TECHTIP

Product and Package Testing FAQ

Q1: Per ISO and ASTM standards, is there a recommendation on when a transportation simulation should be performed on aged samples (i.e. after accelerated aging/real-time aging or shelf-life stability testing)?

Answer: ISO 11607 states shelf-life stability testing and performance testing should be performed separately on separate sets of samples.

The formulation of the study will depend on the risk assessment that has been carried out and how the worst-case testing has been defined for the packaged product. This can include how and when the product is transported (i.e. before or after accelerated aging and real-time aging testing), which defines the worst-case scenario.

Transportation testing and aging testing are not dependent of each other but can be included together as worse-case and will depend on the way the packaged product is shipped and stored.

It is important to note the ASTM F1980 testing standard defines transportation testing as event-related whereas accelerated/ real-time aging testing is defined as non-event related.

For more information on accelerated and real-time aging testing click here.

Q2: When does a manufacturer need to requalify package testing?

Answer: Package stability or performance testing is typically only requalified when there is a change to the product, packaging, or sterilization processing.

A risk assessment should be carried out when there is a change and the risk level associated to the change determined. This risk level will guide the scope of requalification. Testing needs to be requalified when there is a major change to the following:

- Sterilization process, parameters, and cycle number
- Sterile barrier system materials used
- Contents of sterile barrier system
- Heat sealing equipment used
- Shipping configuration or methods of distribution
- Manufacturing or processing locations

Q3: Is aerosol challenge testing required for porous sterile barrier systems (SBS) as part of the accelerated aging program or is physical testing (such as bubble leak testing) during accelerated aging sufficient to qualify the sterile barrier during the aging studies? Additionally, should this be a stand-alone activity?

Answer: Microbial/aerosol challenge testing may be necessary for some tortuous path closures, however this has been replaced by physical integrity testing such as bubble leak testing or dye penetration testing. Per ISO 16775, A.7.6., the microbial/aerosol challenge is an alternative to physical integrity testing, but microbial/aerosol challenge methods are not explicitly reliable and are technically challenging to execute. Additionally, there are not currently any universally accepted test methods to perform the microbial/aerosol challenge testing, however these methods may be appropriate for evaluating the integrity of tortuous path closure sterile barrier system when properly validated.

Q4: Is there a recommended temperature when using room temperature in the accelerated aging calculation?

Answer: When using room temperature in the accelerated aging calculation, the recommended temperate is based on where product would be stored during normal storage conditions and the controls available within the storage location. ASTM F1980 states 20-25°C is to be assumed. The example provided within the ASTM F1980 standard uses 23°C in its calculation and this is what many manufacturers use, and is typically what is referred to as “typical laboratory ambient conditions.”

For more information on accelerated aging calculation click here.

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Q5: When defining a storage range label on a packaged product, should the Tamb, or ambient temperature for accelerated aging studies, equal the maximum storage temperature indicated on the labelling?

Answer: When there is a defined storage range labelled on a product it is recommended that manufacturers use the upper storage limit as the real time temperature (TRT) in the aging calculation. This is used instead of the T_{amb} or normal ambient temperature, which is typically 20°C to 25°C. As an example, if the labelled storage temperature range is 15°C to 35°C then the 35°C should be used as the ambient temperature TRT in the aging calculation.

For more information on accelerated aging calculation click here.

Q6: Can a manufacturer perform aging studies of a sterile barrier system without product inside the packaging?

Answer: Product is not required in any of the packaging when performing aging studies, however it is recommended to have some product included to demonstrate that the aging process does not compromise the product's functionality or that the product inside the packaging during aging does not compromise the sterile barrier.

For more information on accelerated aging testing and sterile barrier systems click here.

Q7: If product has a labelled storage range of 2°C to 50°C, should real-time aging be conducted for both temperatures or only for average one?

Answer: Per the ASTM F1980 testing standard, real-time aging is recommended to be carried out at typical ambient conditions (20°C to 25°C) as the labelled ranges are extremes.

For more information on accelerated aging testing click here.

Q8:Can accelerated aging studies be utilized to determine product stability rather than packaging stability?

Answer: Accelerated aging studies can be utilized to determine the product stability in addition to package stability. ASTM F1980, Standard Guide For Accelerated Aging Of Sterile Barrier Systems And Medical Devices, should be followed when performing product stability.

For more information on accelerated aging testing click here.

Q9: Is there a recommended sample size when performing package testing for each test, every time?

Answer: There is no recommended sample size in any standards for package testing. Sample size should be determined by the device owner based on risk assessments and internal validation sampling requirements (if available). The sample size must be documented and justified and it should be consistent across all time points.

Q10: What testing options are available when a product is not suitable for accelerated aging testing? As an example, if a polymer deteriorates at higher temperatures and the standard storage temperatures for the product are 5°C - 35°C.

Answer: The glass transitioning point (Tg) and the material melt point (Tm) for each of the materials in the product should be determined. Once the Tg is established, the temperature can be reduced by at least 10°C in the calculation to determine the accelerated aging temperature. If the highest temperature that can be utilized is 35°C, as in the example, this means the calculated aging duration would be 159 days to simulate one year. Real-time aging may be the only option for the product if Tg is very low.

For more information on accelerated aging calculation click here

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Q11: Does a change to the parameters of a sterilization cycle impact a previously determined product shelf-life?

Answer: Changes to the parameters of a sterilization cycle may impact the packaging or the product depending on the sterilization modality and the scope of the change. A risk assessment should be performed and documented to evaluate the change and its potential impact to the product and packaging. This assessment should then be used to guide the need for requalification of the stability or performance of the product and packaging. A full requalification may be necessary or limited testing may be appropriate based on the risk assessment.

Q12: When manufacturing a medical device, is real-time aging required and accelerated aging optional as a package test??

Answer: When manufacturing a medical device, real-time aging is required per the ISO 11607-1 testing standard. In parallel with accelerated aging, the manufacturer must also conduct a real-time aging study to validate the data generated during the accelerated aging process. The data collected from the accelerated aging study may be used for determination of shelf-life until real-time aging studies are complete.

Accelerated aging is frequently used to release a product to market in a shorter duration. For example, one year can be achieved in 40 days at an elevated temperature of 55°C with an ambient temperature of 23°C and a Q10 factor of two. This provides significant time savings as compared to waiting one full year for real-time aging to be complete.

Q13: When performing integrity testing (i.e. bubble leak testing and dye penetration testing), should manufacturers also test sterility of the product to ensure the inside of a package has remained sterile after aging or other conditions?

Answer: ISO 11607-1 states the maintenance of sterile barrier system integrity may be used to demonstrate maintenance of sterility. Sterility testing is not required as the integrity test (i.e. bubble leak test and dye penetration test) are proving the integrity of the packaging system and can be used at different stages of the validation study. The integrity testing is used to determine if there have been any breaches to the seal or surface of the packaging after aging or other conditions. The ISO 11737-2 test of sterility standard is typically used during the sterilization validation process to determine if the packaged product has been sterilized to the appropriate sterility assurance level (SAL).

Q14: When selling products in different regions of the world, do manufacturers need to perform various product and package testing that simulate the difference of temperature and humidity of the regions?

Answer: During distribution testing, the ASTM D4332 testing standard outlines temperatures and relative humidity levels for all the different environmental conditions and storage conditions that a product may be transported in. For example cryogenic, extreme cold, frozen food storage, refrigerated storage, temperate high humidity, tropical, and desert conditions. It is recommended to perform testing across these conditions that will be based on the risk assessment for the product.

Q15: When referencing ASTM D4169, what assurance level should be used for medical devices and is it acceptable to change the assurance level between test schedules?

Answer: When referencing ASTM D4169 section 8.2, the assurance level chosen is dependent on the risk associated with the distribution of the product and should be based on the probability of damage at the different intensity levels.

> Level I is a high level of test intensity and has a low probability of damage occurrence.
>
> Level III is a low level of test intensity, but has a correspondingly high probability of damage occurrence.
>
> Level II is between these extremes.

The intensity level should be one of three pre-established assurance levels listed above. This must be pre-established

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assurance levels listed above. This must be pre-established based on the product value, the desired level of anticipated damage that can be tolerated, the number of units to be shipped, knowledge of the shipping environment, or other criteria. When evaluating a change within the assurance level between test schedules, the assurance level may be varied between test schedules if such variations are known to occur and the test levels used should be reported.

Q16: Is bubble leak testing constrained by the size of the pouch being tested? As an example, can bubble leak testing be performed on a 30mm x 50mm pouch?

Answer: Bubble leak testing has several variables based on the pouch being tested. It is possible to carry out bubble leak testing on a pouch of the example size (30mm x 50mm), but it can be challenging depending on the method to connect to the pouch and will also depend on the materials in the pouch.

Q17: Do testing laboratories validate the mixing process for preparation of dye solution used in dye penetration testing? How does a laboratory assure that dye solution is properly prepared?

Answer: The creation of the dye solution used in dye penetration testing is part of the test method validation process and is created to a defined recipe as specified in the ASTM F1929 and ASTMF3039 test standard.

Q18: How does burst testing and peel/seal strength testing differ in terms of application and methodology?

Answer: Burst testing determines the ability of a package to withstand internal pressurization, pressurizing the package until the internal pressure causes it to burst. This is a singular test that once performed, the sample pouch cannot be reused and one test value is generated.

Peel or seal strength testing evaluates the tensile strength of seals in flexible barrier materials. Multiple samples can be taken around the sample pouch depending on the size of the sample being taken and the size of the pouch.

Burst testing may be the appropriate test to perform if the pouch does not have peelable seals.

Q19: Is there a limit of detection when performing bubble leak testing or dye penetration testing, and do these tests correlate to microbial ingress?

Answer: Per ASTM F2096, the bubble leak test has been verified as being able to detect a defect down to 250micron.

Depending on the standard being followed (ASTM F1929 porous materials or ASTM F3039 nonporous materials), dye penetration testing can detect defects in seals (porous and nonporous materials) down to 50micron or in the surface of a non-porous material down to 10micron.

The defect sizes that can be used in microbial challenge testing is typically down to 1micron, however detecting these defect sizes in a packaging study takes significant time and effort when compared to the physical tests. Therefore, using the physical testing is preferable to the microbial challenge testing.

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