Cleaning Pharmaceutical Isolators



Pharmaceutical Isolator

I. Overview

Pharmaceutical isolators provide physical isolation of manufactured products from contamination coming from the background environment, the room outside the isolator. They represent the cleanest area of the entire manufacturing facility. They are classed as Grade A/B (EU cGMP) and ISO Class 3 to 5 environments (in terms of air particle cleanliness) and are maintained to sterility assurance levels (SAL) ranging from 10^{-3} to 10^{-6} depending upon the application.

Pharmaceutical isolators are used to conduct aseptic filling operations, sterility testing, cell culturing and purification activities within pharmaceutical and manufacturing facilities.

This Texwipe Technical Note is intended to provide guidance on the cleaning of pharmaceutical isolators. It includes details such as product selection, cleaning procedures, protocols and step-by-step guidelines for effective cleaning.

II. Cleaning and Disinfecting Pharmaceutical Isolators

1. Wipers and Mops for Cleaning and Disinfection of Isolators

Much of the literature on isolator cleaning refers to the need for "low-linting" fabrics that do not shed. However, little guidance is provided as to which fabric types are best. The lint that is shed from wiping or mopping materials is made up of loose fibers and particles that are not bound to the fabric surface or that are broken free during the cleaning process. For more information about low lint wiper, we refer to IEST-RP-CC004.4. Cleaning and disinfecting solutions can promote this linting or shedding activity if inappropriate fabrics are used.

A wide variety of fabrics can be fashioned into wipers or mops for use in cleaning isolators. These include natural materials such as cotton, rayon (viscose) and cellulosics, synthetic materials such as polyester, nylon, polypropylene, foams, or blends such as polyester-cellulose combinations. Of these choices, only polyester knit fabrics have the requisite cleanliness, low particle and fiber counts, low endotoxin levels, low extractable residues, durability, and chemical compatibility that are needed for the cleaning and disinfection of pharmaceutical isolators. Furthermore, polyester knit fabrics can be sterilized by Gamma or X-ray irradiation to an SAL of 10^{-6} without loss of structural stability. The characteristically low levels of releasable particles and fibers associated with polyester knit fabrics are especially important in aseptic applications since it is well known that particles are potential carriers of bacteria.
Put simply, polyester knit fabrics used for wipers and mop covers reduces the likelihood to contaminate isolator surfaces when used in cleaning and disinfection operations. Consequently, they represent the best choice for "non-linting" or "non-shedding" materials. The same cannot be said for other fabrics.



Photomicrograph of polyester knit fabric

Sterile polyester knit wipers are used during production to clean up spills, wipe down gloves (when wetted or pre-wetted with sterile 70% isopropyl alcohol[1]), or provide clean work surfaces.

These wipers can be wetted with:

a. Detergents to clean the isolator
b. Deionized water or WFI or 70% IPA solution to remove cleaning agent residues
c. Disinfecting agents to disinfect the isolator
d. Deionized water or WFI or 70% IPA solution to remove disinfectant residues

Pre-wetted sterile wipers, containing 70% IPA solution are also available for these activities.

2. Frequency

Good contamination control practice would suggest that isolators and associated transfer devices be cleaned and disinfected after a production campaign[2] has been concluded (referred to here as "post-cleaning" which includes disinfection) and again before a new production campaign is started (referred to here as "pre-cleaning" which also includes disinfection). This will avoid cross contamination. If the isolator has not been opened after "post-cleaning" and if a new manufacturing campaign starts within a short time (say one hour) after "post-cleaning", then an additional "pre-cleaning" step may be unnecessary. In that case, a surface cleaning of the isolator interior with sterile wipers and/or mops wetted with sterile 70% IPA solution may be sufficient to ready the isolator for production. Decisions on cleaning/disinfecting frequency and procedures are the province of the Standard Operating Procedure (SOP).

3. Cleaning and Disinfecting Specifics

Since the isolator is most often cleaned and disinfected while closed to maintain the sterility of the isolator, sterile cleaning and disinfecting consumables - wipers, pre-wetted wipers, mops, cleaning/disinfecting agents, water, 70% IPA solution, etc, - must be introduced through an appropriate transfer device. Even if a facility's SOP calls for the isolator to be opened for cleaning and disinfection, the use of sterile wipers and pre-wetted wipers is recommended, since they can be introduced into the isolator for in situ cleaning needs. Having only sterile wipers also eliminates the confusion of having both sterile and non-sterile wipers on hand and the need to sterilize wipers prior to use within the isolator. The usual sequence for cleaning and disinfection includes a cleaning step, a rinsing step, a disinfecting step, another rinsing step, and if needed, a gaseous sterilization step, and a cleaning validation step. As a side note, wipers can be used to wipe down any hard surface particles that are introduced into the transfer device for use within the isolator, and the risk of contaminating the sterile environment. This will remove surface contaminants that might otherwise compromise disinfection or sporicidal treatments.

a. Cleaning

To ensure that each production run will be conducted in a pristine environment, it is necessary to clean the isolator to remove any residues and soils produced from the prior run. These contaminants, if not removed, would otherwise unnecessarily consume disinfectant and mitigate its efficacy. Typically, small flat surface mops known as isolator cleaning tools (Figure 1), wipers, swabs and detergents are most commonly employed for these cleaning applications. Detergent formulation selection is based on the type of soil to be removed. Also, cleaning mechanism factors such as wetting, dissolution, oxidation, hydrolysis, enzyme action, emulsification, deflocculation, sequestration, saponification and rinseability can all be important in determining which detergent formulation to use. The detergent is applied to the surface in the manner described in Section 5 "Optimum Cleaning Procedures" - using quarter-folded wipers with linear overlapping strokes, wiping from clean areas to dirty, renewing the wiper surface after each stroke. Wipers are used for all surfaces within arm's reach. Isolator cleaning tools are used for surfaces further away.

b. Rinsing Following Cleaning

After cleaning, detergent residues are removed from the surfaces with wipers or mops that have been wetted with sterile deionized water or sterile 70% IPA solution. This will ensure that disinfectants have the opportunity to contact bare surfaces. Surfaces are considered clean when devoid of visible surface contaminants. Verify visually that the last wiper used to wipe down the surface is also devoid of visible contaminates.



Figure 1. *Isolator cleaning tool in use*

[1] All IPA solutions described here are assumed to be 70% IPA /30% water (v/v), where the "water" is either water for injection (WFI) or deionized water (DIW). Before IPA solutions are used for cleaning, rinsing or sanitizing isolator surfaces, ensure that the materials of construction in the isolator will withstand repeated exposure to IPA. Some transparent materials, e.g. polycarbonates, may cloud over or crack when exposed to IPA solution.

[2] A production campaign is considered a session in which multiple product units of the same product type are manufactured.

c. Disinfection

The same procedures are followed for disinfection, except that liquid disinfecting agents are substituted for detergents. Disinfecting agents can include phenolics and quaternary ammonium compounds[3] ("quats"). Aqueous mixtures of IPA will provide some measure of disinfection, but they are ineffective against spores. Occasionally, liquid sporicides such as sodium hypochlorite (bleach) and peracetic acid/hydrogen peroxide solution will be substituted for disinfectants when sporicidal activity is needed. These sporicides can be corrosive to surfaces and are therefore used intermittently. Again, isolator cleaning tools and wipers are used as described Section II.1.

d. Rinsing Following Disinfection

The same procedure is followed here as described earlier in Section II 3b. Disinfecting agent residues are wiped from the surface with wipers or isolator cleaning tools that have been wetted with sterile deionized water, WFI or sterile 70% IPA solution. This will eliminate the buildup of residue deposits that become difficult to remove in subsequent cleaning operations, and that will cause staining of work surfaces.

e. Gaseous Sterilization

Once the cleaning and disinfection steps are completed, if required, the isolator can be sterilized, with a suitable sterilant such as Vaporized Hydrogen Peroxide (VHP).

f. Cleaning Validation

Surface sampling with swabs to verify the absence of cleaning and disinfecting agents may be required after step d.

See Texwipe's publications on cleaning validation[4] (Figure 2) and the Texwipe Swabbing Guide (Figure 3) for additional details.

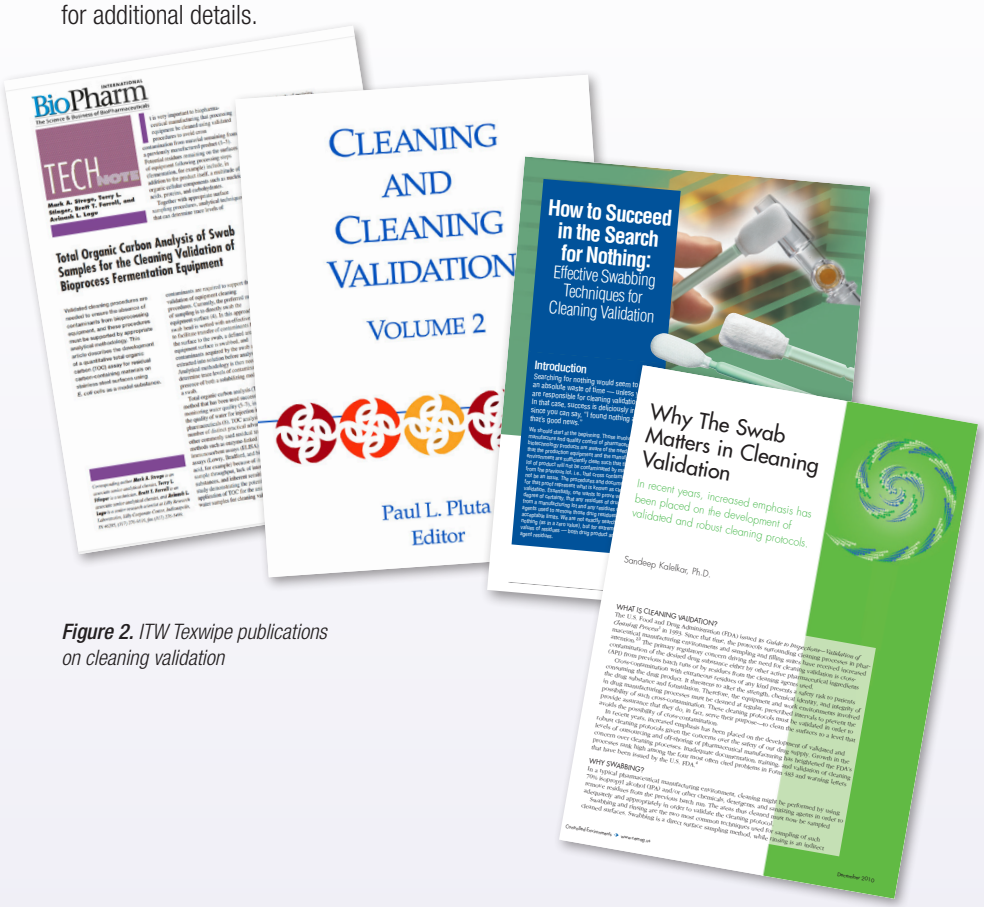


Figure 2. *ITW Texwipe publications on cleaning validation*

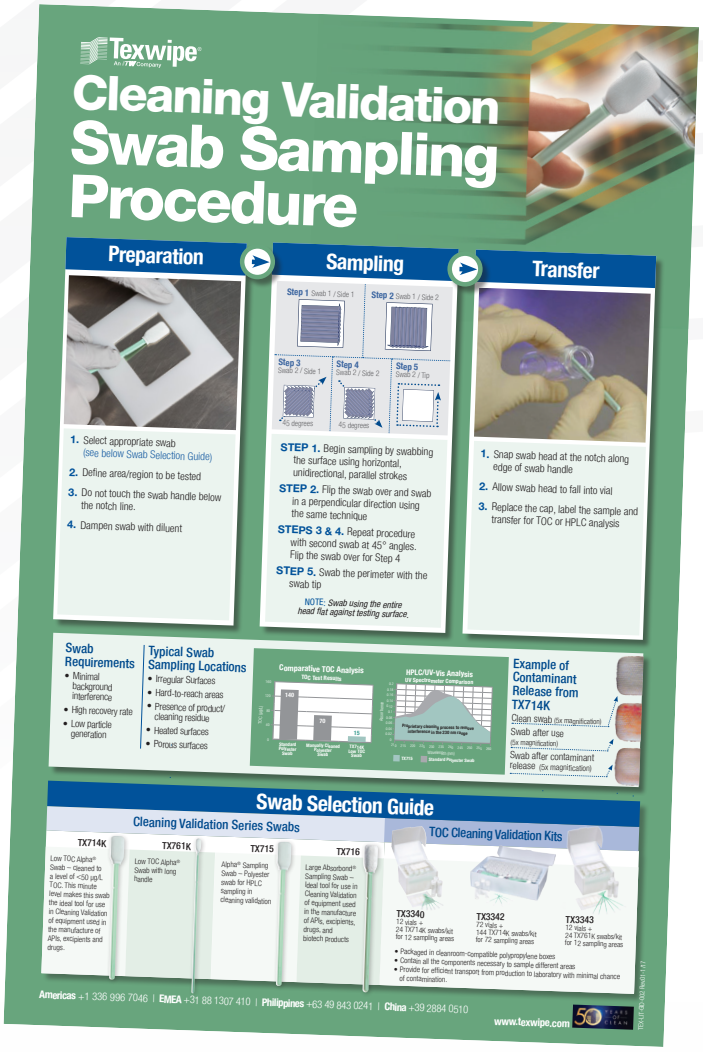


Figure 3. *Cleaning Validation Swab Sampling Procedure*
This document is available on the Texwipe website

[3] Use either phenolic- or quat-based disinfectants, never both together

[4] Mark A. Strege, Terry L. Stinger, Brett T. Farrell, and Avinash L. Lagu, "Total Organic Carbon Analysis of Swab Samples for the Cleaning Validation of Bioprocess Fermentation Equipment", BioPharm international, April 1996

Paul L. Pluta, "Cleaning and Cleaning Validation Volume 2", 2013

Texwipe, "How to Succeed in the Search for Nothing: Effective Swabbing Techniques for Cleaning Validation", 2021

Sandeep Kalelkar, "Why The Swab Matters in Cleaning Validation: In recent years, increased emphasis has been placed on the development of validated and robust cleaning protocols", December 2010

III. Cleaning Tasks and Recommended Products

Following is a table of cleaning activities performed on Compounding Aseptic Isolators (CAIs) and the recommended Texwipe products for those tasks.

Cleaning Task	Recommended Products		
	Use one or more of the following:		
a. Cleaning of interior walls, ceiling and deck of closed isolators	1 Mini AlphaMop	**TX7101**	Mini Isolator Cleaning Tool Kit
	Mop Covers	**STX7114**	Sterile Mini AlphaMop™ Covers
		STX1720	Revolve™ Sterile Mini AlphaMop Cover
		STX7114M	Sterile Microdenier Mini AlphaMop™ Covers
	Sterile IPA	**TX3270**	Sterile 70% Isopropanol, 16 oz.
	2 Sterile AlphaSat	**TX3280**	Sterile AlphaSat® 10 12" x 12"
	Sterile Vertex	**TX3049P**	Sterile Vertex® Pre-Wetted 9" x 9"
	Sterile Revolve	**STX1709P**	Revolve™ Sustainable, Pre-Wetted 9" x 9"
	Sterile ThermaSat	**STX4305**	Sterile ThermaSat™ 60 9" x 9"
	3 SterileWipe	**TX3211**	SterileWipe™ LP 9" x 9"
		STX4394	SterileWipe™ SE Polyester Wipers 10"x10"
	Sterile Vertex	**TX3049**	Sterile Vertex® 9" x 9"
	Sterile Revolve	**STX1709**	Sterile Revolve™ Sustainable, Pre-Wetted 9" x 9"
	4 Sterile Swab	**STX714A**	Sterile Alpha® Polyester Large Swab
		STX761	Sterile Alpha® Polyester Swab
b. Cleaning up spills while isolator is in use	1 Absorbing spilled liquid	**TX7101**	Mini Isolator Cleaning Tool Kit
		TX3221	Sterile Vertex®, 11" x 11"
	2 Use products from a.2. for removing surface contamination		
c. Wiping down articles before placing them in the transfer isolator	Products from Section a.2.		
d. Validation of isolator cleaning	TOC Kit (TX3340)	**TX3340**	TOC Cleaning Validation Kit
	Sampling swabs	**TX714K**	Low TOC Alpha® Sampling Swab
		TX761K	Low TOC Alpha® Sampling Swab with Long Handle
		TX715	Alpha® Large HPLC Cleaning Validation Sampling Swab
		TX716	Large Absorbond® Sampling Swab



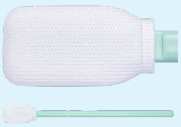




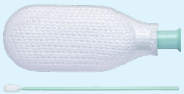




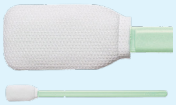




TX714K



TX761K



TX715



TX716

IV. Detailed Product Descriptions

TX7101 Mini AlphaMop™ Isolator Cleaning Tool





The Texwipe TX7101 Mini AlphaMop™ Isolator Cleaning Tool is designed to facilitate cleaning of CAIs. The mop head has a low, flat profile, rounded corners and is totally autoclavable. The swivel joint allows the user to reach otherwise inaccessible areas. The replaceable foam pad ensures that the mop cover conforms to the surfaces that are being cleaned. TX7101 includes two handles, 18" and 24" (46 cm and 61 cm), and is easily used with one hand. Changing the mop covers is quick and easy they are designed to slip on and off, yet remain secure while in use.

Product Number	Description	Packaging
TX7101	Mini AlphaMop™ Isolator Cleaning Toolkit 1 polyester foam pad 6 polyester mop covers	1 mop/case 2 handles (18" and 24")
TX7114	Mini AlphaMop™ covers AlphaWipe® replacement mop covers and pads	150 mop covers/case 25 covers/inner bag 6 inner bags/case 6 foam pads/case

STX7114 Mop Cover

Specially engineered to work with isolators and other small areas, this easy-to-maneuver tool offers lightweight, one-hand operation. With a low-profile, swivel head, the Isolator Cleaning Tool gets into hard-to-reach places. Engineered for quick cover changes during operation, the padded head allows for a consistent mop across different surfaces without losing cleaning power. The rounded edges clean the isolator corners and prevent scratches or damages to surfaces. The low-profile, swivel head Texwipe's Isolator Cleaning Tool/Mini AlphaMop™ Systems feature a 7" x 4" (10 cm x 18 cm) thermoplastic mop head, pads and fasteners. Choose from your choice of handle options: TX7101 offers 2 handles at 12" (30.4 cm) and 18" (45 cm) fixed lengths each, and TX7104 offers a telescoping handle reaching from 29" - 53" (73 cm - 134 cm). Autoclave safe.

STX1720 Mop Cover

Revolve™ 2-in-1 mop covers, the first sustainable covers made for the cleanroom industry, are made from 100% upcycled polyester and are a part of Texwipe's Revolve™ line of sustainable products. Revolve™ mop covers contribute to a company's sustainability goals, reducing the amount of post-consumer water bottles going into the landfill and reducing the level of carbon emissions. Revolve™ 2-in-1 flat mop covers are designed for easy cover changes by combining the cover and the mop pad in one. The polyester mop pad is integrated with the polyester cover, making the mop cover and pad replacement a one-step process. The padded cover allows for consistent contact with a surface. Two sizes available to fit the AlphaMop™ (TX7108, TX7108AH) and the Isolator Cleaning Tool/ Mini AlphaMop™ (TX7101, TX7105). These are available in sterile and non-sterile offerings.

STX7114M Microdenier Mop Cover

Specially engineered to work with isolators and other small areas, this easy-to-maneuver tool offers lightweight, one-hand operation. With a low-profile, swivel head, the Isolator Cleaning Tool gets into hard-to-reach places. Engineered for quick cover changes during operation, the padded head allows for a consistent mop across different surfaces without losing cleaning power. The rounded edges clean the isolator corners and prevent scratches or damages to surfaces. The low-profile, swivel head Texwipe's Isolator Cleaning Tool/Mini AlphaMop™ Systems feature a 7" x 4" (10 cm x 18 cm) thermoplastic mop head, pads and fasteners. Choose from your choice of handle options: TX7101 offers 2 handles at 12" (30.4 cm) and 18" (45 cm) fixed lengths each, and TX7104 offers a telescoping handle reaching from 29" - 53" (73 cm - 134 cm). Autoclave safe.

TX3270 Sterile 70% IPA - 16-oz. (473 ml) spray bottle

This product is used for convenient dispensing of sterile 70% IPA solution onto dry sterile wipers or onto mop covers for cleaning and sanitizing activities during production and to remove cleaning and disinfecting agent residues from surfaces. The spray bottle can also be used to sanitize gloves during production.



Sterile AlphaSat TX3280

Vectra® Alpha® 10 is made from 100% polyester with a sealed border, processed on Texwipe's automated cleaning system. Vectra® advances the cleaning process and brings this technology to a higher level of wiper manufacturing. Available dry (Vectra® Alpha® 10), pre-wetted (AlphaSat® with Vectra® Alpha® 10).

Sterile Vertex TX3049P

Vertex® is made from 100% polyester material with a sealed edge processed on Texwipe's fully automated manufacturing system. Available dry (Vertex®), pre-wetted (Vertex® pre-wetted) and sterile.

Sterile Revolve STX1709P

Revolve™ wipers, the first sustainable wipers made for the cleanroom industry, are made from 100% upcycled polyester material with a sealed edge, processed on Texwipe's fully automated manufacturing system. Revolve™ wipers contribute to the sustainability goals, reducing the amount of post-consumer water bottles going into landfills and reducing the level of carbon emissions. Available dry, pre-wetted, sterile and non-sterile.

Sterile ThermaSat STX4305

ThermaSeal™ 60 is made from 100% polyester with a sealed edge, cleanroom laundered. VHP-safe packaging. Available dry (ThermaSeal™), pre-wetted (ThermaSat™), sterile and non-sterile.



SterileWipe TX3211

AlphaWipe® is made from 100% polyester material with a cut edge, cleanroom laundered. Available dry (AlphaWipe®), pre-wetted (AlphaSat®), and sterile.

Sterile Vertex TX3049

Vertex® is made from 100% polyester material with a sealed edge processed on Texwipe's fully automated manufacturing system. Available dry (Vertex®), pre-wetted (Vertex® pre-wetted) and sterile.

Sterile Revolve STX1709

Revolve™ dry, sterile wipers, are made from 100% upcycled polyester material with a sealed edge, processed on Texwipe's fully automated manufacturing system.

Sterile STX4394

AlphaSorb® HC is made from 100% two-ply polyester with a sealed edge, cleanroom laundered. Available dry (AlphaSorb®HC) and sterile pre-wetted (AlphaSat® with AlphaSorb®HC).





Sterile Alpha® Swab STX714A / STX761

Texwipe's Alpha® Swab Series is constructed from 100% polyester knit material. Complete thermal bond construction eliminates adhesive contamination. Cleanroom manufactured, providing low levels of Non-Volatile Residues (NVRs) and ions, and made to exacting and consistent tolerances using high-precision automated processes. Lot coded for traceability and quality control. Packaged in a silicone-free and amide-free bag. Individually packaged in a peel-apart sleeve.

Sterile Vertex TX3221

Vertex® is made from 100% polyester material with a sealed edge processed on Texwipe's fully automated manufacturing system. Available dry (Vertex®), pre-wetted (Vertex® pre-wetted) and sterile.





Cleaning Validation Kit TX3340

Swabbing is a preferred method to determine the effectiveness of cleaning protocols as determined by the US FDA. HPLC/ UV-Vis and Total Organic Carbon (TOC) analysis are different methods used to validate these cleaning processes. Texwipe's Alpha® Polyester Knit Series Swabs are made from the cleanest 100% polyester material. These swabs are further cleaned using a proprietary process to make the swab suitable for use in TOC analysis:

- TX714K
- TX761K or in HPLC analysis using a UV detector analytical method as part of a cleaning validation protocol:
- TX715

The Absorbond® Polyester Non-Woven Large Swab (TX716) is manufactured with 100% polyester nonwoven fabric which contains no contaminating surfactants. Recommended for HPLC analysis. These swabs are the ideal tools for use in Cleaning Validation of equipment used in the manufacture of APIs, excipients, drugs, and biotech products.

Sampling swabs TX714K - TX761K - TX715

Texwipe's Alpha® Swab Series is constructed from 100% polyester knit material. Complete thermal bond construction eliminates adhesive contamination. Cleanroom manufactured, providing low levels of Non-Volatile Residues (NVRs) and ions, and made to exacting and consistent tolerances using high-precision automated processes for TOC or HPLC. Lot coded for traceability and quality control. Packaged in a silicone-free and amide-free bag. The swabs have a light-green colored handle with "TEXWIPE" name embossed on handle.

Sampling swabs TX716

Texwipe's Absorbond® Swabs Series is made from 100% polyester (hydroentangled) nonwoven material. The complete thermal bond construction eliminates the risk of adhesive contamination. Cleanroom manufactured, made to exact and consistent tolerances using high-precision automated processes. Lot coded for traceability and quality control. Packaged in a silicone-free and amide-free bag. The swabs have a trademarked light-green colored handle with "TEXWIPE" name embossed on handle.



TX714K

TX761K

TX715

TX716

Sterile dry wiper selection guide

Product Number	Product Name	Wiper Characteristics
TX3211	SterileWipe™ LP	9" x 9" (23 cm x 23 cm)
TX3049	Sterile Vertex®	9" x 9" (23 cm x 23 cm)
STX1709	Revolve™ Sterile Wipers	9" x 9" (23 cm x 23 cm)
STX4394	SterileWipe™ SE Wipers 10"x10"	10"x10" (25 cm x 25 cm)
TX3221	Sterile Vertex®	11" x 11" (28 cm x 28 cm)

Sterile Prewetted wiper selection guide

Product Number	Product Name	Wiper Characteristics
TX3280	Sterile AlphaSat® 10	12" x 12" (31 cm x 31 cm)
TX3049P	Sterile Vertex®	9" x 9" (23 cm x 23 cm)
STX1709P	Revolve™ Sterile Wipers	9" x 9" (23 cm x 23 cm)
STX4305	Sterile ThermaSat 60	9" x 9" (23 cm x 23 cm)

V. Optimum Cleaning Procedures

Cleaning of separative enclosures such as pharmaceutical isolators requires specialized procedures for optimum results - procedures termed as “critical cleaning”. These procedures are counterintuitive and differ from the casual, cursory wiping approach that is used to clean a kitchen counter at home. While old and worn cotton dishtowels (often not replaced for many days) may be used in a circular motion to clean up spills or soils on kitchen countertops, this approach cannot be employed for separative enclosures or clean environments in general. Neither the wiping material nor the wiping action would be appropriate for isolators and safety cabinets. The kitchen counter may look clean - in fact, it may appear clean enough to eat on - but it is still not clean enough for the contamination requirements of a separative enclosure or critical environment. The wiping action puts the fabric in intimate contact with the surface, allowing the application of strong physical forces for the removal of contaminants such as bioburden. Wiping has a long and successful history for removal of contaminants from cleanroom surfaces. However, to be successful, the wiper must be used properly. The table below addresses the primary concerns in the use of wipers and mops for critical cleaning and provides corresponding best practices with explanations. This information is also summarized in the wiping guide *(Figure 4)*.



Figure 4. *Wiping Guide. Wiping Guide posters are available on our website at www.texwipe.com*

Concern	Best Practice	Comment
Effective removal of surface soils	Select wiping material that entraps soils Fold wiper in quarters Use appropriate cleaning agent	Soils are collected in the fabric and discarded with the wiper Ensures full contact of wiper to surface Cleaning agent must be compatible with materials of construction used in isolators or safety cabinets
Re-contamination of surfaces already cleaned	Select non-linting fabrics Wipe in linear, overlapping strokes from clean area to dirty area Refold wiper to expose fresh wiper surface after each stroke	Prevents contamination of wiped surface from particles and fibers from wiper fabric Wipe vertical surfaces from top to bottom Circular wiping action re-contaminates area just cleaned Prevents re-deposition of contaminants picked up on previous stroke
Deposition of residues from cleaning and disinfecting agents	Remove residues with wipers wetted with deionized water or 70% IPA solution	Ensures that bare surfaces are disinfected and that unsightly corrosive residues do not accumulate
Cleaning effectiveness	Surfaces should be free from visible contaminants after cleaning	Illuminating surface with high intensity light or blacklight at oblique angle will help to identify soils not removed Examine the last wiper in contact with the surface to verify absence of visual

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