

Qualifying — and Validating — a Temperature-Sensitive Products Package

Thermal mapping of the supply chain gave a biotech leader the data it needed to develop its shipping solution.

For more than 25 years, Amgen has been a leading innovator in the identification, isolation, production, and use of human proteins as therapeutic agents. From the beginning, the company's contributions to the field of biotechnology have been driven by its commitment to meet patient needs. Amgen's manufacturing, process development, quality, and distribution teams are all committed to ensuring that Amgen medicines reach every patient, every time, rapidly, reliably, and safely.

Designing, building, and maintaining a CGMP-compliant biopharmaceutical supply chain is one of the greatest challenges facing the biopharmaceutical industry. Part of the challenge is figuring out how to ship these temperature-sensitive products (TSPs) safely and compliantly around the world.

Amgen reports that the most effective approach to achieving this goal is to use a quality systems approach that meets all CGMP regulatory requirements. FDA offers guidance on the matter, and the Pharmaceutical Cold Chain Discussion Group has issued guidelines in Technical Report No. 39 (TR-39).

"Both groups tell us what to do but to date, neither has told us how," says Don Wilson, senior manager engineering, distribution packaging, Amgen. Wilson is responsible for developing, qualifying, and implementing Amgen's global cold-chain program. As one of the authors of TR-39, he calls for a sound engineering and scientific approach to meeting the needs of the biopharmaceutical supply chain. "The supply chain requires tools to facilitate shipping. The most effective way to deliver the proper tools for the supply chain is through technology transfer. Tech transfer is the process of designing, developing, and qualifying tools from scientific research. To provide

an acceptable tool for the supply chain will require a plan."

It is important for a company to have a Master Validation Plan (MVP), Wilson adds. "The MVP is a documented plan that describes concisely the policy, philosophy, strategy, and methodology for validating the transport process. The scope of the plan covers all aspects, including component qualification (CQ), operation qualification (OO), performance qualification (PQ), training, maintenance, technology transfer, and change control. It may also include schedules for the overall plan. The packaging components should be developed to meet a platform approach."

The MVP requires TSP packaging to be qualified. To achieve the CQ for TSP packaging, it will require the same process per CDER's General Principles of Process Validation, he explains.

In 2002, although having already characterized its TSP packaging requirements, Amgen was facing a high failure rate for one of its TSP packaging solutions. The costs of nonconformance

were high, as was the exposure risk from lack of control within its supply chain. Recognizing the risk, Amgen chose to make process changes and partnered with EnviroCooler (Huntington Beach, CA) to design and qualify solutions to meet the temperature requirements of products stored at 2° to 8°C, and of frozen products.

Amgen's business requirement was to have a finished-goods TSP packaging configuration available to achieve the following:

- Maintain 2° to 8°C for a minimum of 72 hours through hot and cold profiles; with minimum or maximum loads (single pack-out).
- Maximize the payload within an LD3 airfreight container.
- Be independent of external influences.
- Have one energy source conditioned and handled consistently.
- Be easy to use (assembly and disassembly) for distribution personnel.
- Be Montreal Protocol compliant

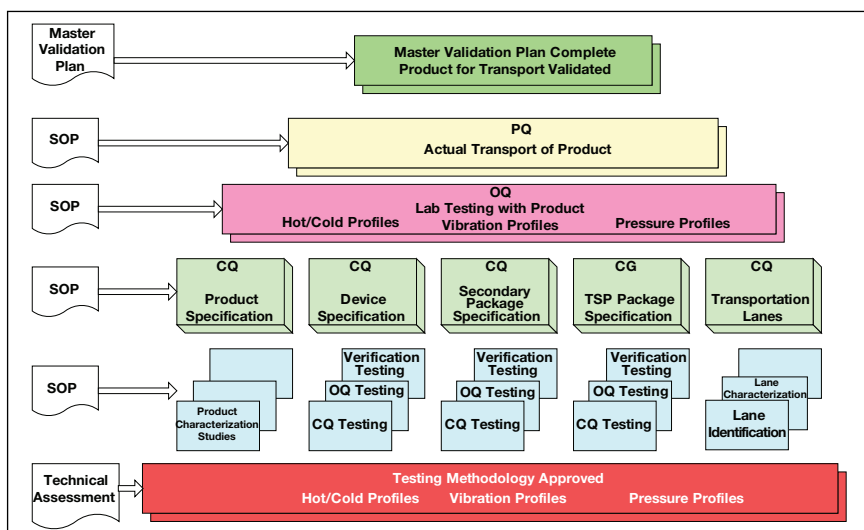


Figure 1. The Master Validation Plan describes the policy, philosophy, strategy, and methodology for validating the transport process.

(environmentally friendly).

Based on the project requirements, EnviroCooler worked with Amgen to formulate the product design specifications document, which included:

- Polyurethane foam to be used as the insulation material, given the 72-hour minimum duration.
- A standard LD3 was specified and loading tolerances provided by an independent freight company.
- No electrical components.
- Frozen gel packs only.
- Modular assembly of unit.

- Polyurethane foam containing no CFCs or HCFCs.

- Platform based.

“The design specifications document provided EnviroCooler with the solution to a puzzle to which we held the pieces,” explains Rod Derifield, EnviroCooler’s chief executive officer. “EnviroCooler had in place a portfolio of patented platforms from which to pick and choose. We chose the Air-Locker design to address the need for modular assembly; the sliding ice-tray with premolded Conduction Block for ease of assembly, to meet duration requirements, and to facilitate the use

of frozen gel packs exclusively; and the Convection Engine to maximize duration and minimize temperature gradients within the payload.”

Notes Wilson, “What I think people don’t understand about a project like this is that the entire process of qualifying a TSP packaging solution fulfills only a CQ portion of the Master Validation Plan. The CQ itself contains RD, CQ, OQ, and verification processes.”

The CQ and OQ phases were outsourced to EnviroCooler, which allowed Amgen to focus on other project requirements, such as performance under its testing specifications. Table I outlines briefly the qualification phases of the BioSphere project.

The majority of the project work for Amgen’s team occurred during the design of experiment, before beginning OQ testing. Thermal mapping of Amgen’s supply-chain hot-and-cold profile was a large, but critical, undertaking for the team.

“Don’t you think it would be extremely difficult to tell FDA or USP that you have confidence in your TSP packaging solution if you have not qualified it through the thermoprofile it is going to be shipped?” asks Wilson. “Sure, mapping the thermoprofiles is a lot of upfront work. But now that it has been done, we can use them repeatedly in the testing phase of a solution to ensure confidence.”

The BioSphere exceeded performance expectations under OQ and verification conditions.

“At the end of the day, this is all about risk management. How much risk are you willing to carry before you need to invest in a project solution that will bring control back to your supply chain?” asks Wilson. “This was a big project for us—it took us almost two years to get the BioSphere into OQ. But now Amgen can say with high confidence that those shipments will not experience temperature excursions during transit. Amgen’s risk of nonconformance and our costs of nonconformance have been significantly reduced by implementing the BioSphere.”

To date, more than 2000 shipments have been successfully and safely transported in the BioSphere. ■

Q-Phase	Definition	Project Specifications
Design of experiments	Proof of design.	<ul style="list-style-type: none"> • EnviroCooler and Amgen designed prototype(s) for testing. • Testing (physical and thermal) performed on prototype(s) until acceptance criteria were met in singular.
CQ	Establishing confidence that ancillary components are capable of consistently operating within established limits and tolerances.	<ul style="list-style-type: none"> • Gel packs; corrugated inner and outer boxes, foam inserts, and the insulation material were characterized. • Third-party suppliers provided proof and supporting documentation to ensure acceptance criteria.
OQ	Establishing confidence that the process is effective and reproducible.	<ul style="list-style-type: none"> • Testing (physical and thermal) performed on prototype(s) until acceptance criteria were met in triplicate. • Minimum and maximum payload configurations tested until acceptance criteria were met in triplicate. • EnviroCooler’s documentation package was submitted to Amgen for approval. • Qualification documentation package submitted internally in Amgen for approval by quality and regulatory departments.
Verification	Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality.	<ul style="list-style-type: none"> • Live shipments were monitored within the designated shipping lane. • 100% shipment success required.

Table I. The qualification phases of the BioSphere project.