asertain

Validation Services

As per regulatory requirement, the pharmaceutical industry has to provide a high level of assurance that the sterile drug product manufactured through aseptic processing offers the identity, strength, quality, and purity it purports to have or is represented to posses (Ref. USFDA 21CFR 211.100(a)). Consequently it has become increasing critical to establish/quantify the impact on the drug due to its interface with various process components under different process conditions.

Sterilizing grade filters are key components of the aseptic process as these not only ensure sterility of the filtered drug but, as they provide a large surface area for drug interface, can also have a significant impact on other parameters such as purity and strength of the drug.

mdi offers a wide range of validation services to establish the functionality, testability, and compatibility of the sterilizing grade filters with the drug product.

mdi Membrane Technologies

mdi asertain Filter validation services are designed to meet customer specific needs and help achieve regulatory compliance are include the following tests.

- **Filter Integrity Test Values Specific to Product**
- **Filter Fluid Interaction**
  - Physico-Chemical Compatibility
  - Extractable/Leachable Studies
  - Adsorption Studies
- **Microbial Retention Studies**

All of these studies are executed under pre-approved test methologies establishing the test conditions and acceptance criteria.

Filter Integrity Test Values Specific to Product

For aseptic processes, filter integrity tests are required to be performed on critical filters immediately before and after batch filtration in order to assure filter efficiency during the filtration process. In order to optimize processing, it may be more convenient to integrity test the filter cartridge wet with the product or process fluid.

However, drug products/process fluids due to different components may have different surface tension impacting the drug-filter interface and consequently the integrity test values exhibited by the filter. Thus, it is critical to establish drug product wetted integrity test specifications for the filter.

mdi validation services for establishing product specific filter integrity test specifications help correlate product wetted integrity test values with those exhibited with the reference fluid (filter manufacturer specified) which in turn are already correlated to bacterial retention as per ASTM F-838-05(ref. **mdi** Validation guides).

Product wetted integrity test values are compared with reference fluid wetted values for 3 different filter lots and an integrity test ratio so established is used to establish the product wetted integrity test specifications. Special consideration is given to process conditions such as temperature that may also have an impact on filter integrity test values.

Physico-Chemical Compatibility

Physico-Chemical Compatibility studies evaluate the interface between filter components and the pharmaceutical product after exposure to"worst-case"fluid and process conditions to ensure that the filter experiences no adverse effects in the pharmaceutical product.

The filter is exposed to the process fluid for a specified period under pre-determined conditions that include simulated filter sterilization conditions, exposure times exceeding the maximum process time, temperatures exceeding maximum process temperature, and differential pressures that exceed process pressures.

Compatibility is determined by comparing:

- Integrity test results using the reference fluid
- Flow Rates
- Membrane Thickness
- Pore Morphology

Tests are performed on the filter prior to and after worst-case exposure.

Extractable/Leachable Studies

Leachables are compounds that leach out form the filter into the drug product under normal process conditions, whereas extractables are compounds extracted from the filter in solvents exhibiting varying physicochemical properties, under conditions designed to maximize extraction.

Potential sources of extractables/leachables from a filter can be membrane filter components such as plasticizers, surfactants, antioxidents, residual solvents, device support layers, and plastic components such as end caps, housings, cages, O-rings etc.

Although it is recommended to establish the quantum of leachables from a filter in direct interface with the drug product or its placebo, sometimes due to possible drug component interference it is not possible to accurately do so. In such cases, model solvent streams, selected on the basis of their ability to simulate the extraction abilities of different drug components, are used to carry out extractable studies under simulated worst case process conditions.

Adsorption Studies

It is critical that filters are selected to minimize adsorption and loss of product components. Laboratory scale filter tests are used to generate adsorption profiles to help with filter selections and process qualification.

Process conditions such as temperature and filter fluid contact time (flow rates) are simulated as these vmay have an impact on adsorption.

Microbial Retention Studies

USDFA CDER guidance document to Sterile Drug Products Produced by Aseptic Processing as well as PDA Technical Report No. 26, Revised 2008 to Sterilizing Filtration of Liquids, stress on establishing documented evidence for the sterilizing grade filter to reproducibly remove bacterial contamination from the process stream.

asertain microbial retention studies qualify the filter under test to repeatedly produce a sterile filtrate with the drug product under simulated worst case process conditions.

The drug product or simulant is inoculated with the challenge organism at a concentration $>1x10^7$ viable organisms/cm^2 of filter area and the test is performed on filters from three different lots, with at least one having a pre-filtration physical integrity test value at/or near the filter manufacturer specified limit.

This involves establishing the viability of the test organism in the drug product and testing the filter for bacterial retention test under simulated process conditions.

Test Organism Viability Study

Establishes whether the drug product is bactericidal to the test organism under simulated process conditions of temperature and contact time. This in turn helps establish the test methodology for the bacterial challenge/retention studies.

Bacterial Retention Study

For non-bactericidal drug products the filter is challenged with the test organism suspended in drug product.

For bacterial products viability studies are carried out with modified formulation, modified process conditions, or in product surrogate. In such cases filter preconditioning with the product under worst case process conditions is carried out followed by bacterial challenge test with modified formulation/process under which test organism viability has been established.

Validation Facilities

mdi asertain validation facilities are specially designed to comprehensively meet international regulatory requirements and are well supported by stringent Quality Management System which includes calibrated measuring and test equipments and auditable data generation.

Physicochemical Test Lab

A well equipped Analytical Instrumentation Facility with modern scientific equipment to develop and validate test methodologies, to test filter performance parameters, and to validate the impact of filter-drug product interface.

- HPLC
- UV Spectrometer
- FTIR
- TOC
- Digital Mass Flow Meter
- Digital Pressure Gauges
- Viscometer
- Air Particle Counter
- Liquid Particle Counter

mdi Integrity test data generation lab is equipped with latest scientific equipment for filter integrity testing (FilterCheck) along with specially designed jigs and fixtures that incorporate simulation of critical parameters such as test temperature to ensure accuracy and reliability of data generated.

Microbial Test Unit

A world class 2500 square feet microbiology test facility with dedicated HVAC systems for bacterial challenge test lab, sterility test lab,culture handling lab, MLT lab etc., is well equipped to conduct viability studies and bacterial challenge testing with specific drug products including modified formulations as well as modified process conditions. The Bacterial Challenge Test lab houses a unique test jig with a special design incorporating online positive controls and special arrangements for online pre-conditioning of the test filters.

Simulation/Preconditioning

State of the art instrumentation and monitoring equipment coupled with flexible simulation jigs are used to achieve near perfect simulation of worst case process condition, an essential pre-requisite to filter validation with specific drug products.

What's Unique About mdi Validation Services

At **mdi**, the **asertain** filter validation package is designed to meet your specific needs and establishes the suitability of the filter for a specific product/process. Some unique components of **mdi asertain** validation services that differentiates it from others are:

Miniaturized Truly Representative Test Filters

mdi provides specially designed miniaturized test filter devices that truly represent the process filters to be used in terms of materials of construction of the filter membrane, support layers and plastic components, and fabrication processes such as sealing etc. to accommodate minimal availability of drug samples, specially in case of new molecules.

Maximum Simulation

As per USDFA, CDER guideline document on sterile products produced by aseptic filtration, filter should be validated for performance parameters with specific drug product under simulated actual use conditions.

mdi supported by it's vast engineering experience and capabilities offers specially designed jigs and fixtures to simulate all critical process parameters such as temperature, pressure, flow rates, contact time etc.

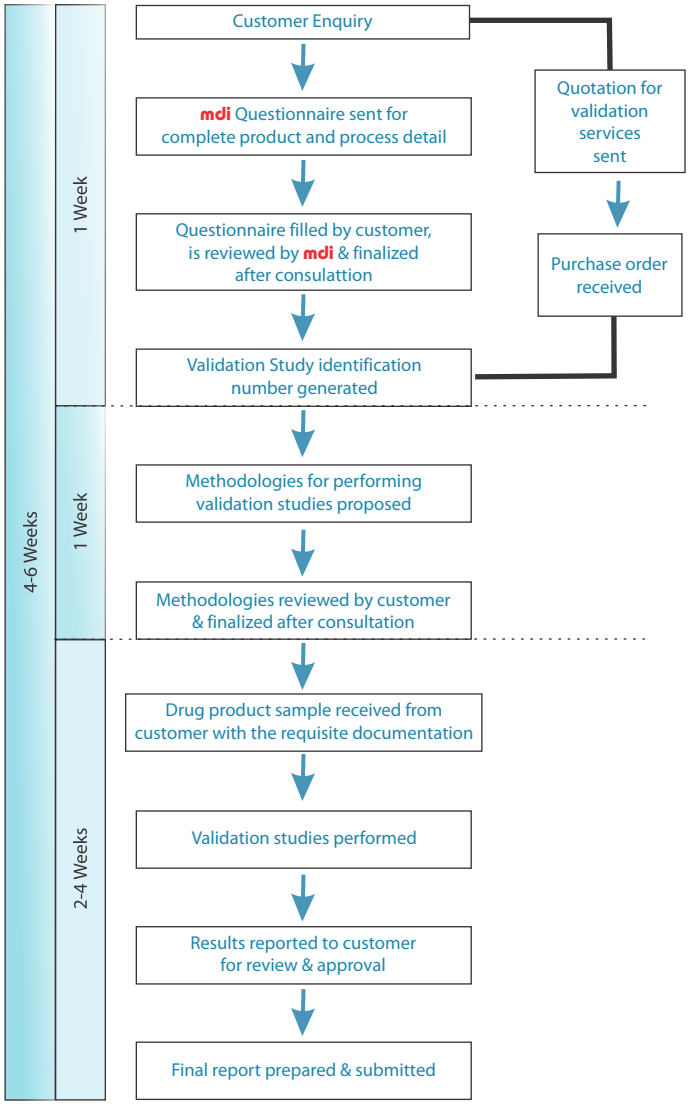
Regulatory Assistance

mdi Technology Executives provide valuable information on current regulatory requirements and industry trends related to filter validation, and provide compliance assistance through documentary and technical support.

Accurate and Fast Services

mdi provides fast validation services from initial exchange of information (Questionnaire) to methodology approvals and finally validation reports fulfilling regulatory requirements within 4-6 weeks.

How to Proceed



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