MODALITY SOLUTIONS

13 Keys to a Successful Monoclonal Antibody BLA Submission

Is your cold chain ready?

Introduction

So, you have a mAb in a clinical trial (or you're in the planning process).

When a monoclonal antibody therapy advances through its development lifecycle, planning ahead and optimizing the biopharmaceutical cold chain is key to advancing towards approval.

Monoclonal antibody treatments have specific requirements for shipping validation and require a more precise and thorough regulatory submission process—which starts with a BLA (biologics license application) filing.

In this guide, we'll go over what you need to know to ensure your cold chain is ready for a successful filing.

However, there's no substitute for the expertise of a team that has engaged in hundreds of successful regulatory interactions. Request a consult at modality-solutions.com to learn how the Modality Solutions cold chain engineering team can support your current clinical trial phase.

The BLA Filing Process

The Biologics and Price Competition and Innovation (BPCI) Act of 2009 established the current requirement that all biologics are approved via the biologics license application (BLA) process rather than a new drug application (NDA).

A BLA establishes a request to introduce a biologic into interstate commerce and is regulated by the Center for Drug Evaluation and Research (CDER). As defined by Section 351 of the PHS (Public Health Service) Act, "the term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine…applicable to the prevention, treatment, or cure of a disease or condition of human beings."

Because biologics can be derived from or mimic living sources, they have complex structures which are not easily defined. They tend to be temperature-sensitive and more susceptible to contamination than other drugs, which results in atypical steps for research, manufacturing, testing, and the supply chain.

The BLA process ensures that these factors (which are not as relevant to an NDA submission) are all accounted for, which means strict approval criteria to ensure a consistent performance from the final biological product, from manufacturing through shipping and the entire cold chain.

The Biologics License Application Process

From the FDA:

"The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards."

Source: U.S. Food & Drug Administration

Cold Chain Challenges for Biologics

As the treatment possibilities for biologics increase, so does the importance of ensuring safe and effective methods for their packaging and delivery. However, these therapies carry challenges for the cold chain process:

(1) **Maintaining a suitable shipping environment for a temperature-sensitive therapy** is more difficult due to mAb's sensitivity to temperature changes and other environmental hazards.

(2) **Shock, vibration, pressure and humidity** vary during delays or unexpected conditions during shipping. mAbs are susceptible to shock and vibration and are easily damaged if exposed to temperatures outside a very tight range.

(3) **Biopharma manufacturers** need to invest in a master validation plan to qualify their packaging solutions for their specific products and validate their transportation lanes.

Monoclonal Antibody Cold Chain Requirements

Monoclonal antibodies have been shown to offer better therapeutic outcomes than many other traditional medications and are some of the fastest growing biologics on the market and in clinical trials.

While these have successfully treated COVID-19 and many other viruses and diseases, monoclonal antibodies have increased fragility due to their size and complexity compared to conventional pharmaceuticals. They are particularly sensitive to shock and vibration and are easily denatured if exposed to temperatures outside of a very tight range during transport.

As a result, additional thermal packaging requirements, **including precautions for other environmental hazards such as shock and vibration**, need to be evaluated, including thermal insulation choices and new pallet configurations.

mAbs must be studied against their worst-case shipping conditions on the edges of their operating space in **transport simulation studies**, where they are exposed to conditions encountered across the entire commercial lifecycle of the logistics process and evaluated for physical and chemical integrity.

As of 2021

- The global biologics market is forecast to reach $625 million by 2026. [source]
- 100+ mAb treatments have been approved by the FDA. [source]
- The market for mAbs is expected to expand at a compound annual growth rate of 14.4% through 2027. [source]

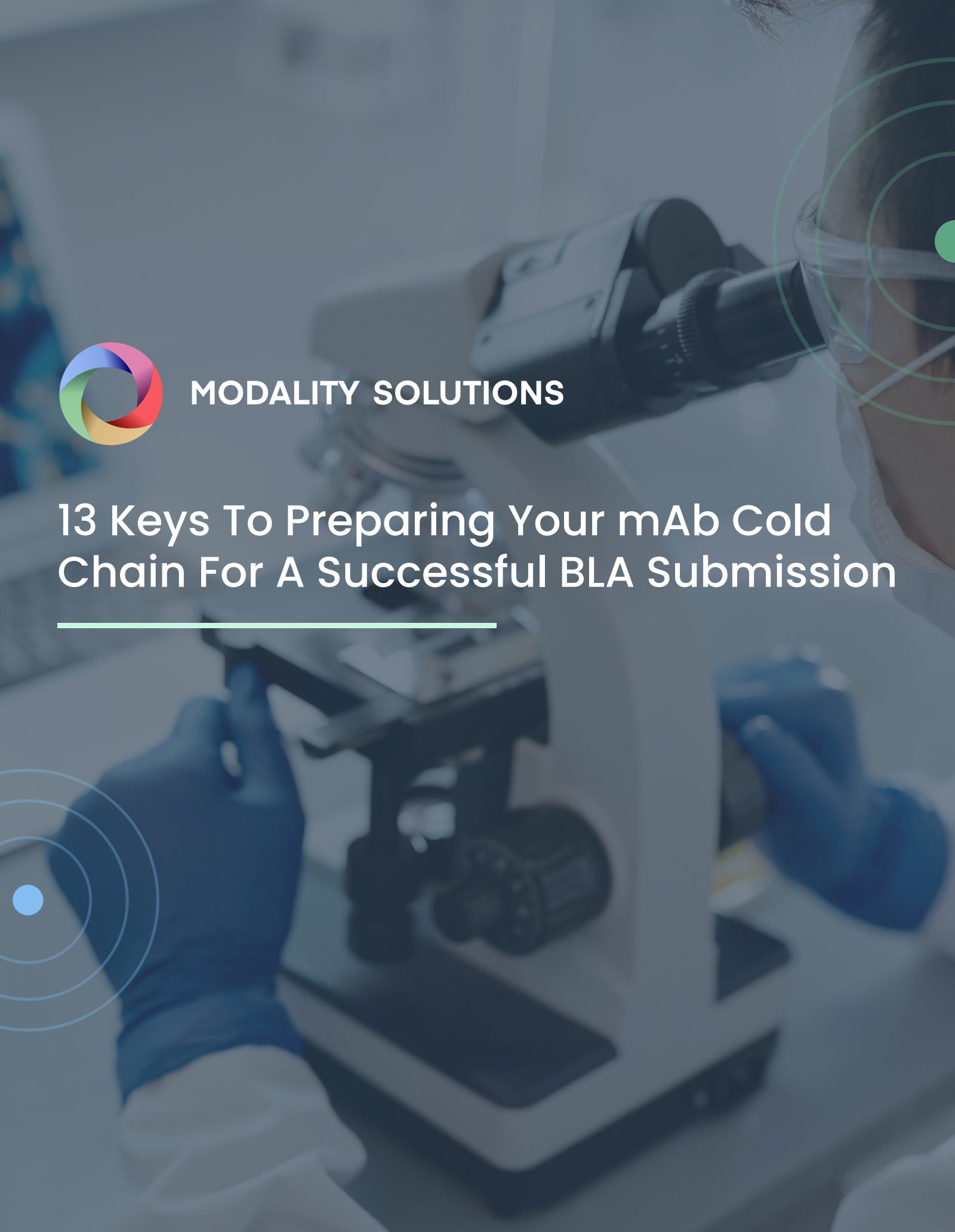
Cold Chain Requirements for a BLA

Process validation for cold chain logistics (packaging, storage, and distribution) is required as part of the Common Technical Document (CTD) for any BLA for a mAb. A review of the submitted dossier and subsequent pre-approval inspection on-site will most likely include an assessment in the following areas:

- **Stability Testing**
- **Validation Master Planning**
- **Thermal Packaging Qualification**
- **Process Validation**

As such, you'll have to prepare for a documentation strategy that provides this information upfront when filing.

Follow our checklist to make sure you're prepared—and make sure you get the regulatory filing support you need from a team of engineers with the know-how and experience like Modality Solutions.



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13 Keys To Preparing Your mAb Cold Chain For A Successful BLA Submission

Typically done during Early Phase Clinical (Phase I/II)

#1: Primary Packaging Qualification

Documentation for BLA filing should include primary packaging qualification information. This documentation should establish suitability for the packaging's intended use.

The type and extent of **primary packaging** qualification information you include will depend on several factors, including drug type and the route of administration. However, in general—and especially in biologics like mAbs—what is approved for one treatment type will not necessarily be approved for another.

Consider each of the following items which are necessary for primary packaging qualification for each part of filing documentation:

- Container closure integrity
- Sterile barrier
- Physical integrity
- Leachable and extractables after agitation
- Plunger movement in syringe barrels

#2: Formulation Optimization

For some biologics, you will have to provide documentation for any variations in formulations developed to withstand exposure to environmental hazards identified with simulated transportation.

Optimizing formulations for increased stability and have data to confirm their robustness will:

- Simplify packaging and logistics needs,
- Reduce logistics expenses, and
- Expand the market for novel and existing therapies (especially in the developing world, where refrigeration is unreliable).

However, an absence of written procedures with precise data supporting formulation robustness could trigger **a warning letter from regulators** that will delay BLA timelines.

Typically done during Late Phase Clinical (Phase II/III)

#3: Risk Assessment

A thoughtful, structured approach to risk assessment is the first step to any successful BLA filing submission. That means:

- Identifying any potential source of harm,
- Assessing what damage could occur from loss of product quality or availability, and
- Weighing the probability of the occurrence of harm against the severity of that harm.

A multivariate analysis of the risks in transportation includes an assessment of five factors: **temperature, shock and vibration, pressure, and humidity**, all of which can affect any biologic individually or concurrently, but especially mAb's.

It would be best if you defined the operating dimensions of these environmental hazards to determine limits for each potential risk.

#4: Transport Validation Master Plan

A validation master plan for distribution can align the activities into a comprehensive and cohesive approach to distribution process validation. The validation master plan allows discussing all of the above, including risks and mitigation strategies, qualification approach, validation approach, and monitors and controls. Sections can include discussion on warehousing and storage, product transportation, shipping configurations, methods of temperature control, and packaging.

The transport validation master plan serves as a figurative (and literal) roadmap to your cold chain. Consider product quality and thermal control in your validation master plan strategy.

Product Quality Assurance

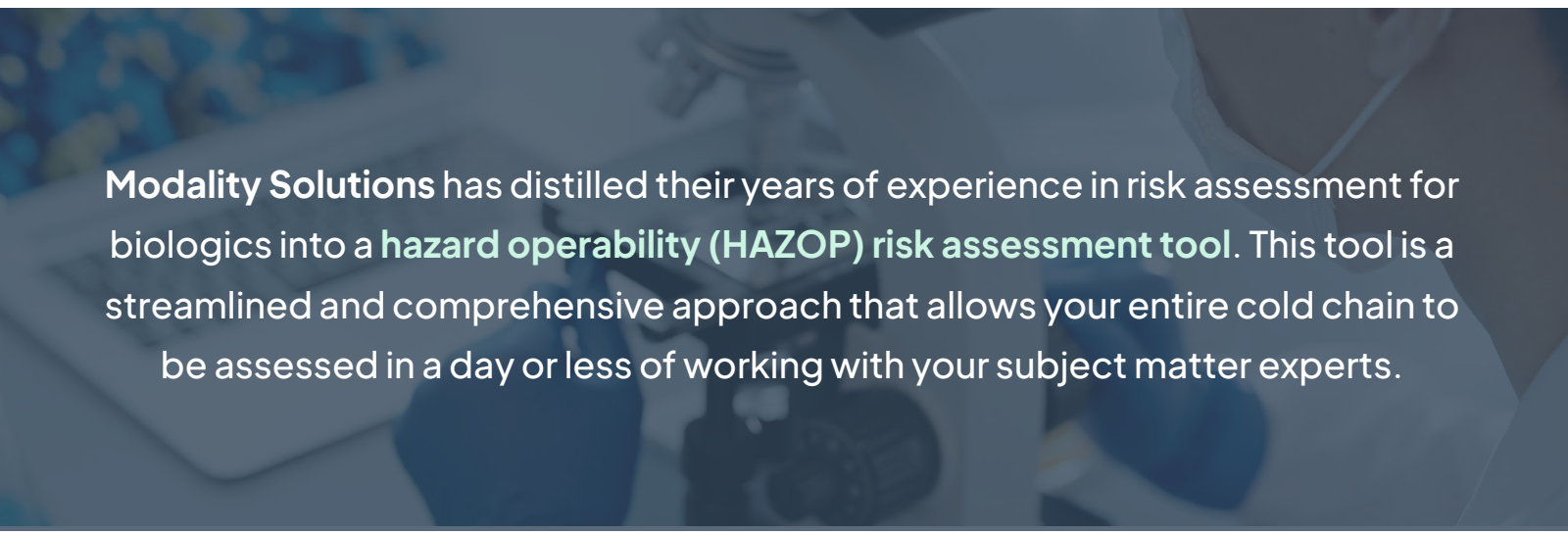
Demonstrate that the produce quality is not adversely affected by distribution through:

- Simulated exposure to worst-case supply chain hazards (shock, vibration, temperature, humidity, and/or pressure)
- Batch release and stability studies post-simulation to assess product quality

Thermal Control Assurance

Demonstrate that storage & shipping temperatures will be maintained through:

- OQ testing of equipment (shippers, freezers, etc.)
- PQ testing of shipping process (real-world shipments)



Modality Solutions has distilled their years of experience in risk assessment for biologics into a **hazard operability (HAZOP) risk assessment tool**. This tool is a streamlined and comprehensive approach that allows your entire cold chain to be assessed in a day or less of working with your subject matter experts.

#5: Drug Product Simulation Testing

Now considered an industry standard, transport simulation can be a valuable technique in determining the physical stability of monoclonal antibodies.

Testing for hazards that occur in transport should mimic real-life transportation in the real world, which means testing for thefollowing hazards **concurrently**:

- Temperature
- Pressure
- Shock
- Vibration
- Humidity

If these hazards are tested individually, you may not be getting the worst-case scenario for each potential shipping condition, rendering your testing inaccurate or incomplete and exposing your therapy to hazards you haven't discovered, let alone know how to mitigate.

Modality Solutions' Advantage Transportation Simulation Laboratory™ is the only independent contract lab with the ability to simulate and test these five significant hazards concurrently. View this video to see our Lab in action.

#6: Thermal Packaging Qualification

Thermal packaging qualification testing for the BLA submission should demonstrate that the selected thermal shipping systems provide adequate thermal protection for the entire supply chain, including shipments to the distribution centers. The FDA regulatory scope starts at the manufacturer and ends at the point of distribution. However, the best-demonstrated industry practice is to include your last-mile logistics thermal packaging as well. The recommended critical-to-quality attributes are:

- Temperature range and duration
- Physical integrity

Qualification of the shipping system to maintain thermal and payload integrity during the distribution process requires several components:

- Component qualification (e.g., gel packs in passive systems) or factory acceptance testing (e.g., C-SAFE refrigerated pallet system)
- Operational qualification in a controlled environment (e.g., simulation testing in a laboratory) at anticipated worst-case extremes at the edges of your operating space
- Performance qualification with multiple field tests to confirm suitability for use

#7: Logistics Network Design

Assessing and designing an effective and efficient cold-chain logistics network will be crucial for regulatory approval.

New therapies, accelerating costs, sustainable technologies, and emerging markets demand validated cold chain networks that consistently produce low-cost and high-quality patient outcomes with minimal variation. Ensuring this can build your reputation of reliability with regulators.

When designing a cold chain logistics network, the following aspects are vital to address, assess, and reconfigure.

- Qualification and Training of Personnel
- Premises and Equipment
- Material Handling, Storage, and Inventory Control
- Transportation Networks
- Reverse Logistics/Product Returns

In addition, developing mature quality systems is one of the biggest challenges and one of the most effective tools to manage a world-class cold chain logistics network. Quality systems at their best establish, implement, and maintain a set of processes to provide the highest quality service to customers, the highest level of effectiveness for management, and the most robust compliance approach for regulators. At their worst, they get in the way, adding only administrative burden and redundant reviews to an already complex and fast-moving network.

#8: Third-Party Logistics (3PL) Selection

Third-party logistics (3PL) entities are increasingly involved in product handling, storage, and distribution of biologics. These partners include contract manufacturers, repackaging companies, wholesalers, distributors, hospitals, mail delivery, and distribution companies, retail pharmacies, logistics companies, freight companies, etc.

All related entities along the entire pharmaceutical supply chain should ensure that product handling, storage, transportation, and distribution are being performed appropriately for temperature, relative humidity, light, oxygen, and other relevant environmental conditions. Adequate control and monitoring for these conditions should be established and validated to assure product identity, strength, purity, efficacy, quality, and safety.

That's why it's essential to select only those 3PL providers who can comply with cold-chain requirements for product distribution and continue to assess their performance along the way. That process will look something like the following steps:

- Confirm expected channels of distribution as soon as possible
- Select channel partners and physical location(s) for each channel of distribution
- Conduct site assessment and quality management systems review
- Prepare assessment report and track improvement against recommendations
- Execute quality agreement as part of commercial terms
- Implement management review metrics as part of the management review process

Documentation of compliance from 3PL entities will be important in receiving BLA filing approval.

To complete when Ready to File (Phase III/Filing)

#9: 3PL Good Distribution Practices (GDP) Audit

#10: 3PL Quality Agreements

#11: Performance Qualification (PQ) Protocols

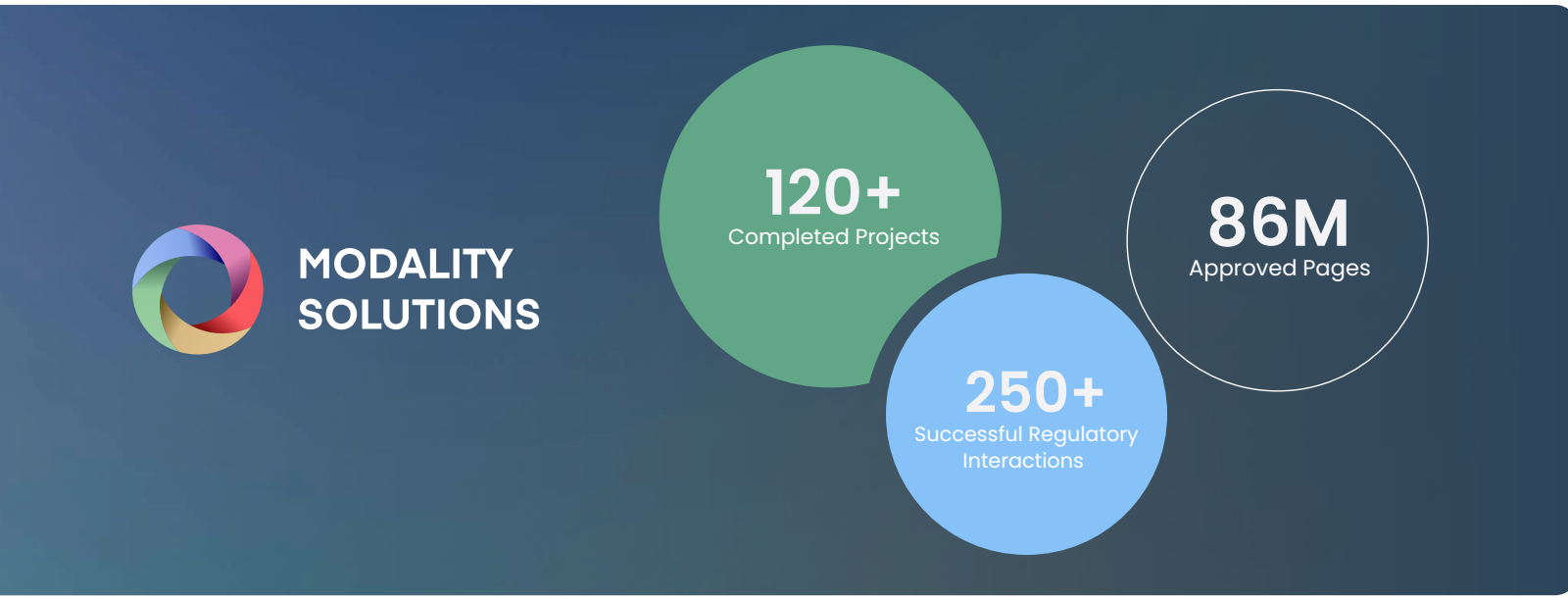
#12: Regulatory Filing Submissions & Information Request (IR) Responses

#13: Training for Pre-Approval Inspection (PAI) Responses

For more information on these steps and all of our cold chain solutions, request a consult at modality-solutions.com.

Modality Solutions: Solving the world's toughest biopharmaceutical cold chain challenges

With this overview of the 13 keys to a successful BLA filing for mAbs and other biologics, you could go out and attempt to gather this information with your existing resources. Or, you can consult outside expertise from a team of engineers who have engaged in hundreds of transport simulation engagements that have yielded the robust data expected from BLA filings—resulting in 250+ successful regulatory interactions.



Modality Solutions has experience unlike any other team in areas like stability testing, packaging qualification, and validation master planning. Our team of engineers can design a logistics network, validation master plan, and simulation testing strategy that can help your biologic gain faster approval with fewer delays.

Our Advantage Transportation Simulation Laboratory™ takes regulatory filing to the next level, providing the data you need to optimize your strategy and feel confident in your cold chain for BLA submission.

Whether you're just getting started designing the cold chain for a new mAb or other biologic, preparing for a BLA filing, or looking to solve a cold chain problem with a biologic that's already in the market, Modality Solutions can help. We have the in-house Cold Chain Engineering™ expertise to optimize and enhance the cold chain for your biologic, ensuring it stays safe, stable, and efficacious.

Contact us for a free consultation today at modality-solutions.com.

About Modality Solutions

Modality Solutions is a privately owned biopharmaceutical cold chain engineering firm that supports expedited regulatory approval for biologics and specialty drugs. Our expertise in validation engineering and cold chain regulatory guidance is unmatched.

Learn more at modality-solutions.com or on LinkedIn