DPT Thought Leadership
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QbD BASED SCALE UP SERVICES — THE DPT LABS APPROACH

INTRODUCTION

This paper describes the approach and benefits of using DPT Labs' QbD Scale Up service and follows the third paper in our Thought Leadership Series, "QbD Based Process Development Services – The DPT Labs Approach."

In that paper, we emphasized the importance of DPT's approach to process development, in particular the rigorous analysis of both raw materials and process steps from which to advance the drug product development process. The key components of DPT's Process Development service – a risk assessment and feasibility batches – combine to lay a solid foundation that minimizes the risk of future unanticipated events.

Like the Process Development service, DPT Labs' QbD Scale Up service leads a customer through the steps necessary to manufacture drug product, consistently, at commercial scale. Leveraging the rigor of determining both raw materials and process steps in the Process Development service, the Scale Up service meticulously determines and documents the transition from clinical scale production to commercial scale production.

If a customer worked with us during the process development stage, it is an easy transition to the QbD Scale Up service. Some customers, however, come to us for the first time at this point in the drug development process. In either case, DPT provides a dedicated, experienced, and talented group of scientists, state-of-the-art equipment and facilities in which to perform the work necessary to prepare the drug product for commercial scale production. The goal is the same – to produce drug product in a reliable, consistent, and repeatable way. Simply finding a stable formulation is only the first step in a development process. Building a documented capability to manufacture drug product the same way, every time, is a critical step on the road to approval. We work with major pharmaceutical companies as well as smaller drug development customers – and both benefit from our vast experience and knowledge of the FDA's expectations regarding process, methods, and documentation.

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QUALITY BY DESIGN FOR SCALE UP

As described in our first paper, "What Is Quality by Design (QbD) – And Why Should You Care?" there are numerous benefits to the modern, scientific approach that formalizes product design and streamlines troubleshooting. The QbD approach reveals a thorough understanding of the compatibility of a finished product to all of the components and processes and provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified.

Once a stable formulation has been identified, the next step in developing this understanding occurs in the Scale Up stage where critical material attributes (CMAs) and critical process parameters (CPPs) are examined further. This examination measures the extent to which any variation can impact the quality of the finished product. The more information generated on the impact – or lack of impact – of a component or process on a product's quality, safety or efficacy, the more business flexibility Quality by Design can provide.

DPT Labs works with each customer to understand the process needs to manufacture drug product at commercial scale. Through a series of batch analyses, the production process is refined and then documented to ensure repeatability. Analysis of these batches helps drive a more thorough understanding of the process and equipment, isolating and identifying risks. This detailed understanding helps minimize surprises during commercial scale manufacturing.

SCALING UP THE PROCESS

The transition to Scale Up begins once the feasibility batches produced in the process development stage are shown to be stable. From there, the move to manufacturing drug product at commercial scale quantities, or "scaling up," begins. The Scale Up service is the final push to get your drug product development project across the finish line.

The DPT approach to Scale Up follows a path similar to the Process Development service. Our team conducts a risk assessment and feasibility batches, this time for changes that enable larger scale production. As before, examination of the ranges of material attributes and process steps defines the boundary and limitations associated with the ranges of process parameters.

A transition from one scale to another often requires modification of the process – for example, an equipment change may trigger a new feasibility study in order to maintain droplet or particle sizes. Critical process parameters defined during the Process Development service need to be re-evaluated in light of any change in equipment, material attributes, or process changes.

As before, the combined understanding of the critical material attributes (CMAs) and critical process parameters (CPPs) contribute to meeting the critical quality attributes (CQAs), this time for a scaled up manufacturing capability.

The importance of redefining CPPs and CQAs during scale up cannot be overstated. This is the how commercial scale product will be made – and validated. Possessing a thorough understanding – with data backup – of defined, parameter ranges is critical to validation success.

Once the scale up risk assessment is complete, the team again authors "compounding modules," this time for the scaled up process. These become the batch instructions that will be used to manufacture the batch(es) in the commercial manufacturing environment. Depending on the outcome of the initial batch, the team makes modifications as needed. It typically takes 1-2 feasibility batches at commercial scale to verify the new process.

A COMMON MISTAKE – NURSING THE BATCH

While the concept of scaling up may seem simple and straightforward, DPT's Scale Up service is designed to overcome a common misstep. Just as a gourmet cook determines, with precision, the finer points of applying different temperatures to the pot on the stove, the type of utensil to use while stirring, and when to remove heat, scientists do the same thing in the lab.

Our experience has shown us time and again that it is easy to "unintentionally nurse" a smaller batch, or give attention to a small sample that you otherwise couldn't give when producing a larger amount – just like the gourmet cook in the example above. This might happen by simply scraping the side of a mixing bowl with a handheld spatula if you notice the mixture becoming too thick. In doing so, the technician has unintentionally added a step to the mixing process – though this step may not be included in the documentation, as it seems unimportant.

Our experience helping numerous customers scale up has revealed the notion of "unintentional nursing" is quite common. Observing this and many other unintentional steps led us to develop the Scale Up service. Often, it is the smaller details that matter most when transitioning to a different scale of production. In scaling up, product uniformity is a key indicator of success.

NOT JUST PAPERWORK

We create highly detailed process development reports on every batch to document:

1. EVERY step of the process we followed
2. Why we did what we did and the logic behind it
3. What went wrong that we need to pay attention to for future batches
4. What went well and what was critical to ensuring success
5. Overall results of the batch

Documenting to this level of detail is critical for several reasons. Many customers are forced to delay projects for various reasons. Detailing every piece of the journey in such a report makes it easy to restart the project later. A team could review these reports months from now and have the critical details necessary to get the project moving again.

Secondly, these reports serve as reference to the project team and a way to build foundational knowledge for future related projects for the customer. This knowledge helps us efficiently deliver QbD based services to our customers and allows us to streamline our approach to the customer's development projects that may use similar materials or formulations. This knowledge and subsequent efficiency are critically important to helping reduce the time and money spent on your project.

LOST IN TRANSLATION

Our last two papers in this series described DPT's Formulation and Process Development services. While each of these services are available to customers independently, our experience shows that working together through the full life cycle of drug product development yields the best results – lower overall development costs and quicker time to approval (assuming the drug meets the efficacy bar).

We understand some customers may simply want one of DPT's QbD based services. Whether DPT has helped a customer with formulation or process development, some decide to use their own commercial scale manufacturing capability or another contract manufacturer when transitioning to large-scale production.

Customers face two important risks at this stage:

1. Not all contract manufacturers will have the equipment necessary to scale up, and
2. "Switching costs" are often underestimated as the transition to a new location, different equipment, and different personnel often leads to key steps of the operation getting "lost in translation."

The thorough, meticulous approach used in our QbD based services is designed to minimize the variability of your operation. When you work with us, you work with the same team throughout the development project – a team that knows their equipment and knows it well, a team that has been anticipating which equipment will be necessary as a customer is ready to scale up, and a team that has intimate knowledge of your drug product's development to this point.

Our experience and highly systematic approach permits us to know with a high degree of confidence what works well – and more importantly, what won't. The benefit of our experience saves you precious time and money. An external manufacturer will need to spend time testing your process and will frequently waste time testing something we may already know will not work.

Most importantly, why would you create variability in an environment where variability is the enemy? QbD aims to reduce uncertainty with the goal of producing expected results. Changing manufacturers mid-project may negate all the hard work and predictability gained from the rigor and discipline you've invested to this point.

Simply put, if each component of the entire end-to-end process can take place with the same team, at the same location, using known equipment, why risk adding more variables to your operation? There is no question – transporting your process often costs significantly more time and money.

BENEFITS OF DPT LABS' QBD SCALE UP SERVICE

The ultimate deliverable of DPT's Scale Up service is a complete packet for the customer that consists of:

- Raw materials testing and supplier information
- Process development report
- Clinical/registration supplies of formulated product
- Validated analytical methods
- Pathway forward to validation and commercialization

The customer receives various reports that can be included as part of an FDA submission package. For those customers who desire, DPT Labs also offers a service to complete the CMC portion of the submission for you.

At the completion of the Scale Up service, DPT Labs offers follow-on cGMP manufacturing capabilities. DPT is one of only a handful of contract development and manufacturing organizations that offer complete end-to-end services from Formulation to commercial manufacturing. We offer the unique guarantee of staff continuity, that is, the team and scientists that begin work with you will remain with you throughout the length of our development relationship. This unparalleled continuity assures that DPT Labs has a deep understanding of your drug product, and its development and manufacturing processes, and can represent it effectively for FDA submissions.

You can read more about these services in our previous Thought Leadership series papers.

SCALE UP BEGINS WITH A RELIABLE QBD PARTNER

Our earlier papers highlighted the benefits of systematically selecting an initial formulation, selecting well-understood raw materials, and establishing repeatable process steps in the lab. Taking a similar disciplined approach when scaling up production to commercial scale is the final piece in the long journey to launch a valuable drug product. Many companies have short-term resource and/or time constraints that prevent them from using the thorough approach that QbD demands. This creates a "pay now or pay later" choice that ultimately results in development that spirals out of control.

The challenge of adopting QbD begins shortly after a molecule is discovered. Systematically selecting an initial formulation, well-understood raw materials, and establishing repeatable process steps can be the beginning of a successful journey to launching a valuable drug product.

Given the FDA's commitment to QbD and the incentives they provide for adopting it, companies now have the imperative to find a way to adopt this scientific approach. Many companies have tried and given up in frustration. As the saying goes, "If it were easy, anyone could do it." How do you give your company the best chance at success with QbD?

One way is to join forces with an experienced, knowledgeable partner who can help your team benefit from QbD with minimal disruption. DPT Labs brings together multiple sources of information, vast experience, and practical insights into issues with your product. Our experienced team has delivered many QbD-based Process Development services to its customers. We can help take the mystery out of QbD and get you moving toward your goal of launching a valuable drug product in the most cost-efficient and robust manner.

CONCLUSION

As with our first three papers in this series, we see the importance of leveraging a systematic, scientific approach to drug development, especially as a customer approaches the need to produce at commercial scale. This paper describes the approach and benefits of using DPT Labs' QbD Scale Up Services and is the final paper in our Thought Leadership Series about Quality by Design.

After reading this paper you should possess the information to help you better decide the benefits of using DPT Labs' QbD based Scale Up service in your operation.

When it comes to drug development, the old saying of "pay now, or pay later" holds true. Overlooking key material attributes or proceeding without full understanding of critical process parameters will only compound problems later and can lead to a never-ending attempt to troubleshoot issues. The perceived savings of time and money in the near term will be lost as the cost of discovery after the fact escalates.

DPT Labs' Scale Up service can provide several benefits:

- High level of confidence in producing a consistent product at commercial scale
- More efficient use of development time and costs
- Ability to meet FDA submission guidelines and expectations
- Reduced approval times – and fewer queries – from the FDA

To discuss your Scale Up needs and how DPT Laboratories can help, including gaining timely FDA approval and minimizing the cost of your development project, call 1.866.CALL.DPT or visit www.DPTLABS.com.

ABOUT DPT LABORATORIES:

DPT is a contract development and manufacturing organization (CDMO) providing companies the best solutions to their sterile and non-sterile pharmaceutical development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive manufacturing capabilities, and an exemplary regulatory compliance record. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

CONTACT:

DPT Laboratories, Ltd.
1-866-CALL-DPT
www.DPTLABS.com/Contact-Us

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