Technical Brief

Mobius® Validation Services

Helping you with Single-Use assembly validation

INTRODUCTION

The pharmaceutical industry has shown an increasing demand for Single-Use equipment employed in a wide array of unit operations. Single-Use systems and components are now utilised in many different processes with varying validation requirements. The objective of this document is to provide a comprehensive overview of industry practice in support of current US and EU regulatory requirements.

Note: *Mobius is the "umbrella" brand name that will be applied to Millipore's current Single-Use manufacturing product and service offering.*

REGULATORY REQUIREMENTS

The objective of validation is to provide a high level of assurance across a number of areas that a Single-Use assembly will perform reliably within predefined process conditions. The first decision that must be made when designing and manufacturing a Single-Use assembly is the choice of material to be used. Regulatory agencies require that Single-Use equipment be constructed of material with surface contact which does not alter a drug product's safety, identity, strength, quality, or purity (ref.1, 2 and 3)

Furthermore, it is important to qualify the aseptic process' ability to produce and protect a sterile product from contamination and document compliance with cGMP's (21 CFR parts 210 and 211) and related guidance documents like FDA's Guidance on Sterile Drug Product Produced by Aseptic Processing (ref.4), EU cGMP Annex 1 (ref.5) or PDA Technical Report 26 (ref.6).

SINGLE-USE ASSEMBLY DEFINITION

Single–Use technologies are becoming available for an increasing number and range of applications. These Single-Use assemblies include stand-alone devices as well as multi-component systems.

- Single-Use Components: Single-Use parts, modules or sections of a system which may include but are not limited to filters, membrane chromatography units, tubing, connectors, fittings, flexible bags, Single-Use mixing or rigid containers and probes (Ref.7).
- Single-Use System: An assemblage or combination of components in a single-use format.

MOBIUS® by MILLIPORE

Millipore offers several qualified Bioprocess Single-Use components with associated documentation such as Validation Guides (VG) and Certificates of Quality (CoQ). Each of these components is ideally suited for a broad range of applications. A non-exhaustive list of Millipore components includes Lynx® ST & S2S connectors, Durapore® and Millipore Express® filter capsules, Pureflex™ flexible containers, and qualified tubing. The gamma-sterilized assemblies are ideal for a wide range of liquid transfer and/or purification applications, and are easily integrated into both the bulk production and final fill processes, ensuring the secure processing of your valuable product. Best of all, the entire assembly is disposable and does not require any CIP and associated cleaning validation.

Single-Use assemblies' components need to be pre-qualified for this use. Critical components such as filters bags and connectors are supported by Millipore Validation Guides, and as an example Gamma-irradiated Pureflex film is tested to USP Biological Reactivity Test Class VI. The plastics used for component manufacture are qualified in accordance with current practice in order to fulfill US and EU Pharmacopeia requirements. The qualification test methods and results are summarised in each component Validation Guide, and a Certificate of Quality assures that each lot of Single-Use components is manufactured, tested and released to the specifications designated in the Validation Guide.

Each disposable assembly has its own lot release criteria, and depending on its design (type of components involved) and validation, the procedure is adapted accordingly. In order to provide flexibility, lot release testing requirements and validation information are available at different levels depending on the end-user needs. One of these following levels can be selected (Figure 1):

QUALIFICATION SERVICES

Description and rationale

It is important to understand the interactions between the product and the process components. Single-Use technology literature and end-user focus is mainly concentrated on extractables and leachables determination. But to ensure that a Single-Use solution fully meets requirements, we must take into account several other factors such as chemical compatibility, assembly options and their validation implications such as sterility, containment, and filtration. Before beginning the validation exercise, a Validation Master Plan (VMP) could be set up to define the validation strategy and justify the protocols and subsequent testing.

Once the application of Single-Use components is well understood and all risks have been assessed, we will need to determine which standards apply and what additional testing is needed.

Risk assessment

This consists of identifying the hazards, and analysing and evaluating the associated risks. Preliminary Hazard Analysis (PHA) is the initial screening tool which facilitates making a Risk Matrix taking into account:

- Severity ranking
- Frequency ranking
- Risk levels

When a risk assessment is complete, there may be materials that pose no relevant safety or regulatory risk. In such cases, no further action may be required as long as that can be justified.

The end-user is the decision maker who is responsible for coordinating the quality risk management and assuring that process is defined, deployed, reviewed, etc.

Figure 1. Package Comparison

Gold Features

- Lot release testing
  - LAL
  - Particulate
  - Leak testing
- Validation on file for component materials
- Post gamma irradiation
- Shelf life claim
- Sterility claim
- Certificate of Quality (CoQ)

	COQ	Shelf Life Claim	Sterility Claim	Sterility Claim	Leak Testing	Class VI USP <88>
Gold	YES, in each box	YES, 2 years	Sterile, Qrtly Validation	Lot Release	100% of lot on full assembly and Bag	Post-gamma, component family
Silver	YES, in each box	YES, 2 years	Sterile, Qrtly Validation	Quarterly on representative sample	In-Process leak testing	Post-gamma, component family
Bronze	YES, in each box	NONE	Gamma Irradiated >25kGy, not validated sterile	No testing performed	No testing performed	Pre-gamma resin only

Access Global Compliance Services

Millipore's approach to the validation of an aseptic process is to provide the highest achievable sterility assurance level by eliminating the risks an end-user may encounter. In fact, the cGMP trend is to employ a risk-assessment first and plan the validation exercise accordingly so that all risks will be eradicated.

Millipore's approach to quality is driven by our standards of excellence and those of our customers. Our mission is to offer customers around the world reliable, high performance products and services which are supported by:

- Rigorous production controls and quality assurance systems.
- Qualification of the aseptic process itself, including equipment and procedures.
- Training of personnel assigned to this duty.

Millipore's Access® Global Compliance Services team will provide you with the expertise to establish and qualify your process in compliance with current regulatory requirements.

QUALIFICATION APPROACH

One important factor in risk mitigation is the qualification of the Single-Use assembly's performance with actual drug product, using laboratory experiments that simulate the "worst case" production parameters. As the Single-Use assembly is composed of various components such as filters, flexible bags, connectors, tubing, etc., some tests could be more dedicated to one specific component of the assembly (e.g., bacterial retention for sterilising-grade filter, film thickness for Single-Use containers).

Chemical compatibility (Relevant for Filters, Bags, Connectors, Tubing)

Numerous chemical interactions between Single-Use components and constituents in the drug product may exist. The effects of these interactions should be adequately characterised prior to Single-Use component selection (ref.6, 8).

Millipore proposes the end-user obtain compatibility results by using the theoretical data if documented evidence is available (e.g., this covers a vast range of applications for filters). A full test using the product and specific Single-Use assembly will be conducted if there is no theoretical data available or at the end-user's request.

Test methodologies will be adapted to the assembly's components. A variety of ASTM® tests can be provided to measure physical and mechanical attributes after product exposure.

Figure 2. Test Examples

Component vs test	Integrity	Tensile strength	Pressure resistance	Weight	Surface analysis	Thickness
Cartridge filter	●	○	○	●	○	○
Container (bag)	●	●	●	●	●	●
Sterile connectors	●	○	●	●	○	○
Fitting	○	○	●	●	○	○
Tubing	○	●	●	●	○	○

○= Testing not recommended, ● = Testing recommended

Product adsorption (Relevant for Filters, Bags, Connectors, Tubing)

Some components (e.g. preservative) may adsorb to the polymeric material of the assembly components (ref.8). The underlying mechanisms that govern adsorption can result from a variety of interactions between the drug product and assembly components, such as ionic, Van Der Waals and hydrophobic interactions. In addition, process flow rate and several other processing factors (residence time), may also influence the amount of drug product being bound to the assembly's components.

However, regulatory experiences (based on FDA 483 observations) have taught us that the FDA requires the use of the validated analytical assay for final release of the formulation. In other words, any analytical assay other than the one(s) used for batch release will not be accepted by the FDA. Hence, it is not meaningful for Millipore to provide results using our own analytical equipment.

Millipore can provide documentation that includes a test procedure and results from the end-user using their own analytical assay.

Extractables and Leachables (Relevant for Filters, Bags, Connectors, Tubing)

All materials have Extractables and potential Leachables. Determination of these for Single-Use manufacturing systems must be addressed as part of process validation

(ref.3, 8). Once all materials that have product contact have been identified, an Extractables and Leachables risk assessment can be performed. Based on the assessment analysis, appropriate testing can be determined and executed (see Figure 3).

Figure 3. EMEA Guideline (Ref.4) on immediate packaging materials proposes the following decision tree for nonsolid active substance:

Plastic Material as described in European Pharmacopeia	
YES	**NO**
General information(1) Specification(2) Leachables studies(3)	General information(1) Specification(2) Leachables studies(3) Extractables studies Toxicological documentation

(1) - Chemical name of the material, monomer, additives, etc.
(2) - Specification of plastic material. See Validation Guides.
(3) - Leachables studies can be omitted if, based on the outcome of the extractables studies, the calculated maximum amount of the individual leachables substance that may be present in the drug product leads to levels demonstrated to be toxicologically safe.

Extractables

GMP guidance requires testing for extractable substances pertaining to the filter and container closure system/ packaging material used for processing drug product.

Extractables are compounds that can be extracted from the elastomeric or plastic components in solvents of different physicochemical properties under aggressive conditions. The model solvent(s) used for testing must be relevant to the actual drug product with respect to its ingredients and solvent vehicle. Commonly used model solvents include water, low and high pH water and alcohol. The rationale for the selection of worst-case extraction conditions has to be justified, taking into consideration processing time, temperature and sterilisation conditions.

Millipore can provide the Extractables documentation that includes the test results as well as the analytical methods used.

Leachables

Leachables are compounds that leach from the elastomeric or plastic components into the actual drug product under normal use conditions. Because Leachables are expected to be a subset of the Extractables, the Extractables profile should be pre-determined. For the Leachables studies, the preferred solvent would be the drug product or placebo vehicle. When use of the drug product or placebo is not feasible due to analytical interference, a model solvent simulating the extraction capability of the drug product may be considered. Given the diversity of the drug products commercially available, it is the responsibility of the drug manufacturer to ensure that the Leachables are appropriately addressed.

Millipore can provide technical information and method development to facilitate the Leachables studies.

Particle shedding (Relevant for Filters, Bags, Connectors, Tubing)

In addition to extractable substances testing, a particle shedding qualification needs to be performed in order to test for possible particle release from the assembly components into the product. Typically, fiber shedding or particle release studies are performed by the assembly supplier to investigate robustness of their manufacturing process.

Normally, Single-Use assemblies will not shed any fibers into the final formulation unless the product or processing conditions are not compatible. More important, however, is to investigate the production line after the filter, because both the EU and US Pharmacopoeia look for particles in the final container, not only for the filter downstream and/or process line. Any plastic material used after the filter (e.g., silicone tubing, connector) could release particles and thus add to the total particle content in the final container.

In those cases, the best method is to obtain samples in the actual product line at different volumes filtered. This would allow for particle shedding qualification using actual conditions. Therefore, Millipore will supply a protocol with the proposed test method and explanation. The report will contain the test results and the conclusion.

Flushing procedure (Relevant for Filters, Connectors, Tubing)

Pre-use rinsing/flushing of Single-Use assemblies may reduce the level of extractables, leachables, and particles, and may be effective in reducing the level of non-specific adsorption (ref. 6).

Millipore may help determine your flushing needs by setting up a laboratory experiment which monitors the reduction of organic carbon (TOC) and/or filter integrity with flush volume. The Single-Use assemblies are flushed with a pertinent fluid, and effluent is sampled and tested for TOC when needed.

Millipore will supply a protocol with the proposed test method and details. The report will contain the test results and the conclusion.

Bacterial retention (Relevant for Filters)

The main reason for using a sterilising-grade filter is to retain micro-organisms prior to filling and finishing. With respect to filter performance, this means that the ability of the filter to retain bioburden is to be qualified in combination with the product and its manufacturing parameters (ref.4, 5, 6).

Millipore will qualify the retention of *Brevundimonas diminuta* (*B. diminuta*) in the presence of drug product. As the product and/or processing conditions may be antagonistic to the test organism, the qualification of bacterial retention is split into two parts, first the viability test and second the actual retention test.

Viability

The purpose of the viability test is to determine which type of bacterial retention test protocol is to be issued. Should the product and/or processing conditions be toxic to *B. diminuta*, a two step/preconditioning method will be used. If not, a direct inoculation protocol will be established. The report will describe both the method and acceptance criteria and will state the results and discussions.

Bacterial retention

Based on the results of the viability test, a protocol for bacterial retention testing will be forwarded.

One of the following protocols could be prepared:

- Drug product has no bactericidal effect on *B. diminuta* for the duration of the process. Therefore, the challenge organism can be suspended in drug product according to the direct inoculation method.
- Drug product has a bactericidal effect on *B. diminuta* for the total duration of the process. Therefore, a modified product, time or Saline Lactose Broth (SLB) solution will be used to suspend the test organisms and a two-step test method will be used.

Millipore will provide the protocol that includes the test method and its justification, the acceptance criteria and re-test provisions as well as the report that includes the test results, discussion and conclusion.

Product-related filter integrity (Relevant for Filters)

Pre-use and post-use integrity testing of sterilising-grade filters is a regulatory requirement (ref.4, 5). However, since most drug products contain components that change the surface interactions between the filter and the wetting fluid, they may alter the integrity test results. Therefore, it is often useful to determine the product-specific integrity value. Integrity test ratio determination (e.g. bubble point ratio) is a proven method for providing the minimum integrity values for a non-specified wetting fluid. The laboratory derived integrity test ratio must be confirmed under normal processing conditions as part of the Performance Qualification (PQ).

Millipore will provide the protocol that includes the test method and the acceptance criteria, as well as the report that includes the test results, discussion and conclusion.

Process validation

Although it is not the objective of this document, the following should be considered when validating the entire aseptic process (Ref.10).

Process design

After designing the filtration system (URS, FD, P&ID, flow schematic, etc.) and establishing the process SOP's, the Installation Qualification (IQ) and the Operational Qualification (OQ) shall be performed. IQ is the action of establishing documented evidence that the equipment is installed according to the original design and specification. The OQ ensures that the testing equipment is able to consistently operate within the pre-set limits and tolerances.

Training and certification of operators

cGMP regulations require that personnel receive appropriate training for assigned duties. Part of the Performance Qualification (PQ) is to check that SOP's are adequate and all operators can understand and apply them. It is necessary that a training program be established for each person that is part of the manufacturing operation, that records are kept to prove that the training was delivered and the person has understood the contents of it.

As part of the validation service, Millipore will provide assistance and expertise to the end -user for interpretation of regulatory guidances with respect to the aseptic process as well as filtration and bioburden testing. Millipore will provide protocols and comprehensive documents for all testing and results.

SERVICE OFFERING

Mobius Single-Use assemblies are mostly composed of Millipore components such as filters, connectors, and flexible bags which are fully qualified (Validation Guide and Certificate of Quality). These components are part of Millipore's standard library which also includes tubing and various accessories which are also qualified for drug processing applications, i.e., USP<88> Class VI plastics post-gamma irradiation, compliant with 21 CFR, etc.

The validation of assembly performance should be conducted with actual drug product and process conditions (see Figure 4). It is necessary to pre-define the overall operating procedures based on the User Requirement Specifications (URS) in order to identify those critical steps of the process requiring a thorough validation program. This risk analysis generally leads to careful consideration of the Single-Use assembly and associated SOP's.

Figure 4. Validation of Assembly Performance

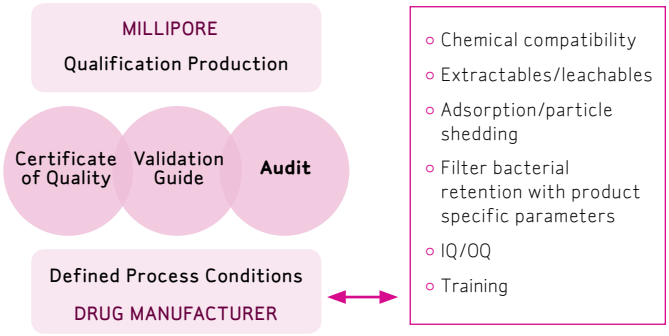

Figure 5. Main validation services that Millipore proposes to end-users.

Services	Filter	Flexible Bag & Mix Sytem	Connector	Tubing	Assembly
Chemical Compatibility	Y	Y	Y	Y	Y
Adsorption	Y	Y	Y	Y	Y
Particle Shedding	Y	Y	Y	Y	Y
Extractables	Y	Y	Y	Y	Y
Leachables	Y	Y	N	N	Y
Bacteria Retention	Y	N	N	N	N
Integrity	Y	√	√	N	√

√ = lot release test. Filters are also released after confirmation of integrity test results.

All testing required for the validation of the Single-Use assembly used for aseptic processing must be documented, and all raw data and results must be recorded (cGMP practice). The validation documentation ensures that all the requested testing has been conducted under specified and controlled conditions.

Taking such an approach to the validation ensures safe, reproducible and consistent product quality, increases the aseptic assurance level and is the best guarantee of successfully passing a regulatory inspection.

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