DPT Thought Leadership
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QbD BASED FORMULATION SERVICES — THE DPT LABS APPROACH

INTRODUCTION

This paper describes the approach and benefits of using DPT Labs' QbD Formulation service and follows the previous paper in our Thought Leadership Series, "What is QbD and Why Should You Care?"

DPT Labs' QbD Formulation service leads a customer through a rigorous process that minimizes risks to development success. Beginning with a Quality Target Product Profile (QTPP), the service further examines and narrows down formulation choices by conducting a pre-Formulation study, followed by formulation development (to include preliminary stress testing) and analytical method development, ending with an informal stability study.

DPT Labs works with customers of all shapes and sizes, from a small team and their new molecule discovery to major pharmaceutical companies. Major drug makers partner with us because they know the rigor with which we conduct Formulation development. Smaller customers leverage our vast experience and knowledge of the FDA's expectations regarding formula, process, methods, and documentation.

Regardless of why a customer chooses DPT Labs to assist with Formulation, each one knows the first step to identifying and understanding risks in a long development process begins in Formulation. Risks that may otherwise remain hidden until much later in development can be eliminated early saving valuable time and money.

QUALITY BY DESIGN FOR FORMULATION

As described in our previous 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.

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The first step in developing this understanding occurs in the Formulation stage where all critical formulation attributes and process parameters are examined, including 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 provides.

We work with each customer to understand their view of the molecule and through a series of specific questions begin a dialogue to narrow their focus. It is this narrowing of focus and the design of subsequent studies that drives the thorough understanding of a drug product to isolate and identify risks. This detailed understanding helps minimize surprises throughout the remainder of the development and manufacturing process.

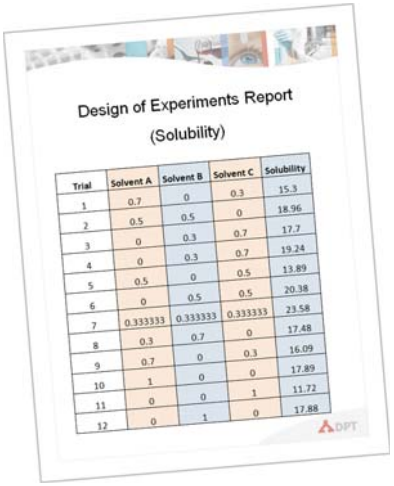
PRE-FORMULATION

The DPT Approach to Formulation involves a series of steps to eliminate or significantly reduce risks with various formulation options. At this stage, a customer typically has discovered a molecule to address a particular indication. The first stage of this service is the pre-Formulation stage. The goal in this stage is to conduct risk analyses of various formulations, identify which components pose increased risk, and set the stage to design studies as narrowly as possible.

Pre-Formulation begins with defining the Quality Target Product Profile (QTPP). ICH Q8 defines key items in the QTPP including:

- Intended use in a clinical setting
- Route of administration
- Dosage form
- Delivery systems
- Dosage strength(s)
- Container-closure system

A series of experiments are performed across a number of different formulation possibilities, e.g. gel, ointment, liquid, lotion, cream, foam, spray, etc. to determine the drug substance's Solubility, Compatibility, and Stability with each formulation type.


Design of Experiments Report

(Solubility)

Trial	Solvent A	Solvent B	Solvent C	Solubility
1	0.7	0	0.3	15.3
2	0.5	0.5	0	18.96
3	0	0.3	0.7	17.7
4	0	0.3	0.7	19.24
5	0.5	0	0.5	13.89
6	0	0.5	0.5	20.38
7	0.333333	0.333333	0.333333	23.58
8	0.3	0.7	0	17.48
9	0.7	0	0.3	16.09
10	1	0	0	17.89
11	0	0	1	11.72
12	0	1	0	17.88

This Design of Experiments solubility study, an example of which is shown to the left, is just a small part of the comprehensive set of experiments conducted to lay the groundwork for minimizing risks at the very beginning of the development process. Following statistical analysis of the results of each individual study using software such as JMP®, formulation options can then be narrowed based on actual data and risk analysis versus convenience.

Such a purposeful, systematic approach is designed to minimize risk to your development efforts down the line by reducing development cost and time.

The recurring theme of a QbD approach is that a small investment of time and effort, at each stage of development, helps develop a thorough understanding of your drug product. This understanding can eliminate or minimize seemingly mysterious problems later. Discovering and struggling with these problems later will prove far more costly and potentially catastrophic to your development project. DPT Labs' Pre-Formulation rigor exemplifies this theme.

FORMULATION DEVELOPMENT

Once formulations have been eliminated from contention, those that remain undergo preliminary testing, also referred to as "stress testing." These basic tests serve to further narrow the formulation choice by exposing environmental and other risks that could affect a final drug product.

Temperature sensitivity tests are completed at both extremes to observe how a formulation reacts. Formulations are heated to +40-50° C as well as taken through a series of freeze/thaw cycles. Another preliminary test uses a centrifuge for a time simulation study to observe how a formulation might react to sitting on a shelf for its projected lifespan.

This preliminary testing weeds out the formulations that would be obviously unacceptable. Though this approach may seem obvious, it does require a systematic approach, with controlled environments, and documented procedures.

INFORMAL STABILITY

The Informal Stability test is an initial examination of a formulation to identify and eliminate more obvious stability issues.

If the customer has identified a preferred packaging type in the QTPP, the test is conducted in that package e.g. aluminum tubes, etc.

If a customer has not yet identified the type of packaging in the QTPP, this test is conducted by placing the formulation in a glass container to examine its overall stability. Once the packaging type has been identified, a more thorough stability test will be conducted.

The first test is a physical examination of the formulation. Characteristics such as physical and microscopic appearance, pH, viscosity, and specific gravity are examined and reactions are noted.

In addition to physical tests, chemical and microbiological tests are also conducted. At this stage, the Analytical Development group begins work on methods development for the drug product, preservatives, and anti-oxidants. Degradation tests are also conducted on the API, and if they do degrade, the extent to which they become harmful or toxic will be determined. The figure to the left shows a sample report from Informal Stability testing.


Stability Testing Report

Test	Time =0	T=1	T=2	T=3
Description				
pH				
Viscosity				
Specific Gravity				
API Assay				
Preservative				
Impurities				
Total Impurities				

While other formulation contractors may skip this step, because it is not simple, DPT leverages our tools and talented scientists to develop and study formulations simultaneously. This unique ability separates us from the competition and provides another layer of drug development risk reduction.

Finally, our Formulation service helps you keep the big picture in mind. We won't move ahead with a formulation that uses scarce raw materials (either in short supply or not commercially available.) Although a formulation such as this may be stable, it won't permit the reliable manufacture of your drug product. In such instances, we will take the time to find a reliable supplier and if unable, reformulate and provide you with a sustainable product, able to be manufactured to meet the demands of your market.

BENEFITS OF DPT LABS' QbD FORMULATION SERVICE

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

- Documented formulation development
- Clinical supplies of formulated product
- Validated analytical methods
- Raw material supplier recommendations

The customer receives various reports, such as the one to the left that can be used as part of an FDA submission package. For those customers who have limited capability or experience with FDA submissions, DPT Labs also offers a service to complete the submission for you.

At the completion of the Formulation service, some customers may choose to take the valuable information back to their company to leverage their process development and manufacturing capabilities. However, many of our smaller customers are not equipped for this.

DPT Labs offers additional follow on services for Process Development, Scale Up services and cGMP manufacturing capabilities, and is one of only a handful of contract development companies that offer complete end-to-end services from Formulation to commercial manufacturing.

For customers who choose to work with DPT Labs beyond the Formulation stage, 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 relationship. To our knowledge, no other contract partner offers such a service. This unparalleled continuity assures that DPT Labs has a deep understanding of your drug product, its development and manufacturing processes, and can represent it accurately during FDA submissions.

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

FORMULATION BEGINS WITH A RELIABLE QbD PARTNER

The challenge of adopting QbD begins shortly after a molecule is discovered. Initial formulation, when performed systematically, can be the beginning of a successful journey to launching a valuable drug product. As discussed earlier, many companies have short-term resource and/or time constraints that prevent them from using the thorough approach that QbD demands. This results in a "pay now or pay later" choice that ultimately ends in development that spirals out of control.

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 Formulation services to dozens of clients. 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

This paper describes the approach and benefits of using DPT Labs' QbD Formulation Services and follows the previous paper in our Thought Leadership Series, "What is QbD and Why Should You Care?"

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

When it comes to drug development, the old saw of "pay now or pay later" holds true, particularly in the Formulation stage. Overlooking key parameters or proceeding without full understanding of why a specific formulation was selected 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 only haunt your efforts later as the cost of discovery after the fact will surely escalate.

DPT Labs' Formulation service can provide several benefits:

- 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

Look for future papers in the Thought Leadership Series that will address QbD Services for Process Design and QbD Services for Scale Up.

To discuss your Formulation needs and how DPT Labs 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.

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