



PUPSIT

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What is PUPSIT?

Pre-Use Post-Sterilization Integrity Testing (PUPSIT)

Presentation main topic points

1. Current regulatory agency view point
2. Rational for performing PUPSIT
3. How to perform PUPSIT
4. Risk assessment for PUPSIT

In 2002 it was already in the TGA GMPs

T G A

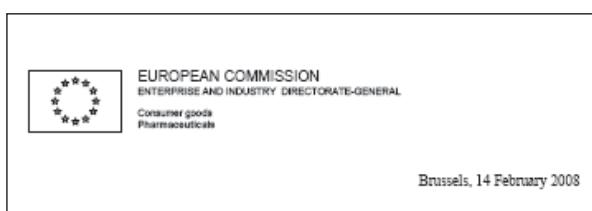
THERAPEUTIC
GOODS
ADMINISTRATION



AUSTRALIAN CODE OF GOOD
MANUFACTURING PRACTICE FOR
MEDICINAL PRODUCTS

16 August 2002

85. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences during routine manufacturing from this should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.



EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products

113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

16/09/2019

page 6

Also in the WHO GMPs from 2011

WHO Technical Report Series, No. 961, 2011

Annex 6

WHO good manufacturing practices for sterile pharmaceutical products

7.7 The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from these during routine manufacturing should be noted

ISO (International Organization for Standardization) anno 2003

INTERNATIONAL STANDARD

ISO 13408-2

First edition
2003-03-15

Aseptic processing of health care products —

Part 2: Filtration

*Traitemen aseptique des produits de santé —
Partie 2: Filtration*

8.10 The filtration system should be designed to permit in-place integrity testing as a closed system prior to filtration.

Care should be taken not to compromise the sterility of the filter.

9.5 The validated physical integrity test of a sterilizing filter shall be conducted after each use without disturbing the filter in its housing. Physical integrity testing of a sterilizing filter *in situ* should be conducted before use after sterilization where the design of the filtration system permits.

Care should be taken not to compromise the sterility of the filter.

PIC/S



PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

RECOMMENDATION
ON THE

PI 007-6
1 January 2011

VALIDATION OF ASEPTIC PROCESSES

9.5.2 In addition to the validation of the filter type the integrity of each individual product filter used for routine production should be tested before and after use.

9.6 Vent Filters

9.6.1 It is important that the integrity of critical gas and air vent filters is confirmed immediately after the filling and if it fails, the disposition of the batch determined. In practice vent filters fail the integrity test more frequently than product filters as generally they are less robust and more sensitive to pressure differentials during steam sterilisation.

Regulatory requirements are not homogeneous worldwide (US FDA)

- FDA
 - 2004 Aseptic Processing Guidelines

**Guidance for Industry
Sterile Drug Products
Produced by Aseptic Processing —
Current Good Manufacturing Practice**

After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filters (e.g., of identical polymer construction and pore size rating) are used in production runs. Sterilizing filters should be routinely discarded after processing of a single lot. However, in those instances when repeated use can be justified, the sterile filter validation should incorporate the maximum number of lots to be processed.

Integrity testing of the filter(s) can be performed prior to processing, and should be routinely performed post-use. It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration. *Forward flow and bubble point* tests, when appropriately employed, are two integrity tests that can be used. A production filter's integrity test specification should be consistent with data generated during bacterial retention validation studies.

Regulatory requirements are not homogeneous worldwide (CFDA)

6.3 “The integrity of the sterilizing grade filter should be verified by proper method after use. Results of these checks should be included in the batch record. An appropriate method includes bubble point, diffusive flow and pressure hold test”

6.3 过滤工艺

【法规要求】

药品生产质量管理规范（2010年修订） 无菌药品附录

第七十五条 非最终灭菌产品的过滤除菌应当符合以下要求：

（一）可最终灭菌的产品不得以过滤除菌工艺替代最终灭菌工艺。如果药品不能在其最终包装容器中灭菌，可用 $0.22\mu\text{m}$ （更小或相同过滤效率）的除菌过滤器将药液滤入预先灭菌的容器内。由于除菌过滤器不能将病毒或支原体完全滤除，可采用热处理方法来弥补除菌过滤的不足。

（二）应当采取措施降低过滤除菌的风险。宜安装第二只已灭菌的除菌过滤器再次过滤药液，最终的除菌过滤器应当靠近灌装点。

（三）除菌过滤器使用后，必须采用适当的方法立即对其完整性进行检查并记录。常用的方法有起泡点试验、扩散流试验或压力保持试验。

（四）过滤除菌工艺应当经过验证，验证中应当确定过滤一定量药液所需时间及过滤器两侧的压力。任何明显偏离正常时间或压力的情况应当有记录并进行调查，调查结果应当归入批记录。

（五）同一规格和型号的除菌过滤器使用时限应当经过验证，一般不得超过一个工作日。

Suggested change from CFDA

Article 25 [Integrity test time] After the sterilization filter is used, the integrity of the filter must be checked and recorded immediately with appropriate method. Prior to use of the sterilization filter, a risk assessment shall be carried out to determine whether the integrity test is to be implemented before or after sterilization. When performing a pre-use integrity test after sterilization, measures are required to ensure sterility of the filter downstream. Commonly used integrity test methods include bubbling point test, diffusion flow/forward flow test or pressure maintenance test.

PDA PUPSIT Task Force

Rationale for Recommendation

Whereas a PUPSIT could provide added assurance of a filter's integrity throughout processing and reduce the risk of product loss, the risk of implementation of such a test must be assessed for each process and manufacturing site. A PUPSIT procedure may result in a higher risk to product quality. Integrity tests of filters after sterilization and pre-use in many cases may increase the actual risk of product contamination due to downstream manipulations and/or the addition of equipment into the downstream process, and this contamination might not be detected afterward. There is no scientific evidence that a non-integral filter pre-use will not be detected by a post-use integrity test.

However, a PUPSIT may provide the opportunity to detect non-integral filters after sterilization and prior to use, thus preventing potential product loss (in case a refiltration is not possible) and preventing introduction of contamination into an aseptic area.

New Annex 1 draft

The new draft of Annex 1 is not considered by inspectors to bring any paradigm change or any revolutionary new ideas, but it clarifies many things and introduces things that should already be in place including PUPSIT.

The PUPSIT will most probably become a regulatory requirement worldwide. Even the US will be concerned but this will take time...

There may be an approach in the future to demonstrate that for specific applications PUPSIT is not required.

16/09/2019

page 14

Rational for performing PUPSIT

1. Broken membrane due to sterilization?

- Possible, but this kind of failure would be detected by the post use testing.
- A sterilizing grade filter can typically withstand up to 25 SIP cycles ⇒ It is very unlikely that a validated and monitored within specification SIP disrupts the membrane.

Rational for performing PUPSIT

2. A minor failure on the membrane could be masked by filter blocking

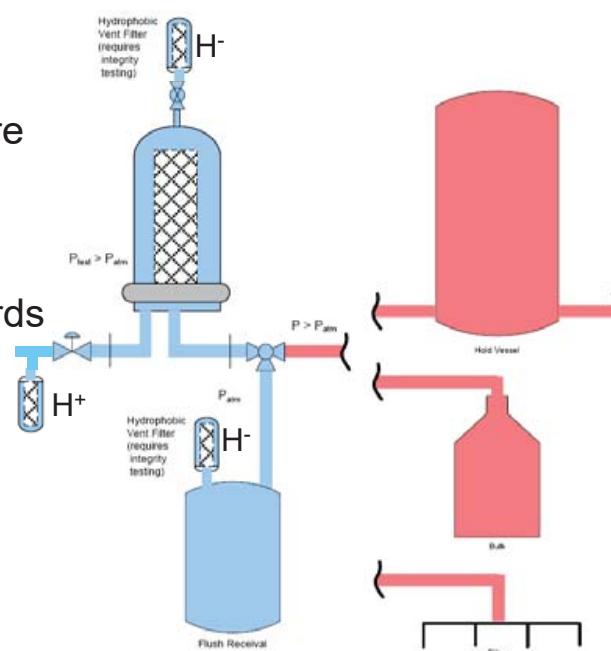
- In theory possible, but extensive SSB trials have showed that even when clogging of the membrane takes place a broken membrane is still detected as such after filtration (publication submitted by M. Jornitz and M. Stering, publication date TBA).
- In addition the last filtration step must not cause filter blocking.
- The post use test must be performed immediately after use to avoid precipitation or denaturation of product.

17

PUPSIT - Stainless steel

Pros:

- No real constraints in terms of pressure resistance due to hard piping.
- Wetting liquid can be evacuated towards a large sterile vented vessel.
- The installation may be automated.



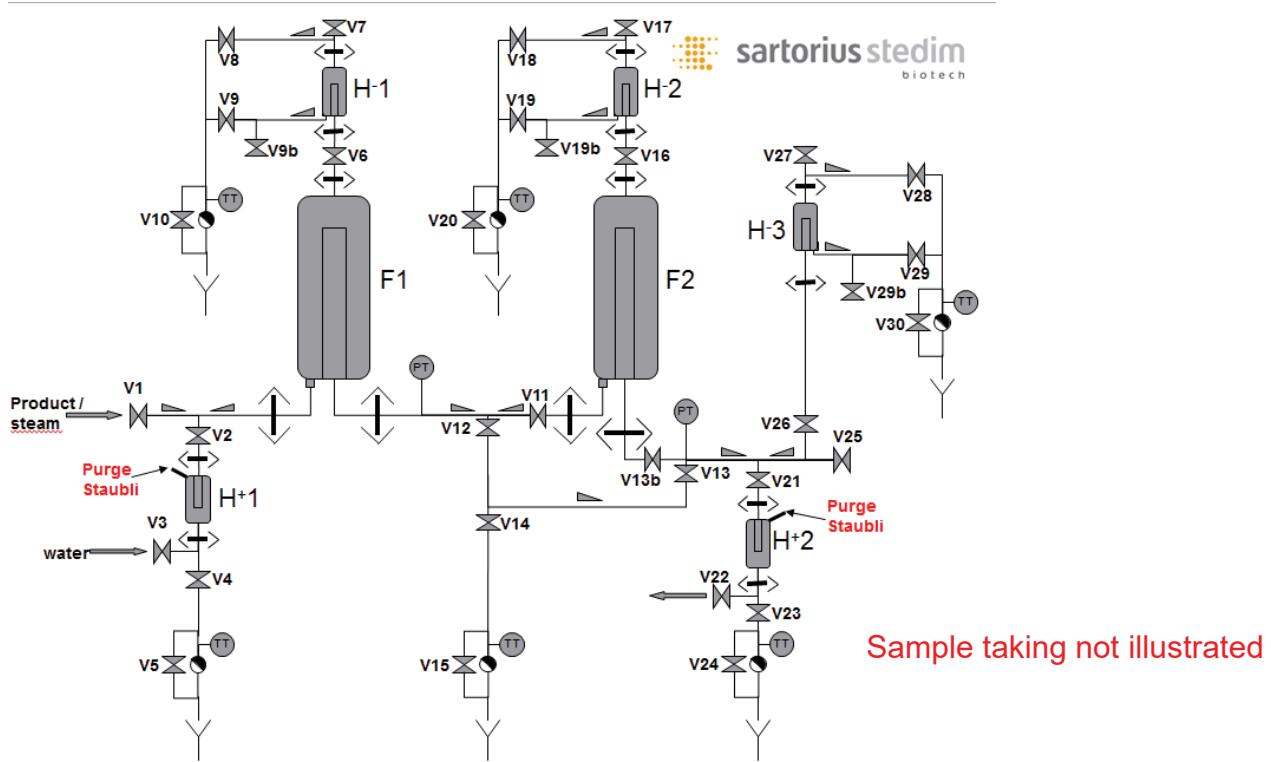
PUPSIT - Stainless steel

Cons:

- The protective filters have to be tested. Should they be tested pre or post use of the product filter?
- Risk of dilution of drug product unless the filter is dried or the first volume is discarded.

20

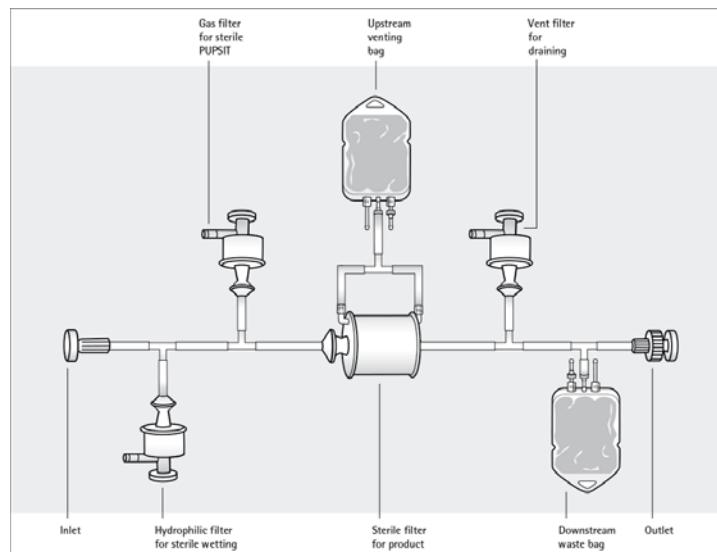
...and in stainless steel...



PUPSIT - Single Use System (SUS)

Pros:

- The installation may be automated in the future = risk reduction



22

PUPSIT - Single Use System (SUS)

Cons:

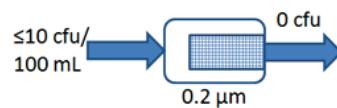
- Difficult handling and complex setup = risk for operator mistakes.
- Pressure constraints.
- Limited wetting volume due to bag size.
- The protective vent filters have to be tested. Should they be tested pre- or post use of the product filter?
- Risk of dilution unless the first volume is discarded; the filter can not be dried easily.

23

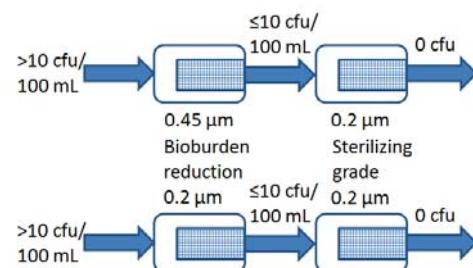
The delivery of PUPSIT also depends on the type of final filtration

There are several types of sterile filtration:

- Single step sterile filtration



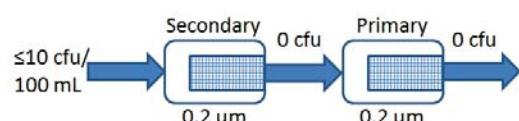
- Single step sterile filtration with bioburden reduction (0.45 or $0.2\mu\text{m}$)



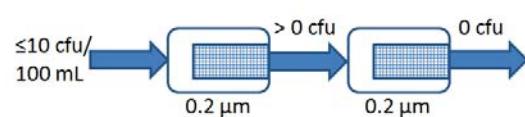
The delivery of PUPSIT also depends on the type of final filtration

Continued:

- Redundant sterile filtration



- Serial sterile filtration

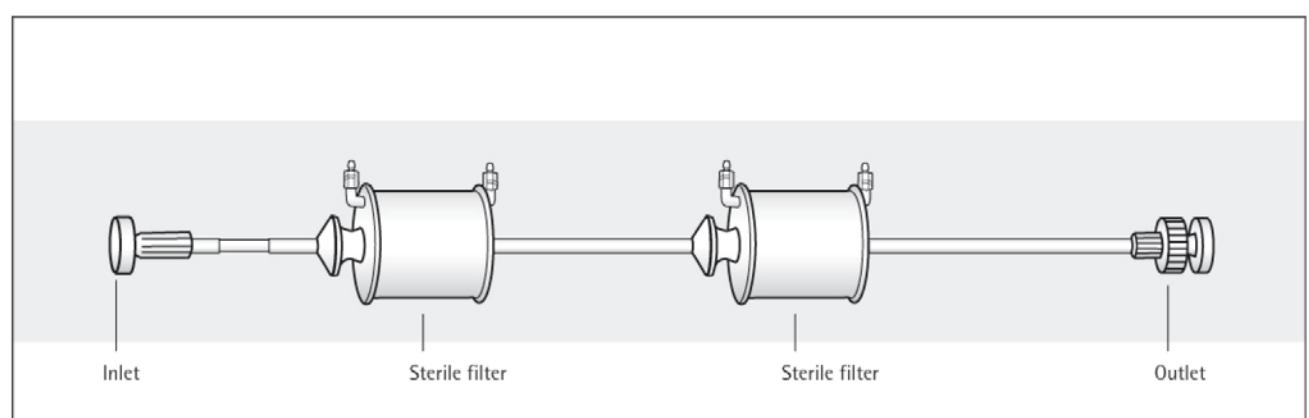


Which filter must be tested?

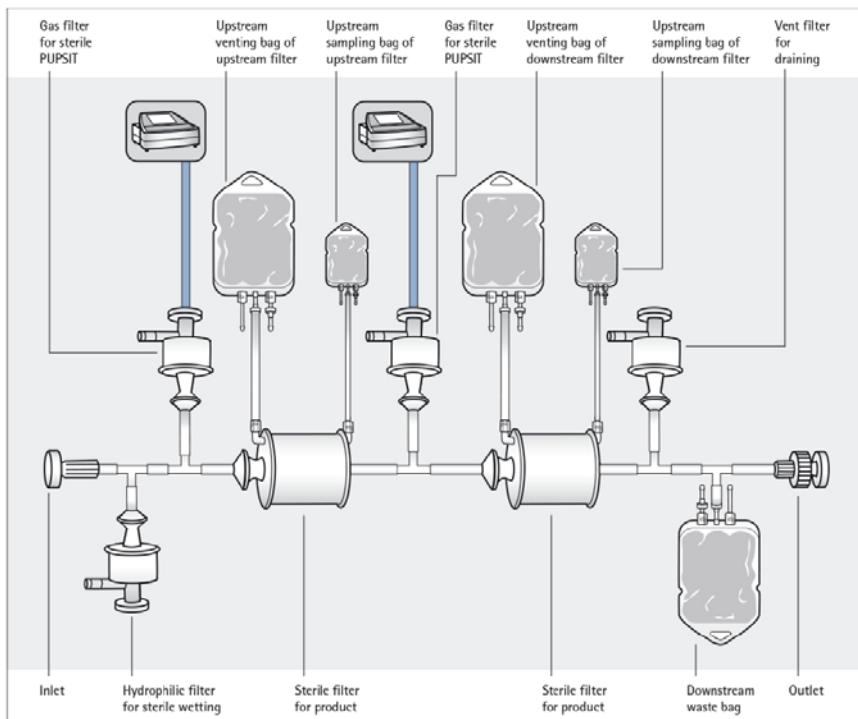
	Single step	BioB. reduction	Redundant	Serial
Before	Only one	Just the sterilizing grade	Both filters	Both filters
After	Only one	Just the sterilizing grade	Both filters	Both filters

Perhaps you want this...

Redundant or serial sterile filtration



...and end up with this



16/09/2019

page 28

Key points to consider when assessing the risk in PUPSIT

- Risk of a "false pass" type result.
- Sterilisation type used for filters?
- False pass in Post Use test due to clogging of filter (main reason for PUPSIT)
- Loss of sterility on downstream
- The PUPSIT introduces more connections and pipe work/tubing
- Failed post use IT of 2 filters (in redundant filtration mode)
- Commercial risk

If you want to know more about PUPSIT and risk assessment...



Risk Assessment for Pre-Use Post Sterilization
Integrity Testing of Sterilizing Grade Filters
(PUPSIT)