continuous project team will have the kind of added familiarity that inspires confidence and empowers project success. A dedicated project team throughout a sponsor's program ensures there is no loss of knowledge between tech transfer and commercial manufacturing.

Choose A Kilo Lab That Mirrors Full-Scale

To ensure the success of your drug, it is critical that the outsourcing partner you choose implements effective but efficient risk management strategies throughout your product life cycle; a kilo lab is crucial. To further derisk your process, opt to work with a CDMO that has designed their kilo lab as a space to mirror large-scale production. It can save you time and money in the long run and, with the support of an experienced and knowledgeable team, a kilo lab that replicates full-scale production can yield a workflow that is proven, robust, and reliable from clinical to commercial scale.

About the Authors

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About Grace Fine Chemical Manufacturing Services

Grace's Fine Chemicals Manufacturing Services is a leading North American CDMO and a full-service provider of fine chemicals to the world's leading companies across the pharmaceutical and specialty materials markets. Grace FCMS helps global customers complete successful projects through a powerful combination of proven chemistry expertise, game-changing PD, high-quality custom manufacturing and exceptional service. Our U.S.-based facilities in South Haven, MI and Tyrone, PA enable us to be a fully integrated domestic partner for the development and manufacture of registered starting materials, intermediates, and custom APIs. From innovative R&D to commercial-scale production, we deliver the knowledge, experience, resources and service needed to move products to market faster and accelerate business.

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