Guidance on Gloves maintenance in Isolator and RABS

Proactive measures to ensure sterility assurance

A faulty glove or sleeve assembly represents a route of contamination and a critical breach of isolator integrity. Within this article we will discuss about all these aspects.

Palash Chandra Das

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From The Author's Desk

Dear Readers,

Through PRES we are trying to connect with the Global Pharma community. Where we discussed, share and explore lots of pharmaceutical hot topics. Being a Pharma professional it is very difficult to get time for own to do something different other than routine responsibilities. Hope you all paraprofessionals are agreed with my views.

That's you, the readers and followers of my blog, who always encouraged me a lot to do something different than my routine schedule. All the information are easily available web media, I am just trying too collating all those information in a single article.

I have collated the information's broadly from the major regulatory guidance document including FDA, PIC,s, MHRA and other pharmaceutical knowledge resources like ISPE , PDA Etc.

Once again I would like to thanks my readers, followers and seniors, who has encourage me a lot.

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INTRODUCTION

To reduce the size of the class 100 areas, Isolator technology was integrated into the facility. Isolator technology ensures environmental control and reduces contamination risk during aseptic processing.

Key features of this filling system include mass flow technology and a filtration skid that can be cleaned and sterilized in place. In addition to accommodating lyophilized vials, isolator technology offers Lyophilization capability. Isolator provided high level of assurance to maintain your product sterility. Gloves leakages play a major role for breaching integrity of isolator and potential cause for sterility failure.

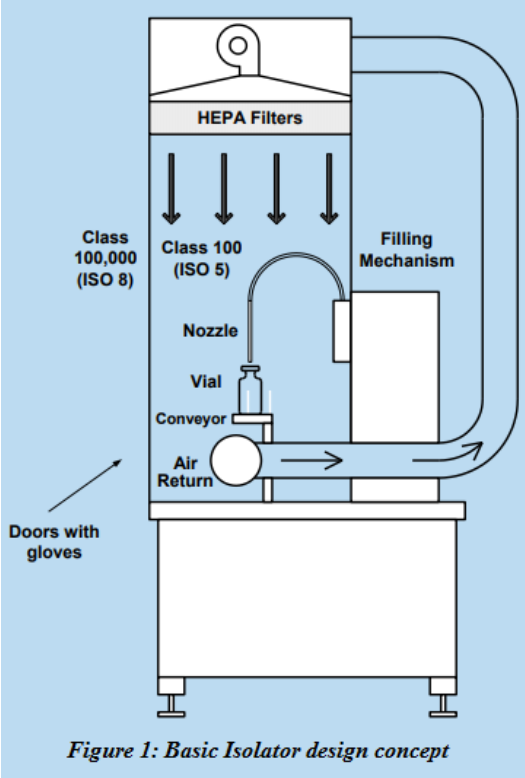


Figure 1: Basic Isolator design concept

The control of leaks in between the isolator and surrounding room and between different parts of the isolator system as necessary should be assured as far as possible. As a guide a minimum of 10 Pascal positive differential air pressure should be maintained to protect against unforeseen circumstances. The maintenance of positive pressure should be monitored and fitted with an alarm system. It will enhance the controls over the sterility assurance.

In this article we will elaborate the all technical aspect for failure of gloves integrity,

Key technical pointes includes- Glove structure, holes types and testing methodology

We will be clarifying following questions, which are generally come into our mind.

- *What is the physical structure of a glove?*
- *Where do failures typically occur?*
- *What can be considered a "reasonable hole size" for testing?*
- *At what pressure should I test?*
- *How long does it take / should it take?*

OPERATIONAL CONCEPT

In recent years, Glove Integrity Testing has been profoundly discussed and numerous articles have been written on this topic. However, many doubts still remain within the industry due to the lack of norms and clear guidance available.

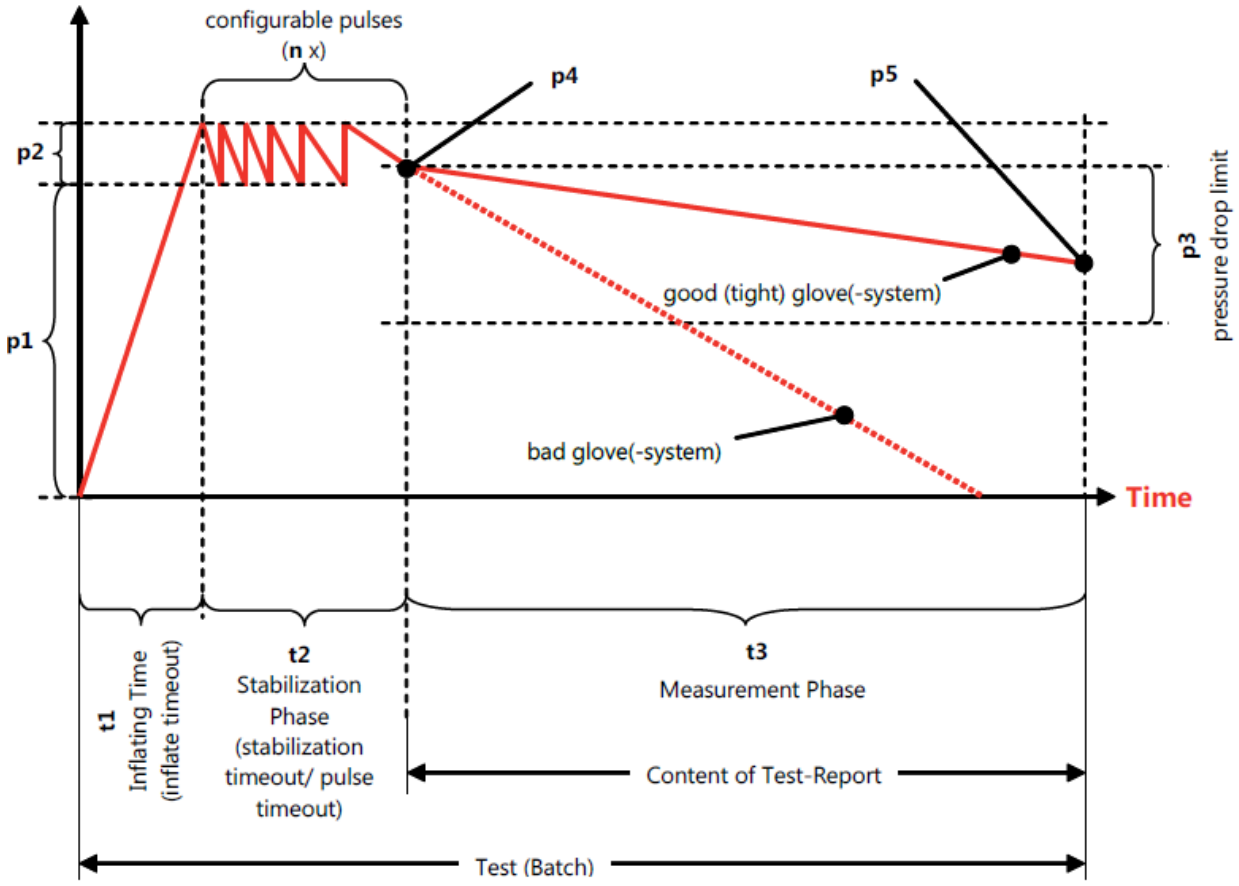
The physical integrity test with the gloves integrity tester is totally automated now a days and it is possible to test several independent glove simultaneously. Integrity of the glove is determined by the air tightness respectively by the ability to hold the pressure.

Principle of measurement is the "pressure change method" (e.g. described in ISO 10648-2). The method consists of measuring the pressure decay per unit time after isolating the glove at a positive pressure. Based on the resulting pressure decay per time and the requirements for the routine testing parameter have been finalized.

Main function of gloves integrity split in to three phases, All the phase are mentioned below,

Phase	Description
Prephase	Inflation of the test cover seal.
Phase 1	**Inflation phase:** In this phase the glove(-system) will be inflated to target pressure level. After set value is reached the stabilization phase starts.
Phase 2	**Stabilization phase:** In this phase the glove will be regenerated and stabilized by controlling the pressure within a defined time. After phase time is elapsed the measurement phase starts.
Phase 3	**Measurement phase:** In this phase the pressure decay per unit time of the glove is measured over the defined measurement time.
Postphase	Documentation of test results with a test corresponding report.

The diagrams as follows show schematically the process of the SKAN WirelessGT ® with the help of physical values: the differential pressure [Pa] (ordinate) during different phases to phase times [sec.].



Parameter	Description	Impact
t0	Inflating time to bring test cover seal to set pressure.	Sealing/closing of test volume to environment. Relevant for correct end position of test cover within glove port.
t1	Inflating time to bring glove(-system) to set pressure.	Parameter for initial and controlled test pressure of the specimen (parameter is specific to specimen material).
t2	Stabilization time to maintain stable condition of specimen. Duration stabilization phase.	Parameter with direct impact to the coordinated stretching/elongation of the glove(-system). Compensation of thermal ingress, stress-deformation behaviour of the glove(-system).
t3	Acceptance criteria [sec.] for defined glove(-system). Duration measurement phase.	Parameter with direct impact to the statement tight or not tight glove. In best case, based on the recommendation of Skan.
n	Number of pulses	Parameter with direct impact to the coordinated stretching/elongation of the glove(-system). Compensation of thermal ingress, stress-deformation behaviour of the glove(-system).

Parameter	Description	Impact
p00	Threshold value of built in seal.	Alerting parameter and informative indicator for the user.
p0	Set pressure of built in seal.	Sealing/closing of test volume to environment.
p1	Test/ start pressure [Pa] (pressure control level during stabilization phase).	Parameter with direct impact to the coordinated stretching/elongation of the glove(-system).
p2	Hysteresis value for the two-level controller during stabilization phase.	Parameter for correct function of pressure controller. Limitation to mimimum hysteresis.
p3	Acceptance criteria [Pa] for defined glove(-system). Pressure decay per time unit (parameter t3).	Parameter with direct impact to the statement tight or not tight glove. In best case, based on the recommendation of Skan.
p4	Start pressure at start measurement phase.	Value with direct impact to the statement tight or not tight glove. Recorded in system for comparison to acceptance criteria [p3].
p5	End pressure at the end of measurement phase	Value with direct impact to the statement tight or not tight glove. Recorded in system for comparison to acceptance criteria [p3].

The pressure decay (p5 - p4) per unit time (t3) will be monitored during the measurement phase.

If this value is less than the pressure drop limit (p3), the tested glove will be released.

This is the basis of the test recipe is explain elaborately to understand the pressure decay method. It always preferred before going to establish the parameter of integrity testing, we should understand the logic behind the experiment.

ADDITIONAL CONTROLS MEASURES

- *A breach of isolator integrity should normally lead to a decontamination cycle.*
- *Integrity can be affected for following reasons but not limited to, by power failures, valve failure, inadequate overpressure, holes in gloves and seams, or other leaks.*
- *An environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particle levels, within the isolator.*
- *A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. A preventative maintenance program should be established.*
- *The choices of durable glove materials, coupled with a well-justified replacement frequency, are key aspects of good manufacturing practice to be addressed.*
- *With every use, gloves should be visually evaluated for any macroscopic physical defect. Training and qualifying operators for visual inspections*
- *(essential, and keeps detection rates high)*
- *Physical integrity tests should also be performed routinely.*
- *Affording attention to the sanitary quality of the inner surface of the installed glove and to integrating the use of a second pair of thin gloves.*

Top Ten Gloves management tips:

1. Glove Cleaning
2. Glove Disinfection
3. Use of "under-gloves"
4. Procedure for Glove Entry and Exit during operation
5. Glove Visual Inspection
6. Glove Mechanical Testing (Glove Leak Tester)
7. Environmental Monitoring of Glove Surfaces and Personnel
8. Glove/Sleeve Change-Frequency
9. Documentation of Glove Maintenance / Log-Books
10. Product Disposition and Investigation Procedure for Glove Deviations

QUALITY RISK MANAGEMENT

Identification of Hazards and Scenarios	*Cause of the hazards*	*Potential effect of failure*	*Severity (S)*	*Frequency (F)*	*Current control/ Mitigation Strategy*	*Detection (D)*	*Risk Score*
Performed Gloves integrity within the Isolator System	*A. Leakage from gloves* *B. Integrity Failed*	*Risk of sterility failure*	High	Low	• *Gloves integrity test performed with approved written procedure with establish test parameter and predefine recipe.* • *Visual verification shall be performed before starting of gloves integrity as a part of pre-checks as per procedure.* • *As a part of production clearance procedure gloves integrity test result has been re-verified before initiating VHP cycle by supervisor or quality assurance personnel.* • *Post gloves integrity test shall be carried out after manufacturing activity to verify any possibility of breaches during manufacturing activity.*	High	Low
	C. Improper sanitization	*Risk of sterility failure*	High	Low	• *Gloves shall be sanitized frequently with validated disinfectant during process as in when required.* • *Inner surface of installed gloves should to be sanitized or wipe with scheduled disinfectant.* • *During batch operation operator must put hand into gloves port by wearing sterile gloves in hand after sanitized with validated disinfectant.*	High	Low
	D. Material Transfer within the isolator	*Risk of sterility failure*	High	Low	• *Precaution taken not to handle any sharp material within the isolator or sharp edge identified with in the filling machine or isolator interior part.*	High	Low
	E. Improper practices	*Risk of sterility failure*	High	Low	• *Operation should to be trained enough to handle the gloves during activity.*	High	Low

Identification of Hazards and Scenarios	*Cause of the hazards*	*Potential effect of failure*	*Severity (S)*	*Frequency (F)*	*Current control/ Mitigation Strategy*	*Detection (D)*	*Risk Score*
Performed Gloves integrity within the Isolator System	*F. Insufficient exposer in H_2O_2 during VHP decontamination*	*Risk of sterility failure*	High	Low	• *Dummy hand Stands should to be fixed in to gloves port to stretch the gloves for better VHP exposer on the gloves surfaces.* • *VHP(Vaporized Hydrogen Peroxide)/Decontamination cycle should to be validated in presence of Biological indicator.* • *Discoloration of gloves color is the indication of gloves ageing, ensure replacement of gloves once observed as discolored.*	High	Low
	G. Improper or inadequate maintenance	*Risk of sterility failure*	High	Low	• *Schedule preventive maintenance program carried out for gloves integrity tester.* • *Gloves replacement frequency is established based on rational before they break down or degrade.* • *Replace of gloves should considered both the cases number of days the gloves was used and number of batches conducted with same gloves.* • *Any failure to gloves integrity shall be investigated for its root cause.* • *Ensure specifications of gloves are same with replaced one and change in the gloves specification should to be evaluated.*	High	Low

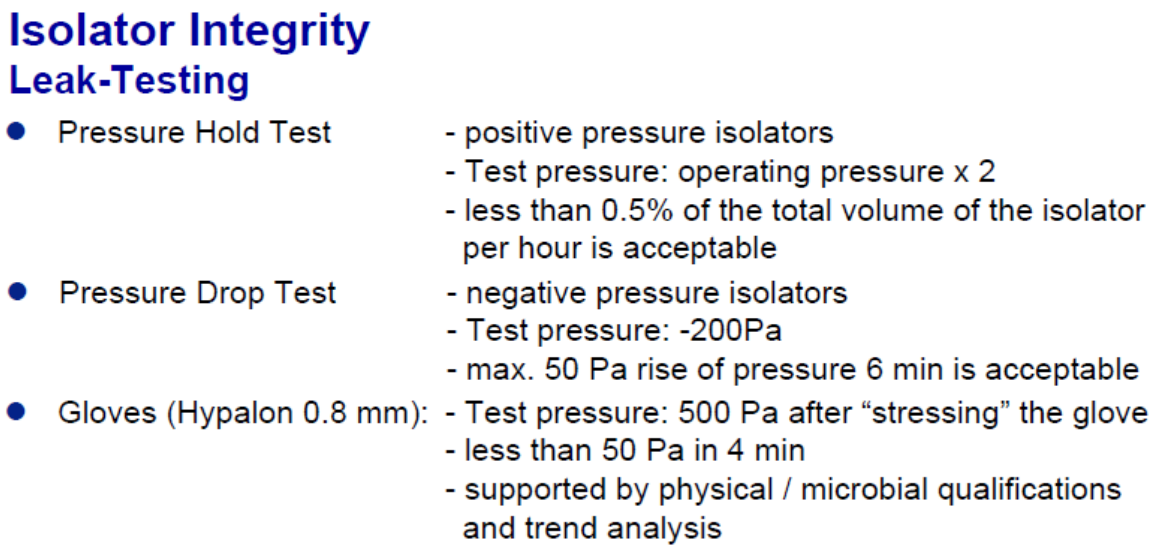
Table 1: *An assessment to identify the inherent risk lies with the Gloves integrity with the Isolator system*

The integrity is a critical part of batch manufacturing activity; it is a largest contributing factor for sterility failure. The question is failure gloves can be sent for repeated integrity test for confirmation. With the presence of supervisor or service engineering personnel test can repeat once again to confirm the leakage. As per the risk assessment in the Table1 it was identified that severity lies with the gloves integrity is very High, as it was directly contributing the risk in patient safety. But based on the control strategy or mitigation proposed in the risk assessment the detect ability is become high, therefore the probability of occurrences become low. So, ensure all the controls are explained in the mitigation strategy are incorporated to your procedure.

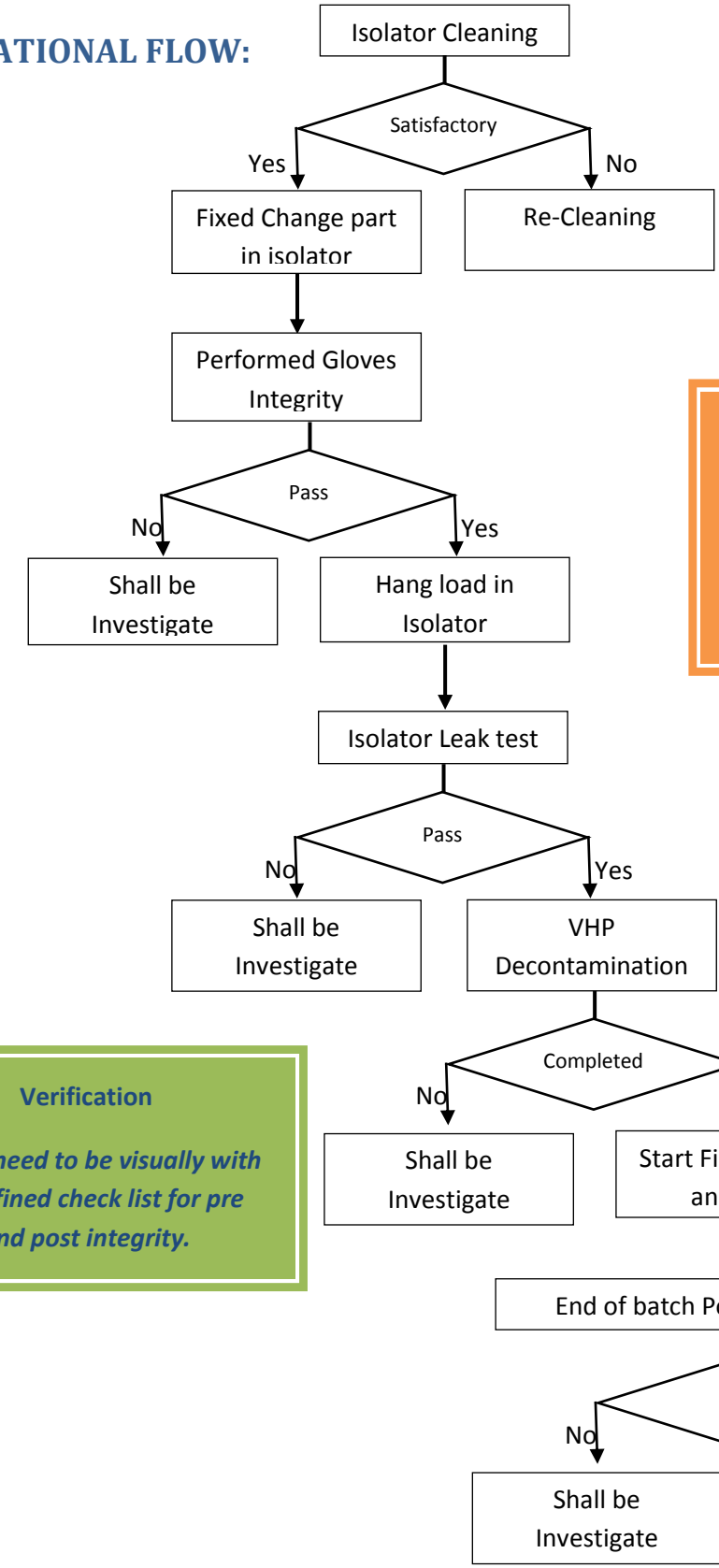
Chang of gloves material need to be justified that that has no impact on the establish recipe. Any changes in the recipe shall be performed under the supervision of subject matter expert, challenge study need to be documented.

When we are elaborating the leak testing, we should not forget that the three important aspect of integrity testing in Isolator,

Apart from the gloves testing Isolator leak test also contributing a major role in sterility assurance, pressure hold test in case of positive isolator and pressure drop test in negative isolator are recommended. Negative pressure isolator is usually considered for human safety, in case of API dispensing or IPQC or sampling isolator.



OPERATIONAL FLOW:



Handling of failure

Handling of GIT failure need to be properly documented and to be reviewed and investigated to identify the root cause.

Verification

Gloves need to be visually with predefined check list for pre and post integrity.

CONCLUSION

- *A program to minimize the risk of loss of integrity of gloves, sleeves and suits should be present. This should include operator practices, vigilance and the absence of sharp edges. There should also be an all encompassing preventative maintenance program that includes specification of examination and preemptive replacements.*
- *A breach in glove integrity can be of serious consequence. Every failure should to be evaluated for the direct and indirect impact on the sterility. If it is determined that the environment may have been compromised, any product potentially impacted by the breach should be rejected.*
- *Proper corrective and preventive actions should to identified and implemented to prevent repeated occurrence of events.*
- *The periodic monitoring and well structured maintenance program will eliminate the chance of glove integrity; it will minimize the possibility of placing a sterile product at risk.*

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