protein. The nature and quantity of packaging materials can significantly affect the process.

8.74 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

8.75 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load unless parametric release has been authorized by the National Competent Authority.

8.76 Critical process variables that should be considered as part of sterilization process validation and routine monitoring include, but are not limited to: EO gas concentration, relative humidity, temperature and EO gas pressure and exposure time.

8.77 After sterilization, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a sterilizer chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilization process validation.

Filtration of medicinal products which cannot be sterilized in their final container

8.78 If a liquid product cannot be terminally sterilized by a microbiocidal process, it should be sterilized by filtration through a sterile, sterilizing grade filter (with nominal pore size of 0.22 micron (or less) or with at least equivalent micro-organism retaining properties), and subsequently aseptically filled into a previously sterilized container, the selection of the filter used should ensure that it is compatible with the product, see 8.119.. Suitable bioburden reduction and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the primary sterilizing grade filter. Due to the potential additional risks of a sterilizing filtration process as compared to other sterilization processes, a second filtration through a sterile, sterilising grade filter (positioned as per clause 8.15), immediately prior to filling, is advisable

8.79 The selection of components for the filtration system (including air, gas and vent filters) and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the products, documented and justified. The filtration system should not generate fibres, unacceptable levels of impurities or otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should not be adversely affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (see Single-Use-Systems, Clauses 8.117-8.119).

8.80 The filtration system should be designed to:

a) Allow operation within validated process parameters.

b) Maintain the sterility of the filtrate.

c) Minimise the number of aseptic connections required between the sterilizing filter and the final filling of the product.

d) Allow cleaning procedures to be conducted as necessary.

e) Allow sterilization procedures, including SIP, to be conducted as necessary. The sterilization procedures should be validated to ensure achievement of a target sterilization assurance level (SAL) of 10^{-6} or better (e.g. 10^{-7}).

f) Permit in-place integrity testing, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.

8.81 Liquid-sterilizing filtration should be validated during initial processvalidation. Validation can be grouped by different strengths or variations of a product, but should be done under worst-case conditions. The rational for grouping fluids should be justified and documented.

8.82 Wherever possible, the product to be filtered should be used for bacterial retention testing. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.

8.83 Filtration parameters that should be considered in validation and routine processing should include but are not limited to:

a) If the system is flushed or integrity tested in-situ with a fluid other than the product, then flushing with the product should be part of the process.

b) The wetting fluid used for filter integrity testing based on filter manufacturer's recommendation or the fluid to be filtered. For the latter, the appropriate integrity test value specification should be established.

c) Filtration process conditions including:

i. Fluid prefiltration holding time and effect on bioburden.

ii. Filter conditioning, with fluid if necessary.

iii. Maximum filtration time/total time filter is in contact with fluid.

iv. Flow rate.

v. Filtration volume.

vi. Temperature.

vii. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter. Any significant differences from those validated to those observed during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record.

8.84 The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.

8.85 The integrity of critical sterile gas and air vent filters in the filter assembly should be verified by testing after use. The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals.

8.86 For gas filtration, the avoidance of unintended moistening or wetting of the filter or filter equipment is important. This can be achieved by the use of hydrophobic filters.

8.87 Where serial filtration (one filtration is followed by a subsequent filtration) is a process requirement the filter train is considered to be a sterilizing unit and all sterilizing-grade filters within it should satisfactorily pass integrity testing both before use, in case of damage during processing, and after use.

8.88 Where a redundant sterilizing filter is used, the additional filter does not require post-integrity testing unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing. Bioburden samples should be taken prior to the first filter and the sterilizing filter, systems for taking samples should be designed so as not to introduce contamination.

8.89 Liquid sterilizing filters should be discarded after the processing of a single lot. The same filter should not be used for more than one working day unless such use has been validated.

Form-Fill-Seal

8.90 Form-Fill-Seal (FFS) units include blow moulding from thermoplastic granulate and thermoforming from thermoplastic film typically known as Blow-Fill-Seal (BFS) and Vertical-Form-Fill-Seal (VFFS) respectively. VFFS process is an automated filling process, typically for terminally sterilized processes, that may utilize a single or dual web system which constructs the primary container out of a flat roll of thermoplastic film while simultaneously filling the formed bags with product and sealing the filled bags in a continuous process. All such containers are considered to be sealed by fusion and, as such, fall under the requirement to perform 100% integrity testing.

8.91 Process parameters relating to seal integrity should be validated and appropriately controlled. Critical parameters include, but are not limited to: seal strength, seal uniformity, sealing temperatures, pressures, sealing times and dwell time for filling. Seal strength and uniformity should be monitored routinely.