Transport validation is a regulatory expectation and is required for the marketing application

- Provides a high degree of assurance that:
  - Product quality is not impacted by transportation
  - Transport processes function effectively and reproducibly as intended.
Transport Validation consists of two independent work streams

- Shipper Qualification: Demonstrates temperature control (cold chain) in our distribution network functions effectively and reproducibly as intended.

- Product Transport Evaluation: Demonstrates that product can be transported without adverse impact to product quality attributes.
Assuring Shippers Are Fit For Use – Shipper Qualification
Shipper qualification demonstrates appropriateness under actual transport conditions

**Shipper Qualification**

- **Shipper Design Qualification**
  - Assess shipper suitability in conformance with user requirements.
  - Performed through evaluation of internal and/or vendor data.

- **Shipper Operational Qualification**
  - Characterize shipper to verify physical and thermal performance conforms with user requirements in a simulated and/or real-world environment.
  - Performed through internal and/or vendor shipper thermal and physical testing, modeling or historical data.

- **Shipper/Lane Performance Qualification**
  - Testing to verify shipper physical and thermal performance conforms with user requirements in the operating environment.
  - Performed through temperature monitoring and visual physical inspection of shipper in actual transport lanes.
Passive Shipper Qualification ensures that the shipper system operates consistently within the design requirements and established limits and tolerances

| Purpose | To demonstrate that the passive shipper maintains:  
1. Controlled temperatures for a defined duration under a specified external temperature profile and  
2. Structural integrity during transport |
|---------|-------------------------------------------------------------------------------------------------|
| Process | The shipper is qualified on a non-product specific basis and may be used as needed for any product within its design space (e.g., external temperature profiles, payload configurations, controlled temperature)  
The passive shipper qualification process includes:  
• Characterization  
• Thermal Qualification  
• Physical Qualification  
• Component Specifications  
• Transport Packaging Configuration (TPC) Development |
| Timing | Occurs when new passive shippers are requested |
| Maintenance | Shipper performance is reviewed as part of transport process periodic review |
Shipper Qualification Process- Passive Shippers

• **Step 1. Characterization**
  Evaluation of shipper suitability in conformance with the user requirements. Performed through a risk assessment using internal and/or vendor data. Determines if additional testing (thermal qualification, physical qualification, thermal verification) is needed to ensure shipper conformance with user requirements.

• **Step 2. Thermal Qualification**
  Test shipper against heat and/or cold profiles to demonstrate thermal performance conforms with the user requirements in simulated conditions.

• **Step 3. Physical Qualification**
  Test shipper is not impacted by exposure to shock/impact testing per International Standard for Transport Association (ISTA) procedures. This step confirms that the shipper maintains structural integrity during transport.

• **Step 4. Transport Packaging Configuration (TPC) Development**
  Summarize shipper qualification activities and detail packaging instructions in a document. This step is required to provide guidance on how to use the shipper.
<table>
<thead>
<tr>
<th>Distribution Hazard</th>
<th>Major Test Category</th>
<th>Associated Test Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handling Drop and Impact</td>
<td>Shock</td>
<td>Drop • Free-fall, rotational, on hazard, hazard impact, Incline Impact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Horizontal Impact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vertical Impact</td>
</tr>
<tr>
<td>Transportation Vibration</td>
<td>Vibration</td>
<td>Fixed Displacement • Rotary, vertical linear Variable Displacement • Vertical, horizontal Random • Vertical, horizontal, multi-axis</td>
</tr>
<tr>
<td>Stacking Load</td>
<td>Compression</td>
<td>Static (dead load) Machine • Apply &amp; release, apply &amp; hold Dynamic Load Under Vibration</td>
</tr>
<tr>
<td>Atmospheric Conditions</td>
<td>Atmospheric</td>
<td>Temperature • Constant, cycle Humidity • Constant, cycle Pressure • Constant, cycle</td>
</tr>
</tbody>
</table>
Active Shipper Qualification ensures that the shipper system operates consistently within the design requirements and established limits and tolerances

| Purpose | To demonstrate that the active shipper:  
|         | 1. Has the adequate insulation  
|         | 2. Maintains controlled temperature range when operating direct from an energy source or from battery and  
|         | 3. Alarms and data storage / recording operates as required |
| Process | Shippers are qualified on a non-product specific basis and may be used as needed for any product within its design space (e.g., payload configurations, controlled temperature).  
|         | The active shipper qualification process includes:  
|         | • Installation Qualification  
|         | • Operational Qualification (including alarms)  
|         | • Performance Qualification  
|         | • Transport Packaging Configuration (TPC) Development |
| Timing  | Occurs when new active shippers or carriers are required |
| Maintenance | Shipper performance is reviewed as part of transport process periodic review |
Evaluating the performance of the transport process identifies trends and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in a state of control.

The periodic evaluation process has two elements:
1. Lane Performance against Key Performance Indicators are tracked by transportation lane
2. Incident Management review is performed and investigated to identify any trends and prevent re-occurrence

This process is executed monthly and documented quarterly on a Transport Process Periodic Review
Assuring Product Quality is not Impacted During Transport – Transport Qualification
Multiple studies are performed throughout development and commercialization to evaluate product post transport

- **FIH Formulation/Studies**
  - Purpose: FIH Formulation screening
  - Testing: Shock/drop stress followed by stability

- **Scale-Down**
  - Purpose: DP manufacturability/pre-commercial formulation recommendation
  - Testing: Transport simulation profile (temperature, vibration, pressure) and shock/drop.

- **CFD Studies**
  - Purpose: CPD Formulation screening
  - Testing: Shock/drop stress followed by stability

- **Post-CFR Studies**
  - Purpose: Commercial product development/post formulation recommendation
  - Testing: Transport simulation profile (temperature, vibration, pressure) and shock/drop.

- **Transport Validation/Product Transport Evaluation Studies**
  - Purpose: Confirm product quality attributes are not adversely impacted by transport – long term.

- **Secondary Packaging Studies**
  - Purpose: Demonstrate secondary packaging protects product post transport

- **Device Design Verification**
  - Purpose: Demonstrate functionality, CCI of device post transport in secondary packaging.
  - Testing: CCI using Transport simulation profile (temperature, vibration, pressure) and shock/drop; Functionality testing using (ASTM)
Product Transport Evaluation demonstrates no impact to product quality from transport for the intended commercial presentation.

Testing performed during pivotal campaign to verify product quality is not impacted during transport.

Transport studies utilize simulated and/or real-world transport conditions to evaluate product. Product quality testing is designed based on formulation studies performed during development and considers device and secondary packaging systems.

For materials that are not susceptible to transport stresses (such as shock/drop, vibration or pressure – e.g. frozen material), transport studies may not be required if justified by documented scientific rationale (i.e., technical assessment).
Simulation and/or Real-World Transport Studies are used to Assess the Impact of Various Conditions to the Shipper and Product
### Purpose
To demonstrate:
1. Transportation does not impact product quality and
2. Transportation does not impact the packaging system integrity.

### Process
Assess product exposed to a simulated transport environment of shock (e.g., drop), temperature, vibration and pressure based on Amgen’s worst-case transport lane.

### Timing
During the pivotal campaign after the commercial formulation recommendation and transport characterization studies have been completed.

### Maintenance
Assess the need to re-perform transport simulation studies when changes are made to product, packaging configurations, transport lanes or any parameter that may impact product quality.
Transport Simulation Study Process Flow

**Step 1: Design and Approve Protocol**
Identify commercial formulated product/SKUs, qualified primary and secondary packaging representative of commercial packaging configurations, roles and responsibilities, methods to evaluate product quality attributes and acceptance criteria to define the parameters of the study.

**Step 2: Package Samples and Execute Simulated Transport**
Identify product batch and distribution packaging. Expose product in secondary and distribution packaging to shock, extreme temperatures, vibration and pressure in the lab to simulate transport conditions.

**Step 3: Verify Package Integrity/Review Temperature Data**
Identify damage to packaging/product and any temperature excursions that may have occurred during the simulation to confirm that the shipper maintained structural integrity and controlled temperature.

**Step 4: Submit Samples for Quality Testing/Stability Monitoring and Perform Data Analysis**
Compare product quality attributes of exposed (shipped) samples to control (unshipped) samples and determine if acceptance criteria has been met. Initiate stability monitoring on shipped samples for long-term storage to assess impact to product.

**Step 5: Approve Report and Collate Records**
Document final commercial formulated product/SKUs, qualified primary, secondary and distribution packaging used in the study. Document product quality data analysis and conclusions of the protocol. Collate all records and store in document management system for future reference.
Compression Tester and Vibration Table
Cycling Chambers

Chamber Doors

PLC/Control Panel

Thermocouples

Evaporator
Transport Simulation Test Profile
Drug Substance

- The simulation exposes the shipment to continuous extreme temperature, vibration and pressure exposures for 26.5 hours.
- A summary of conditions tested is summarized below.
The simulation exposes the shipment to continuous extreme temperature, vibration and pressure exposures for 91.5 hours.

A summary of conditions tested is summarized below.
Real Life Shipments Confirm No Impact to Shipper and Product
Real-World Transport Studies may also be used to evaluate impact to Product Quality

| Purpose | To demonstrate:  
1. Transportation does not impact product quality and  
2. Transportation does not impact the packaging system integrity. |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td>Assess real-world product shipments transported through Amgen transport lanes of air, ground and ocean modes that are representative of transport between manufacturing and storage/distribution sites.</td>
</tr>
<tr>
<td>Timing</td>
<td>During the pivotal campaign after the commercial formulation recommendation and transport characterization studies have been completed.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Assess the need to re-perform real-world transport studies when changes are made to product, packaging configurations, transport lanes or any parameter that may impact product quality.</td>
</tr>
</tbody>
</table>
Real-World Transport Study Process Flow

Step 1: Design and Approve Protocol
Identify commercial formulated product/SKUs, qualified primary and secondary packaging representative of commercial packaging configurations, transport lane/mode, shipping/receiving sites, roles and responsibilities, methods to evaluate product quality attributes and acceptance criteria.

Step 2: Execute Protocol

Step 3: Review Temperature Data
Ensure no excursions occurred outside of allowable shipping conditions. Verify that qualified distribution packaging maintained controlled temperature through duration of transport.

Step 4: Submit Samples for Quality Testing and Perform Data Analysis
Compare product quality attributes of exposed (shipped) samples to control (unshipped) samples (i.e., lot release) and determine if acceptance criteria has been met.

Step 4: Approve Report and Collate Records
Document final commercial formulated product/SKUs, qualified primary, secondary and distribution packaging used in the TPQ. Document product quality data analysis and conclusions of the TPQ Protocol. Collate all records and store in document management system.
Stability Studies that Support Transport Validation and Real Life Excursions
Stability Study Design to Support Transport Temperature Excursions

• Data to support Transport Temperature Excursions come from both formulation development and formal stability studies.

• Additional Information is gathered during product transport evaluation studies at various product phases.

Stability Studies are Conducted Throughout the Product Lifecycle
Stability studies are conducted at temperatures above and below recommended storage conditions.

- The total allowable times for out-of-temperature exposures are established for each product formulation.
- Stability studies included: accelerated, stress, beginning and end of shelf life, freeze/thaw and/or temperature cycling studies.
- Studies conducted focus on the conditions that cover the normal operating parameters during manufacturing, packaging, labeling, transportation, and end users.
- Humidity consideration are required for lyophilized products and small molecule tablets and capsules.
Stability Support – Temperature Excursions

• The total allowable time is considered the stability time allocation from the fill finish process to the end usage of the product, which may include packaging/labeling, storage, shipping and handling, acceptable exposures described in medical information letters, label claims, and other unexpected out-of-temperature excursions.

• The maximum out-of-temperature exposure time at each step of the process, distribution, and handling is tracked and controlled.

• Assessments are conducted if maximum out-of-temperature exposure time is exceeded in any steps of the process.
Product Quality – Excursion Management

Temperature Excursion management processes exist for both Clinical and Commercial programs

• Observing/Notified Department contact QA with excursion details including range and duration of event.
• QA provides impact assessment on product quality.
• Stability and Product Quality Leader may be consulted when additional support to assess the excursion is needed
• Nonconformance records and trending drive improvement
Main Peak and Aggregate Level Changes at 30°C are Not Impacted After Variable Storage at 5°C

- **Main Peak**

- **Aggregate**

- **Lot 1 New**
- **Lot 2 New**
- **Lot 1 - 24 months at 5 degrees**
- **Lot 2 – 24 months at 5 degrees**
Product Quality—Stability Forms

• Stability Forms are created to support excursions including temperature range and duration beyond recommended storage.
• All stability assessments are supported by real-time real temperature data which meet the specification limits for the given product.
• Ranges are established against regulatory guidelines and stability indicating profiles.
• Products with excursions which are not supported by stability data are discarded to protect the customer.
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