I T W T E X W I P E

TechNote ICT-2

Cleaning of Pharmaceutical Isolators

Pharmaceutical Isolator

I. Overview

Pharmaceutical isolators are used to conduct
(i) aseptic filling operations,
(ii) sterility testing,
(iii) cell culturing and
(iv) purification activities
within pharmaceutical manufacturing facilities. Pharmaceutical isolators provide physical isolation of manufactured products from contamination from the background environment — the room outside the isolator — and they represent the cleanest area of the entire manufacturing facility. They are classed as Grade A ISO Class 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.

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

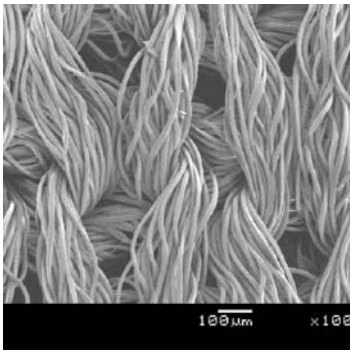
II. Cleaning and Disinfecting Pharmaceutical Isolators

a) 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 that are not bound to the fabric surface or that are broken free during the cleaning process. 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 and cellulosics, synthetic materials such as polyester, nylon, polypropylene or 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. Further, polyester knit fabrics can be sterilized by autoclaving or by gamma 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 will not 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 with sterile 70% isopropyl alcohol (IPA[1])), or to provide clean work surfaces. These wipers can be wetted with
(i) detergents to clean the isolator,
(ii) deionized water or 70% IPA to remove cleaning agent residues,
(iii) disinfecting agents to disinfect the isolator and
(iv) deionized water or 70% IPA to remove disinfectant residues.

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

b) 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 begun (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 sanitization of the isolator interior with sterile wipers and/or mops wetted with sterile 70% IPA may be sufficient to ready the isolator for production. Decisions on cleaning/disinfecting frequency and procedures are the province of the Quality Supervisor.

c) 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, etc. — must be introduced through an appropriate transfer device. Even if a facility's standard operating procedure (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. This also eliminates the confusion of having both sterile and non-sterile wipers on hand and eliminates 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 articles that are introduced into the transfer device for use within the isolator. This will remove surface contaminants that might otherwise compromise disinfection or sporicidal treatments.

(i) 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 application.

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 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 to use. The detergent is applied to the surface in the manner described in Section V "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 beyond arm's reach.

Figure 1. *Isolator cleaning tool in use*

Detergents also have the benefit of reducing the bioburden level on the surface; this lessens the task somewhat for the subsequent disinfection step.

(ii) 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. 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 residues.

[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.

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

(iii) 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 sterilants such as sodium hypochlorite (bleach), peracetic acid and hydrogen peroxide will be substituted for disinfectants when sporicidal activity is needed. These sterilants can be corrosive to surfaces and are therefore used intermittently. Again, isolator cleaning tools and wipers are used as described Section (i).

(iv) Rinsing Following Disinfection

The same procedure is followed here as in Section (ii). Disinfecting agent residues are wiped from the surface with wipers or isolator cleaning tools that have been wetted with sterile deionized water or sterile 70% IPA. 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.

v) 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).

vi) Cleaning Validation

Surface sampling with swabs to verify the absence of cleaning and disinfecting agents may be required after step (iv). See ITW Texwipe's publications on cleaning validation[4] (Figure 2) and the ITW Texwipe Swabbing Guide (Figure 3) for additional details.

Figure 2. *ITW Texwipe publications on cleaning validation*

This constitutes the "post clean" described in the Cleaning Frequency Section. An identical series of steps would be followed for a "pre clean" operation, except that if surfaces have not been contaminated since the "post clean", only disinfection, rinsing and perhaps gaseous sterilization may be needed. Again, the Quality Supervisor determines what cleaning and disinfecting steps are required for any given circumstance.

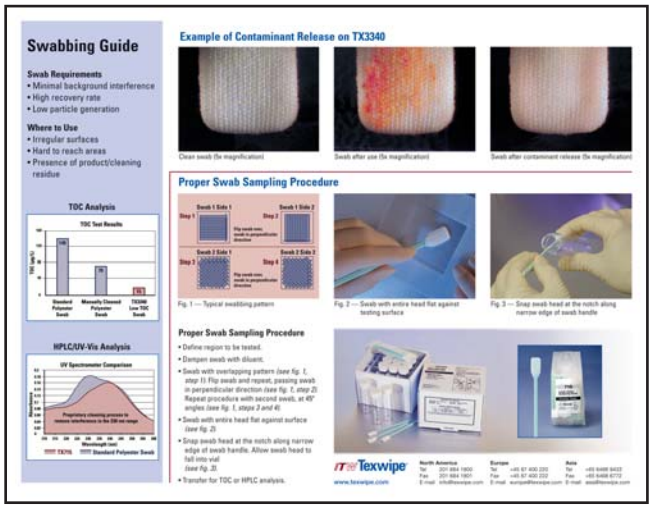


Figure 3. *Swabbing Guide*
Swabbing Guide posters are available on our website at www.texwipe.com

[2] Use phenolics or quats, never both together.
[3] K Miscioscio, "Choosing the Correct Swab for Cleaning Validation," *CleanRooms (Pharmaceutical Supplement)*, January 1997.
DW Cooper, "Using Swabs for Cleaning Validation: A Review," *Special Report on Cleaning Validation*, 1997.
DW Cooper, K Miscioscio, S Weitzel, "How Clean is Clean? Sampling Techniques and Issues for Cleaning," *Pharmaceutical Formulation & Quality*, July/August 1999.
H. Siegerman, M. Strauss and W. Hollands, "How to Succeed in the Search for Nothing: Effective Swabbing Techniques for Cleaning Validation," *Steril Technik*, Volume 1, 2006.

III. Cleaning Tasks and Recommended Products

Following is a table of cleaning and disinfecting activities performed on CAIs and the recommended ITW Texwipe products for those tasks.

Cleaning Task	Recommended Products
Cleaning and disinfecting of interior walls, ceiling and deck of closed isolators	Use one or more of the following: 1. **TX7101 Mini AlphaMop™ Isolator Cleaning Tool** with **TX7114 Mop Covers** to reach all interior surfaces of the isolator. Sterilize the TX7101 isolator cleaning tool and TX7114 mop covers before introducing them into the isolator. Dampen the mop covers with sterile WFI, sterile DIW, **TX3270 Sterile IPA**, detergent cleaning solution, disinfectant solution or liquid sterilant as described in section II. 2. **TX3252, TX3280 or TX3285 Sterile AlphaSats®**, containing sealed-border polyester knit wipers, pre-wetted with 70% sterile-filtered IPA and gamma-irradiated. 3. **TX3215, TX3212 or TX3211 Dry SterileWipes™** containing gamma-irradiated polyester knit wipers. Dampen the wipers with the solutions described in 1 above, as appropriate for the cleaning task at hand. 4. **TX714A Swabs** for cleaning hard to reach spaces or isolator corners. TX714A swabs can be dampened with one of the solutions described in 1 above.
Cleaning up spills while isolator is in use	TX3215, TX3212 or TX3211 SterileWipes for absorbing spilled liquid, then TX3252, TX3280 or TX3285 Sterile AlphaSats for removing surface contamination.
Wiping mating and sealing surfaces between transfer isolator(s) and main isolator	TX3252, TX3280 or TX3285 Sterile AlphaSats
Wiping down articles before placing them in the transfer isolator	TX3252, TX3280 or TX3285 Sterile AlphaSats
Validation of isolator cleaning	**TX3340 TOC Validation Kit** .

TX7101 Mini AlphaMop™ Isolator Cleaning Tool

TX7114 Mop Covers

TX3270 Sterile IPA

TX3252, TX3280 and TX3285 Sterile AlphaSats®

TX3215, TX3212 and TX3211 SterileWipes™

TX714A Large Alpha® Swab

TX3340 TOC Validation Kit

IV. Detailed Product Descriptions

TX7101 Mini AlphaMop™ Isolator Cleaning Tool

The ITW 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 Tool 1 polyester foam pad 6 polyester mop covers	1 mop/case 2 handles (18" and 24")
TX7114	Mini AlphaMop™ covers AlphaWipe® replacement mop covers	150 mop covers/case 25 covers/inner bag 6 inner bags/case 6 foam pads/case

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

This product is used for convenient dispensing of sterile 70% IPA 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 Wipers

ITW Texwipe SterileWipe™, incorporating polyester knit wipers gamma-irradiated to an SAL of 10^{-6}, are recommended for the cleaning and disinfection of CAIs. These wipers are used during production to clean up spills, or to provide clean work surfaces. When wetted with sterile 70% IPA, they can be used to clean surfaces or to wipe down gloves during production. These wipers can be wetted with:

(i) detergents to clean the isolator,
(ii) deionized water or 70% IPA to remove cleaning agent residues,
(iii) disinfecting agents to disinfect the isolator and
(iv) deionized water or 70% IPA to remove disinfectant residues.

SterileWipe™ Selection Guide*

Product Number	Product Name	Wiper Characteristics	Selection Criterion
TX3215	SterileWipe™ AS 10	12" x 12" (31 cm x 31 cm) two ply, sealed-border polyester knit	Highest absorbency Low particle and fiber levels
TX3212	SterileWipe™ LP 10	12" x 12" (31 cm x 31 cm) single ply, sealed-border polyester knit	Moderate absorbency Lowest particle and fiber levels
TX3211	SterileWipe™ LP	9" x 9" (23 cm x 23 cm) single ply, cut-edge polyester knit	Moderate absorbency Cut edges contribute to higher fiber levels Most economical

*Another sterile wiper, TX3210 SterileWipe™ HS II, made of blended polyester-cellulose is also available, but it is not generally recommended for isolator cleaning because of its higher particle and fiber burden compared to the polyester knit wipers shown above.

Sterile Wipers Pre-Wetted with 70% IPA

The following pre-wetted wipers are all polyester knit, laundered, pre-wetted with 0.2 µm-filtered 70% IPA, then gamma-irradiated to a Sterility Assurance Level of 10^{-6}. These wipers eliminate the need to use sterile 70% IPA in the isolator and are used during production to clean up spills or to wipe down gloves. These wipers are also used to remove cleaning and disinfecting agent residues or to sanitize surfaces just prior to production. Note that WFI is used in place of DIW in the TX3280 below.

Sterile AlphaSat® Selection Guide*

Product Number	Product Name	Wiper Characteristics	Selection Criterion
TX3252	Sterile AlphaSat® with AlphaSorb® HC	12" x 12" (31 cm x 31 cm) two ply, cut-edge polyester knit	Delivers largest amount of 70% IPA of the three choices Low particle and fiber levels
TX3280	Sterile AlphaSat® 10 with WFI	12" x 12" (31 cm x 31 cm) single ply, sealed-border polyester knit	Wetting solution is 70% IPA / 30% WFI Lowest particle and fiber levels
TX3285	Sterile AlphaSat® 10	9" x 9" (31 cm x 31 cm) single ply, sealed-border polyester knit	Smallest wiper of the three choices Wipers are individually folded in half, then stacked before pre-wetting and packaging Lowest particle and fiber levels Most economical

*Another sterile pre-wetted product, TX3217 Sterile TechniSat® HS II, incorporating blended polyester-cellulose wipers is also available, but it is not generally recommended for isolator cleaning because of higher particle and fiber burden compared to the polyester knit wipers shown above.

TX714A Large Alpha® Swab

Incorporates AlphaLite® polyester knit fabric thermally bonded to a polypropylene handle. Ideal for cleaning hard-to-reach spaces, crevices, nooks, crannies and isolator corners. Ideal for performing final sampling to verify absence of visible residues. Packaged 50 swabs per inner bag; 2 inner bags per outer bag.

TX3340 TOC Validation Kit

Sampling Kit for Cleaning Validation for use with TOC Analyzers

Kit Components

12 – 40 ml clear vials with bonded septa caps, certified <10 ppb TOC
24 – TX714K Large SnapSwabs™, certified <50 ppb TOC
12 vial labels

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. 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[4] — but it is still not clean enough for the contamination requirements of a separative enclosure.

The wiping action puts the fabric in intimate contact with the surface, allowing the application of strong 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

[4] This probably speaks more to the tolerance of the human body for environmental bacteria than the apparent cleanliness of the counter.

Critical Cleaning with Wipers and Mops

Concern	Best Practice	Comment
Effective removal of surface soils	Select wiping material that entraps soils	Soils are collected in the fabric and discarded with the wiper
	Fold wiper in quarters	Ensures full contact of wiper to surface
	Use appropriate detergent or other cleaning agent	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	Prevents contamination of wiped surface from particles and fibers from wiper fabric
	Wipe in linear, overlapping strokes from clean area to dirty area	Wipe vertical surfaces from top to bottom Circular wiping action re-contaminates area just cleaned
	Refold wiper to expose fresh wiper surface after each stroke	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 at an oblique angle will help to identify soils not removed Examine the last wiper in contact with the surface to verify absence of visual contaminants on the wiper

ITW Texwipe®

North America
ITW Texwipe
300 B Route 17 South
Mahwah, NJ 07430
Tel (800) TEXWIPE ext 120
(201) 684-1800 ext 120
Fax (201) 684-1801
www.texwipe.com

Europe/Middle East
ITW Contamination Control
Skejby Nordlandsvej 307
DK-8200 Aarhus N
Denmark
Tel +45 87 400 220
Fax +45 87 400 222

Asia/Pacific
ITW Singapore
50 Tagore Lane
#02-01 Markono
Distri Centre
Singapore 787494
Tel +65 6468 9433
Fax +65 6468 6772