SINGLE-USE PULSE 2021

A WEBINAR SERIES EXPLORING THE BUSINESS OF SUTS

WEDNESDAY, APRIL 14

10:30-11:30 AM EDT

TRANSIT TESTING GUIDANCE FOR SINGLE-USE COMPONENTS & ASSEMBLIES

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Transit Testing Guidance for Single-Use Components and Assemblies

BPSA 2021 Webinar Series

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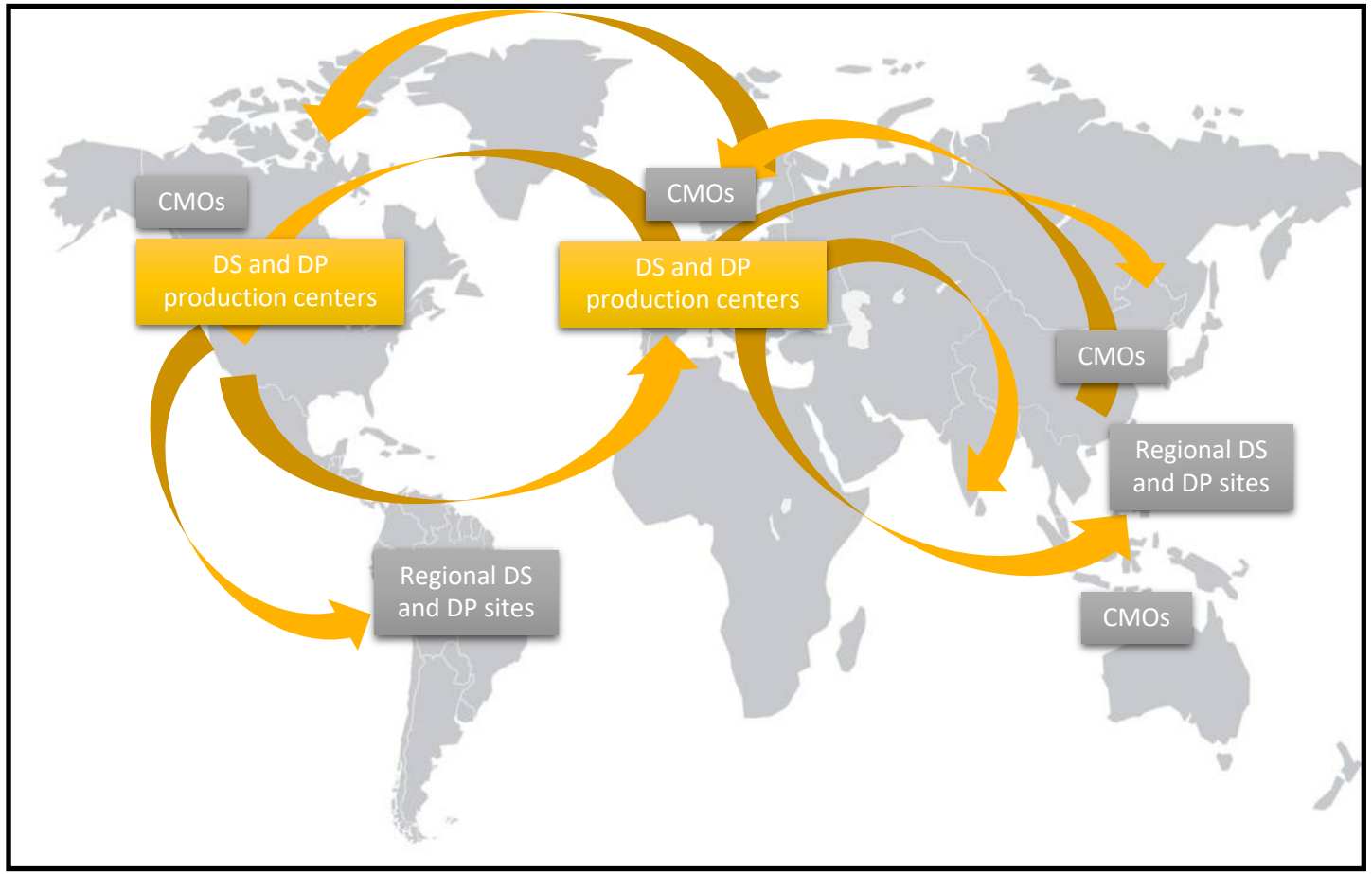
Does Any of This Supply Chain Look Familiar?

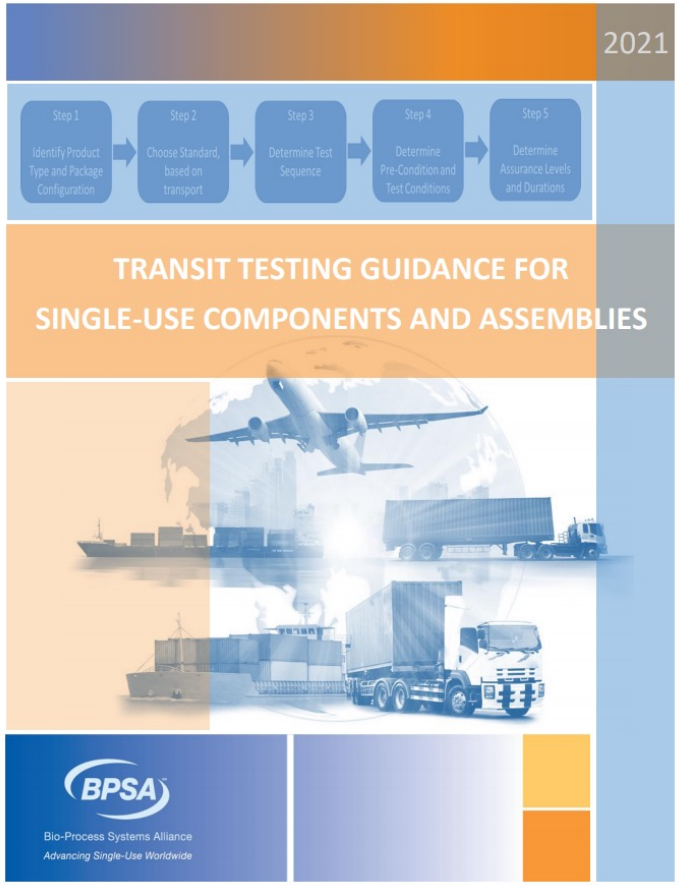


Bio-manufacturing networks are increasing & consist of multiple production centers & CMOs.

Drug substance production sites are often decoupled from drug product final filling facility inducing multiple transportation steps

Introduction

- Manufacturing supply chain for a biotech drug can be complex
  - May require multiple processes at various facilities in different location in the world
- Requires transit of various materials, ingredients, buffers, in-process intermediates and drug substances among facilities, from suppliers to users
- Single-use components, assemblies, and systems (SUS) increasing to facility efficiencies
- Transit hazards: shocks (drops), vibration, compression, temperature, humidity, and pressure (altitude)
- Package transit testing allows manufacturers to qualify design and use of packaging and is required by regulators in line with GMP process qualification requirements
- BPSA Transit Team was formed to provide guidance on transit testing for SUS



Why is Transit Testing Important?

- To ensure product quality / integrity
- To advance product and package design
- To meet regulatory expectations / Process qualification
- To mitigate risk, damage, and loss during transit

Agenda

- Roles and responsibilities
- Risk assessment
- Define the packaging test article
- Define test method
  - Field distribution test
  - Standardized laboratory simulations
  - Tailored laboratory simulations
- Description of laboratory simulation
  - Climatic, Stacking, Shock, Vibration
  - ASTM, ISTA & ISO standards
- Define acceptance criteria
- Write a protocol
- Implement testing
- Reporting
- Summary

Roles and Responsibilities

- FDA/EMA requirements about process validation: “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes”

- PDA TR66: “Shipping systems must be qualified for their intended use through proper design and testing in consultation with a packaging engineer. The ISTA and ASTM D4169 are good references for testing standards.”

Transportation is part of the processes,

As such it needs to be qualified

Roles and Responsibilities

Single-Use Suppliers and (End) Users

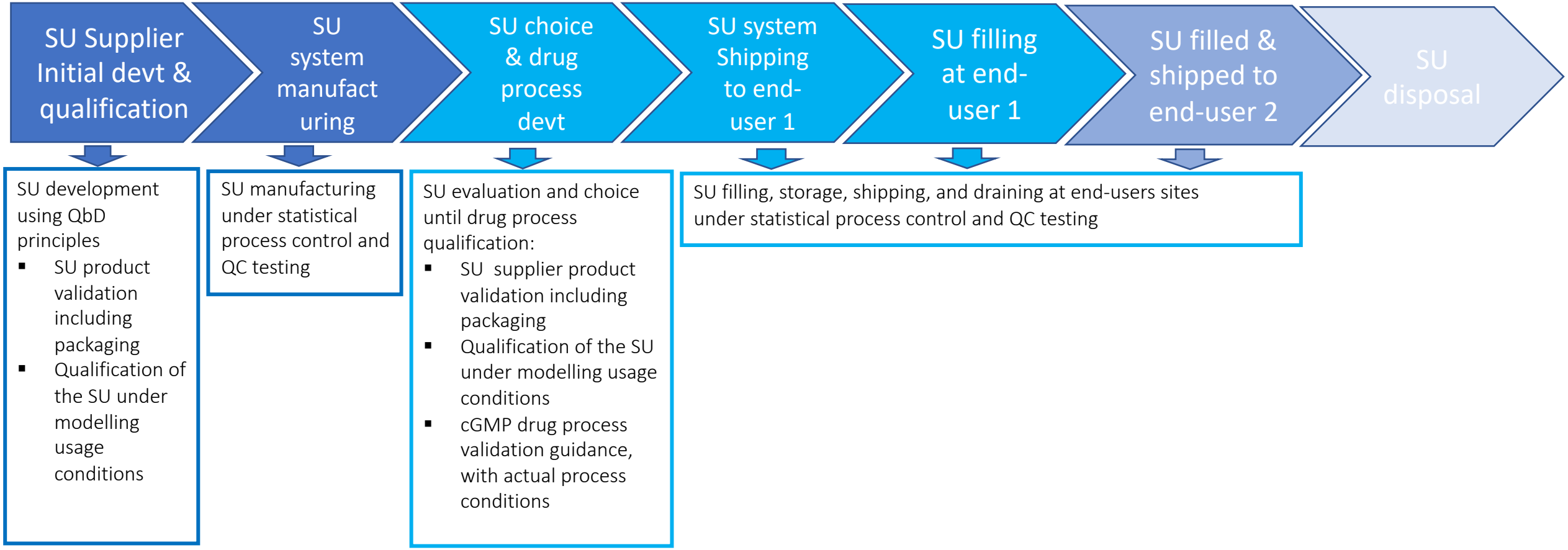
Collaborate to ensure development and validation of packaging according to quality production needs

- Understanding of the life-cycle
- Process/application mapping for intended use
- Define packaging qualification requirements
- Implementation of proper packaging based on needs

Transit test qualification of packaging (empty & filled) under worse case conditions

Single-Use Life Cycle

How Single-Use Suppliers can support End-Users process validation for shipping steps?



Risk Assessment

To be compliant to Process qualification requirements, BPSA recommends a risk-based approach to determine:

- If transit testing is required in different scenarios
- In case it is, what would be the most appropriate transit testing approach

Risk assessment may be based on:

- Process step, type of fluid: media/buffer, BDS, Drug
- Type of distribution cycle
- Existing / historical data
- New package changes / design

Drug process qualification is under the responsibility of the end-user

SU supplier documentation can help with supporting data

Example of Risk Analysis Matrix

Type of Distribution	Process Step		
	Media / Buffer	DSP intermediate	BDS, buffer for formulation or drug product
	Low risk	**Medium risk**	**High risk**
Transportation from clean room to clean room: **Low risk**			
Transportation between buildings at same site: **Medium risk**			
Transportation between sites (national or intl): **High risk**			

Key recommendations:

No tests required

Real world or field-testing checks

Laboratory testing

Risk Analysis

Low Risk	• No testing may be required
Medium Risk	• Real-world or field testing to be considered • Distribution cycles may consider transit hazards: drop, shock, vibration, compression, thermal, and others • Lab simulation testing may also be considered
High Risk	• Laboratory simulation testing to transit testing standards • For products with complex distribution, real-world testing alone is likely insufficient

Defining the Packaging Test Article

Packages within Scope:

- Packaging containing SUS that are empty and shipped to end-users
- SUS that contain various liquid solutions, powders, or materials. This may include buffers, cell and gene therapy components, or bulk drug or other intermediary substances.

Transit testing focus on:

Primary packaging	Protection applied around the SUS product
Secondary packaging	Combination of smaller packages
Tertiary packaging	Stabilization of several cartons on unitized pallet load

Packaging

Packaging	Primary	Secondary	Tertiary
Definition	Material that first envelops the product, holds the SUS, and is in direct contact with the contents.	Outside primary packaging, combining packs	For bulk handling, warehouse storage & transport via full containers
Examples	• Single-use bags • Packaging protecting sterile equipment	• Boxes and crates • Transport trolleys, shells, containers	• Wrapped/sealed pallets • Cleanroom or thermal crates
Purpose	• Containment • Product protection • labeling	• Transportation, storage • Stacking • Protection from dust and debris	• Transportation, storage • Stacking • Protection from dust and debris • Insulation (thermal and physical)
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Use Risk Assessment & Define the Test Method

Risk assessment

Type of Distribution	Process Step		
	Media / Buffer	DSP intermediate	BDS, buffer for formulation or drug product
	Low risk	Medium risk	High risk
Transportation from clean room to clean room: **Low risk**			
Transportation between buildings at same site: **Medium risk**			
Transportation between sites (national or intl): **High risk**			

- Field distribution testing
- Standardized laboratory simulation
- Tailored laboratory simulations

Recommandations

No tests required

Real world or field-testing checks

Laboratory testing

Field Distribution Test

Shipping SUS packages through a selected distribution route & evaluating performance of the shipped packages at end of journey

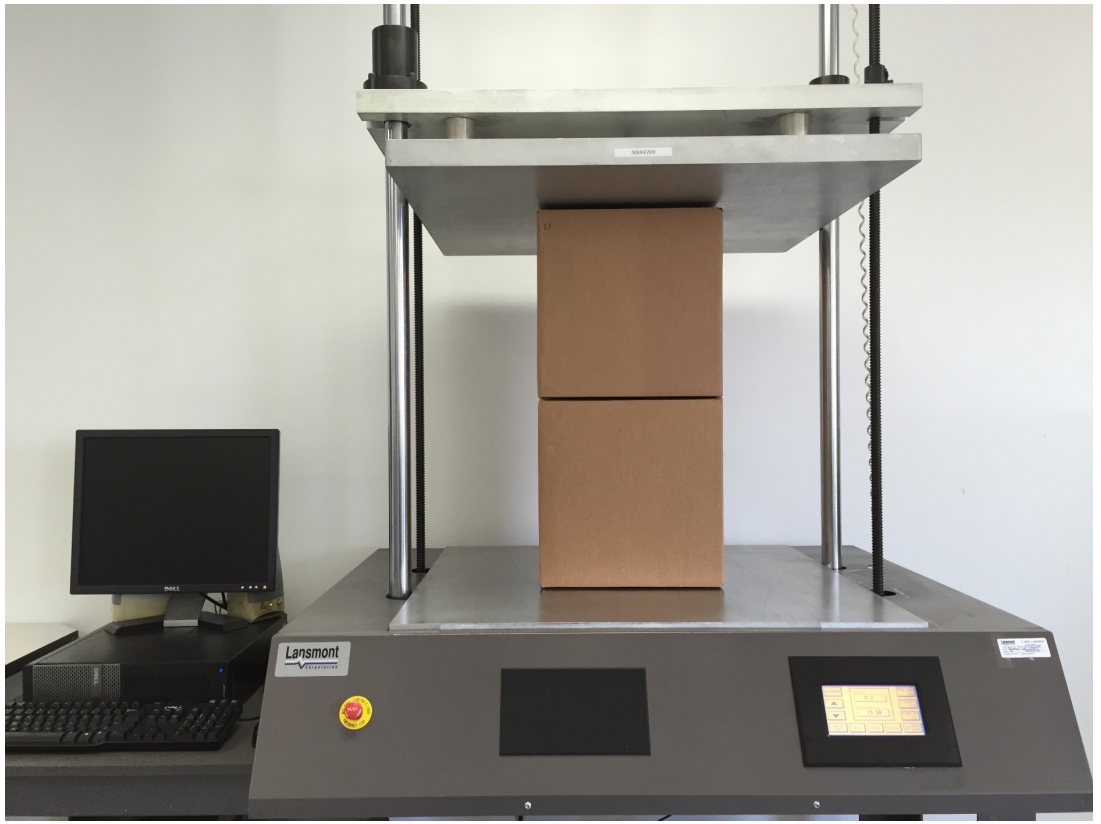
- round trip
- point-to-point

Relevant data monitoring system may be incorporated to develop insights for feeding later tailored laboratory simulations. Examples:

- temperature
- shock
- location

Standardized Laboratory Simulations

- Recognized standards from bodies such as ASTM, ISO, or ISTA
- Some methods formally acknowledged as Recognized Consensus Standards by the FDA



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Standardized Laboratory Simulations

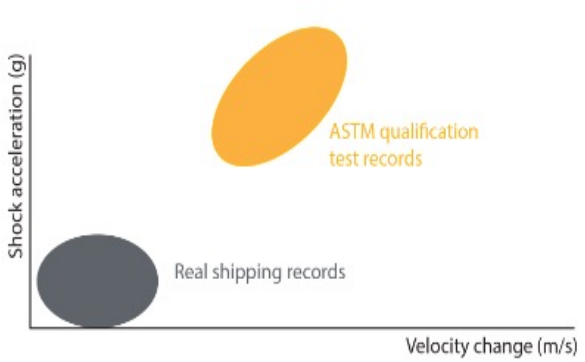
Standard	Title	FDA Recognized Consensus Status
ASTM D4169	Standard Practice for Performance Testing of Shipping Containers and Systems	Yes
ASTM D7386	Standard Practice for Performance Testing of Packages for Single Delivery Systems	Yes
ISTA 3A	Packaged Products for Parcel Delivery System Shipment 70 kg (150 lbs) Or Less	Yes
ISTA 3B	Packaged Products for Less-Than-Truckload (LTL) Shipment	Yes
ISTA 3E	Unitized Loads of Same Products	Yes
Other ISTA Standards	Various	No
ISO 4180	Packaging – Complete, filled transport packages – General rules for the compilation of performance test schedules	No
ISO 11607	Packaging for terminally sterilized medical devices	Yes

Summary: Field Tests vs Laboratory Simulations

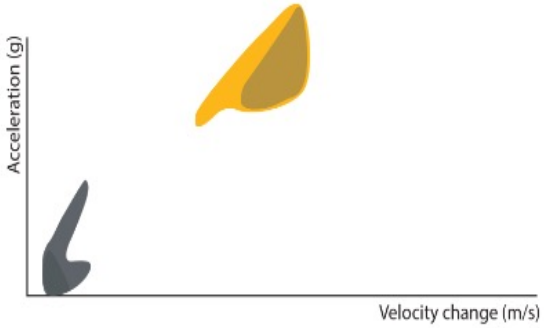
Field Distribution Test	Laboratory Distribution Simulation
• No control over trial conditions • Results affected by truck condition, weather, traffic conditions, driver, route, diversions, etc. • Some trial packs will receive severe treatment, others will be gently handled • Risk of basing decisions on non-representative data	• Controlled, repeatable test • Consistent assessment over time • All trial packs exposed to same tests and treatment • Control over test intensities to cover different event intensities, different markets, level of confidence required in pack performance, etc. • Greater level of regulator acceptance • May over or underestimate real world transit situation

Field Tests vs Laboratory Simulations

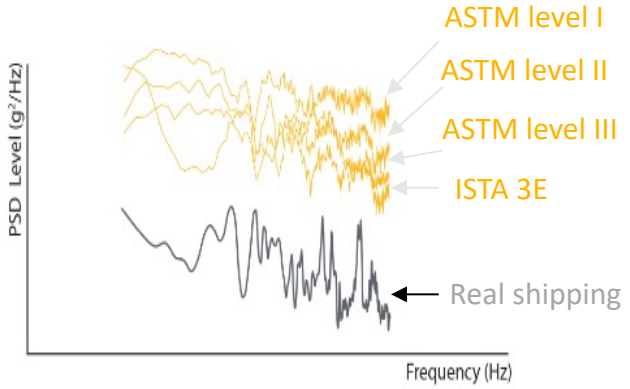
Case study: Comparison between ASTM D4169 all levels, ISTA & field testing



Vertical shock comparison

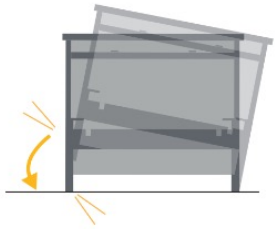


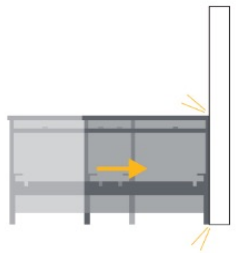
Horizontal shock comparison



Vibration level comparison

ASTM D4169 provides a higher safety margin than other testing programs for this case study with Flexsafe® 3D shipping system





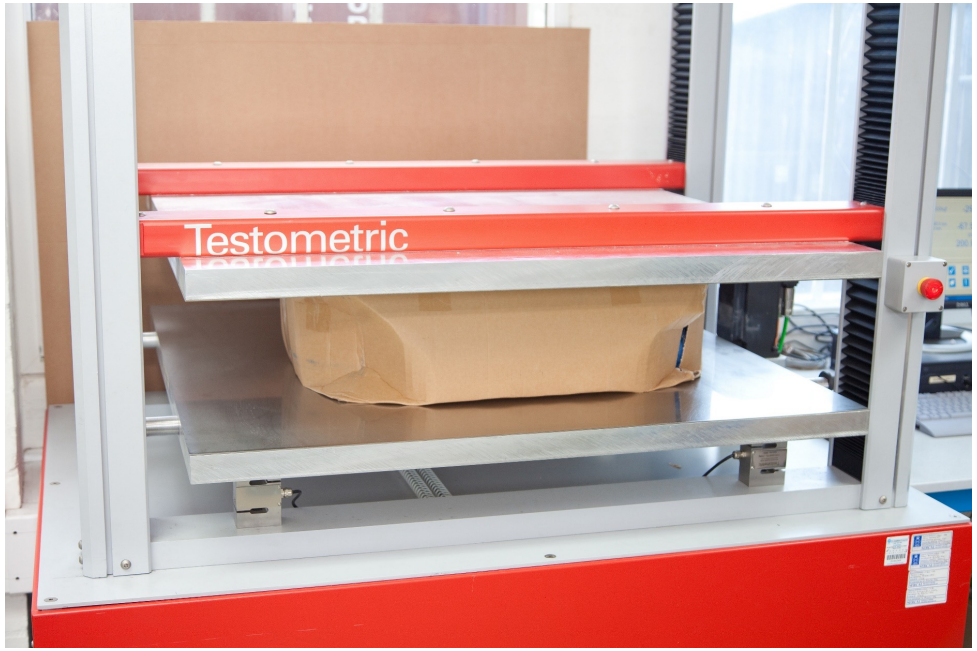
Tailored Laboratory Simulations

Used to assess more severe events or highly specific conditions not addressed in standard test methods

May better match lab with field conditions, while maintaining simulation control.

Examples:

- Modified drop or vibration test challenges for specific packaging
- Custom transit (desert; non-motorized transport)
- Vibration for aggregation-prone drug-substances



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Laboratory Simulations

In most cases, standardized lab testing delivers simplest approach to meeting obligations of qualification of primary, secondary, and tertiary packaging performance.

Most common standard methods:

- ASTM D4169
- ASTM D7386
- ISTA

Test sequences all follow similar fundamental approach, combining a sequence of climatic and physical tests in logical order to simulate most significant transit hazards:

climatic stacking shock vibration

Image provided by courtesy of Smithers

Climatic

Exposure to environmental conditions such as:

- Temperature extremes & swings
- Humidity
- Atmospheric pressure

Image provided by courtesy of Smithers

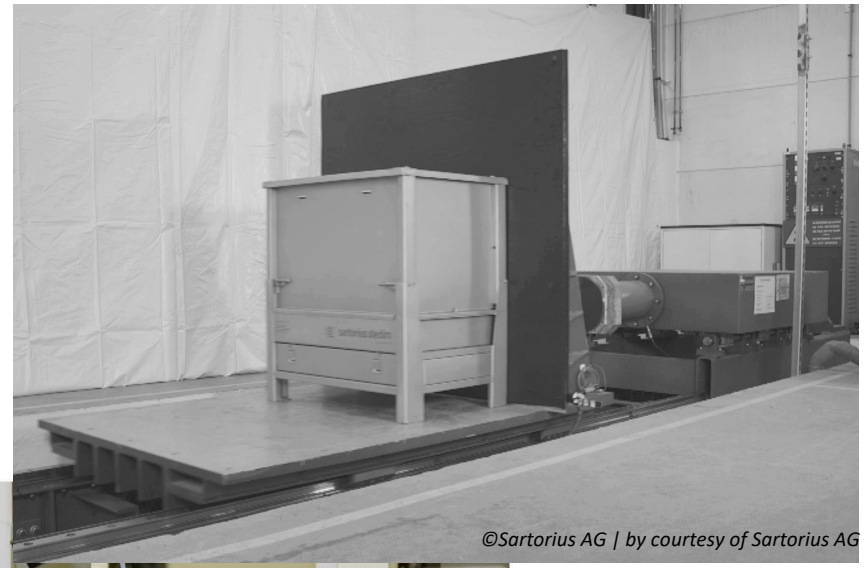
Stacking

Measures impact of compression from stacking packs in warehouse or in transit

Images provided by courtesy of Smithers

Shock

- Horizontal shocks - crash test
- Vertical shocks - Manual handling shocks, such as drop test
- Mechanical handling shocks, such as forklift handling



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Vibration

Intensity & frequency of vibration
from different transportation modes

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ASTM D4169

- Standard lists 18 different distribution cycles (DCs), each representing a different channel or distribution chain
- Includes 3 Assurance Levels (AL) for selection of test intensity based on a risk assessed approach and probability of occurrence in real-world distribution:
  - AL III: lowest, represents events with highest probability
  - AL I: highest, represents events with lowest probability
- Selection of AL based on level of risk that is appropriate for a given SUS or on knowledge of the supply chain. Real world data acquisition can provide direction for severity selection
- AL II is often used as a default position in absence of more detailed data
- AL I can offer an increased level of confidence in pack and SUS performance

ASTM D4169 Distribution Cycles

#	Distribution Cycle	Comments
1	General Cycle—undefined distribution system	When distribution cycle is undefined
2	Specially defined distribution system, user specified (see Appendix X2 in ASTM standard)	Well known distribution cycle, test sequences have to be defined in the protocol
3	Single package without pallet or skid, LTL motor freight	LTL = Less than truck load (small freight) without pallet Air freight not considered
4	Single package with pallet or skid, LTL motor freight	LTL = Less than truck load (small freight) with pallet Air freight not considered
5	Motor freight, TL, not unitized	Not unitized Air freight not considered
6	Motor freight, TL, or LTL—unitized	LTL = Less than truck load (small freight) Air freight not considered

ASTM D4169 Distribution Cycles *(continued)*

#	Distribution Cycle	Comments
7	Rail only, bulk loaded	Motor and air freight not considered
8	Rail only, unitized	Motor and air freight not considered
9	Rail and motor freight, not unitized	Air freight not considered
10	Rail and motor freight, unitized	Air freight not considered
11	Rail, TOFC (trailer on flatcar) and COFC (container on flatcar)	Motor and air freight not considered
12	Air (intercity) and motor freight (local), over 150 lb. (68.1 kg), or unitized	Unitized load with motor and air freight - mostly used for single-use systems

ASTM D4169 Distribution Cycles *(continued)*

#	Distribution Cycle	Comments
13	Air (intercity) and motor freight (local, single package up to 150 lb. (61.8 kg). Consider using Practice D7386 for single parcel carrier shipments.	Same as DC 12 but for weight < 61.8 kg
14	Warehousing (partial cycle to be added to other cycles as needed)	Mostly applicable to cover handling in warehouses
15	Export/Import shipment for intermodal container or roll on/roll off trailer	Includes handling and stacking - partial cycle to be added to other cycles as needed
16	Export/Import shipment for palletized cargo ship	Includes handling and stacking - partial cycle to be added to other cycles as needed
17	Export/Import shipment for break bulk cargo ship	Includes handling and stacking - partial cycle to be added to other cycles as needed
18	Non-Commercial Government shipments per MIL-STD-2073-1	Non-commercial specific cycle

ASTM D4169 Example

- Assess performance of a SUS being delivered by road as a palletized (unitized) load. This is a new product, with no pre-existing experience or performance data. Supplier desires high level of confidence in performance prior to submission.
- Distribution Cycle 6 covers motor freight for unitized loads, and AL I will provide greatest confidence in performance. Sequence of tests:

Mechanical handling	forklift truck handling, side impacts, rotation flat drops
Vibration	Truck vibration profile
Concentrated impact	Impact from a specified cylindrical mass
Mechanical handling (repeat)	
Warehouse stacking	Compression representing pallet storage in warehouse

ASTM D7386

- Follows principles of ASTM D4169 with specific focus on single parcel shipment;
- Similar 3 Assurance Levels for intensity selection;
- 4 different test sequences within the standard, depending on the size, shape, and weight of the complete pack or test specimen:
  - TS-1 – small parcels which are transported and handled in mail bags
  - TS-2 – large, flat packaged products
  - TS-3 – long, narrow packaged products
  - TS-4 – all other packaged products
- For each TS, specific sequence of distribution cycle tests, based on supply chain transit modes.

International Safe Transit Association (ISTA)

- Independent organization focused on performance of packaging in transport.
- 7 different series of packaging performance test methods.
- Most common Series 3 tests (aligns with real world distribution conditions):
  - ISTA 3A, ISTA 3B, and ISTA 3E are FDA-recognized consensus standards.
  - Similar, but not identical, to ASTM methods. Some key differences:
    - Only 1 intensity level.
    - ISTA 3A, for parcel delivery systems, combines vibration & low-pressure test, while ASTM methods separate these steps.
- Based on history, some companies continue to apply Series 1 and 2, but these do not include air vibration tests so may not be suitable.

ISTA Series

Series 1	Non-simulation
Series 2	Partial simulation performance tests; “at least one element of Series 3… in addition to basic elements of Series 1.”
Series 3	General simulation performance tests
3A	Parcel delivery <70 kg (150 lbs.)
3B	LTL – Less than truckload (individual parcel and unitized)
3E	Unitized load of same product
3F	For distribution center to retail (<45 kg or <100 lbs)
3H	Bulk
3K	Fast-moving consumer goods in European retail supply chain

ISTA Series *(continued)*

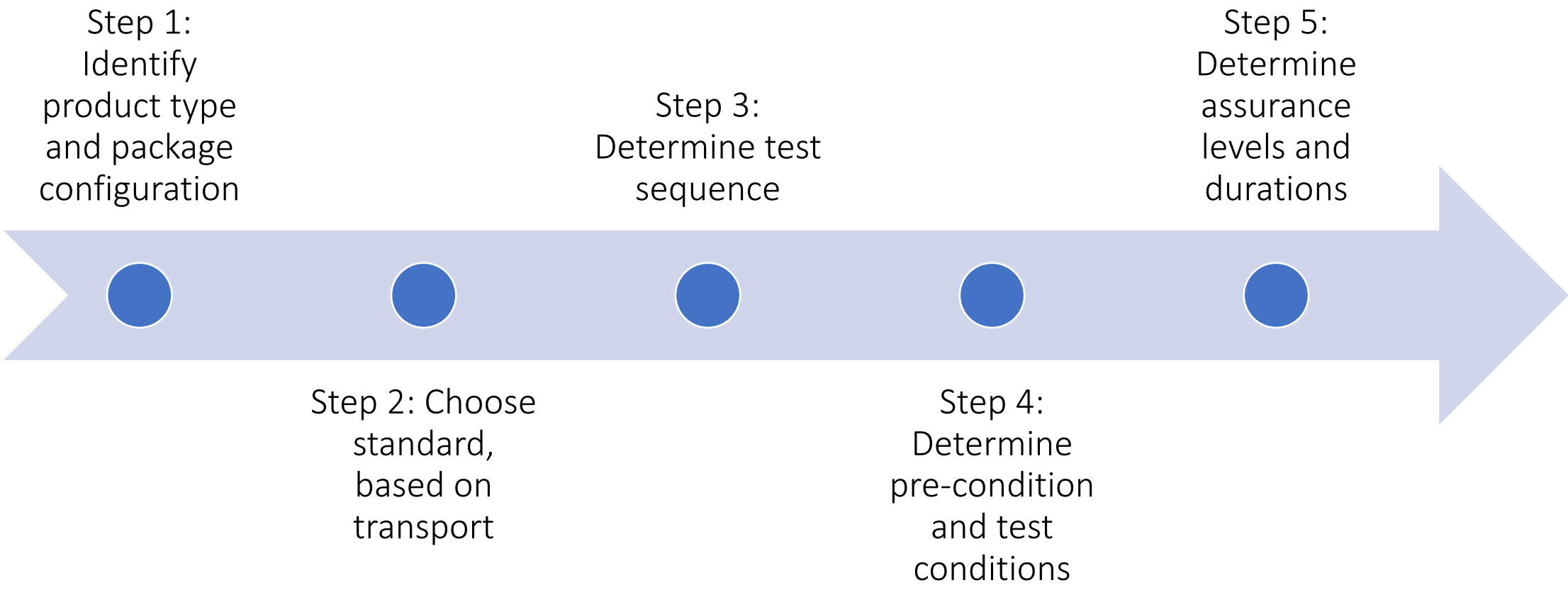
Series 4	Enhanced simulation performance tests; “linked to actual known distribution,” “a web based enhanced simulation test plan generator.”
Series 5 & 6	*Not series for qualification*
Series 7	Development tests: individual package, thermal testing of insulated shipping containers
7D	Temperature test for transport packaging
7E	Testing standards for thermal transport packaging used in parcel delivery system shipment

Define Acceptance Criteria

- User of transit testing protocol should define the acceptance criteria.
- Some current standards provide general guidelines such as:
  - Product should be damage free.
  - Package should be intact, i.e. no excessive particle generation that risks contaminating end-user clean room.
- In addition, acceptance criteria may be adapted to SUS tested in accordance with intended use, such as product functionality, integrity, sterility / bioburden, and particulates. BPSA has provided recommendations for evaluation of particulates along with other quality testing.

Writing the Test Protocol

Defining Test Protocol



Process for Defining Test Protocol

Step 1: Identify product type and package configuration.

- A bracketing approach based on worst-case identification can be helpful
- State acceptance criteria, if determined.

Step 2: Choose standard, based on transport.

- Use life cycle analysis or prior historical data

Process for Defining Test Protocol

Step 3: Determine test sequence:

Define all process handling & transport steps in the supply chain – know your distribution chain.

Choice of schedule in ASTM D4169 or test procedure in ISTA series depends on:

- package type, such as individual package, unitized load, or bulk load.
- distribution type, such as parcel delivery, LTL, or distribution to retail.

Process for Defining Test Protocol

Step 4: Determine pre-condition and test conditions.

- Preconditioning:
  - ASTM & ISTA recommend 72hrs at required temperature & humidity
- Testing:
  - Load on a pallet: ISTA 3B, 3E, or 3H, or ASTM D4169
  - Single parcel: ISTA 3A, 3B, 3F, or 3K, or ASTM D4169 or D7386

Process for Defining Test Protocol

Step 5: Identify appropriate test intensities to cover safety margin

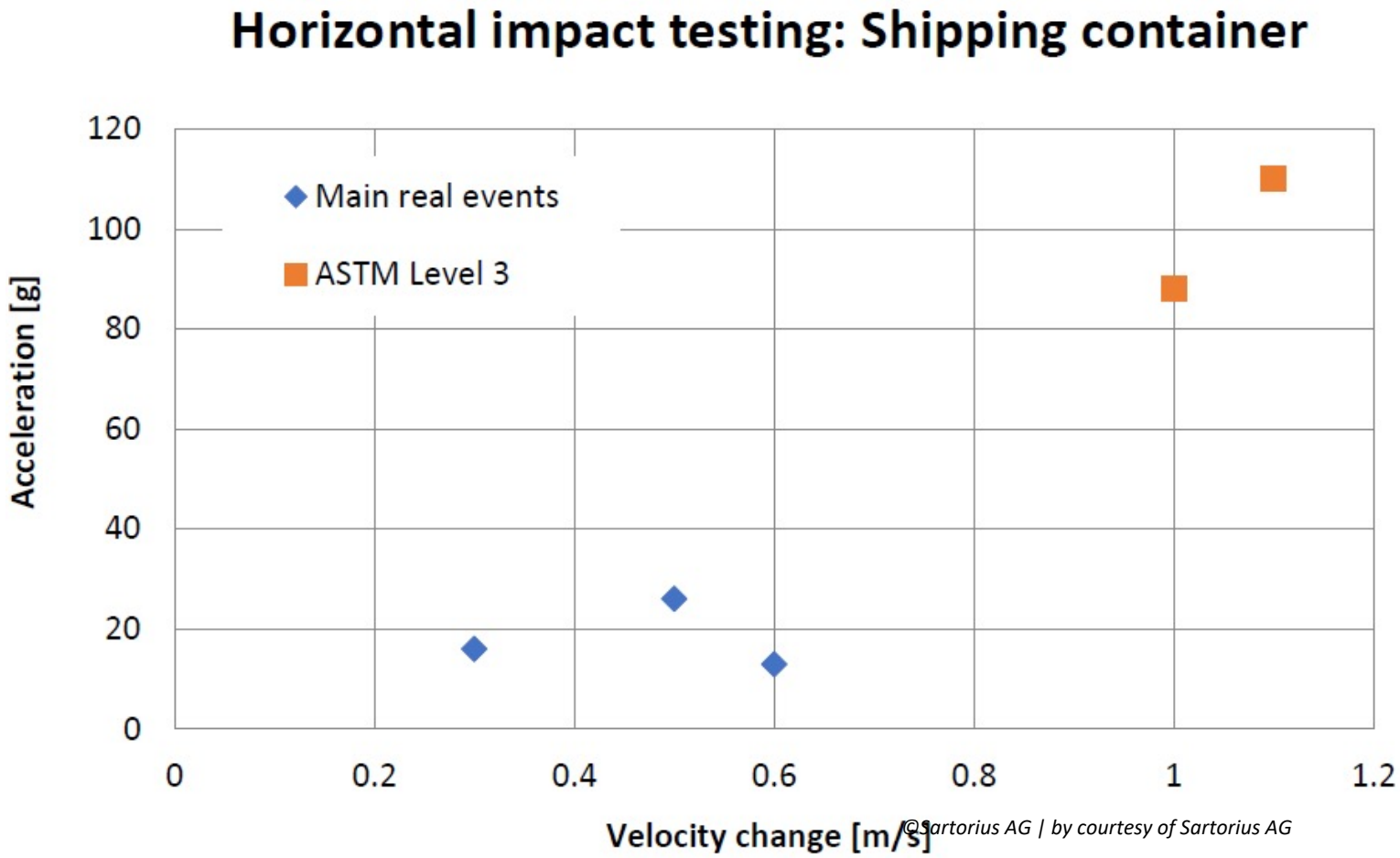
- Select Assurance Levels for ASTM (especially relevant for vibration cycles, and for manual / mech handling)
- Select vibration durations
  - ASTM D4169: 1 hour with mix of the 3 levels of severity that can be repeated for longer duration simulation
    - Range for truck and air vibration: 30 min to 6 hours
  - ISTA: duration is related to expected mileage with a maximum of 4 hrs

Per ISTA, no uniform requirement for number of package replicates to be tested

Process for Defining Test Protocol

Correlation of standard lab testing with preliminary real-world field test may support safety margin considerations.

In this example, ASTM Level 3 severity provides a wide safety margin compared with shock levels measured during real-life shipments.



Implement the Testing

Testing should then be conducted on chosen package system based on the selected protocol.

As noted, per ISTA, no uniform requirement acceptance criteria or for the number of package presentation replicates to be tested.

Packaging engineer should consider the supply chain stakeholders and risk tolerance assigned for package performance.

All test results to be documented and photographed as necessary to support regulatory submissions or internal quality audits.

Reporting

Transit test study report should:

- Reflect the protocol.
- Show testing was undertaken in accordance documented methods.
- Provide detailed results.
- Confirm whether acceptance criteria have been met or not.

If failures occur & acceptance criteria are not met, then review of SUS product, its packaging, anticipated transportation modes & testing should be undertaken to consider changes as needed.

Report should conclude whether package / process is qualified or as needed.

Summary

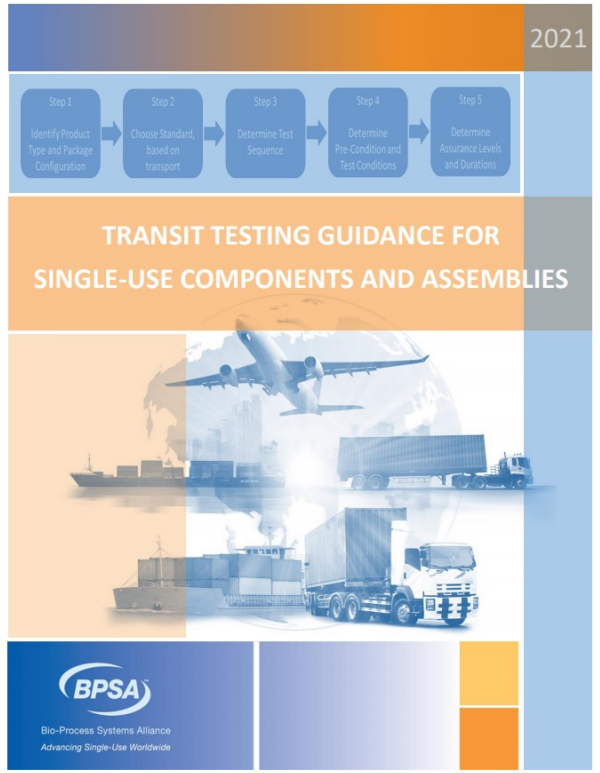
Guidance is provided here on utilization of transit testing to qualify packaging for use by SUS suppliers and end users.

Consideration is given to supply chain of SUS / packaging.

A risk matrix considers when a testing program should be implemented, with field & laboratory testing options.

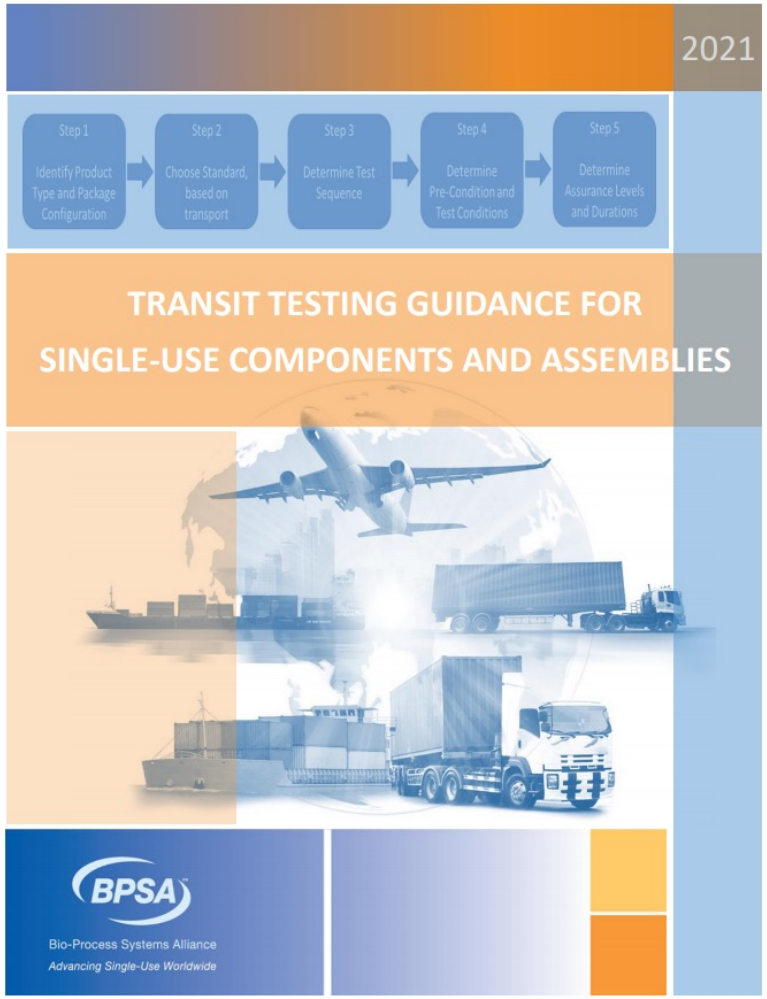
Standardized laboratory simulations from ASTM, ISTA, and ISO are reviewed.

Acceptance criteria and decision tree for defining the testing protocol are provided in order to ensure that qualification will demonstrate that the product performance is maintained throughout distribution chain.



Questions?

White Paper Available for Download



The full document can be found on the BPSA website, along with over a dozen additional white papers and technical documents

https://bpsalliance.org/technical-guides/

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