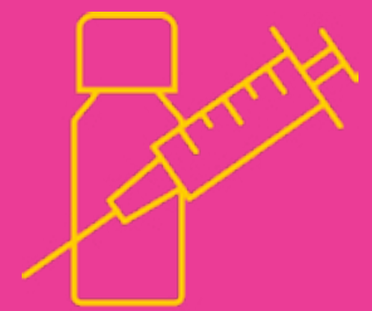
RISK MITIGATION & QUALITY REQUIREMENTS

SUPPORT FOR BIOPROCESSES

This interactive tool guides you through the challenges and quality requirements of your bio-manufacturing process.

Start Now



MERCK

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

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Preparation, Separation, Filtration & Monitoring Products

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WHAT ARE THE RISKS IN YOUR MANUFACTURING PROCESS?

- Increased microbial load
- High levels of endotoxins
- High levels of elemental impurities
- Batch-to-batch variability
- High levels of residual solvents
- Particulate contamination
- Compromised quality due to unknown extractables
- Unsuitable (not biocompatible) materials
- Unknown supply chain
- Process compatibility

INCREASED MICROBIAL LOAD

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Bioburden control is critical during the upstream process.
Any microbial contamination can result in a lost batch.

More Information

DOWNSTREAM

Maintaining low bioburden during the downstream process is important to ensure product quality and to keep endotoxin levels low.

More Information

FORMULATION/FINAL FILTRATION

High bioburden or endotoxin levels during formulation can affect product quality and quality markers. It is a regulatory expectation that bioburden is low prior to final sterilization for increased sterility assurance.

More Information

HIGH LEVELS OF ENDOTOXINS

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

High levels of endotoxin can negatively impact the upstream process. In addition, endotoxin, if present in the upstream process, will need to be removed by the downstream process to meet patient safety requirements.

More Information ▶

DOWNSTREAM

Maintaining low endotoxin levels is important to ensure final product quality and patient safety.

More Information ▶

FORMULATION/FINAL FILTRATION

Endotoxins in the final formulation can lead to out of specification results and can cause patient risk.

More Information ▶

HIGH LEVELS OF ELEMENTAL IMPURITIES

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Elemental impurities can impact the batch-to-batch consistency of the upstream performance.

More Information

DOWNSTREAM

Elemental impurities can negatively influence the downstream process by interacting with the active pharmaceutical ingredient, decrease product stability and affect product quality.

More Information

FORMULATION/FINAL FILTRATION

Elemental impurities can cause stability issues in the final drug product resulting in out of specification results.

More Information

BATCH-TO-BATCH VARIABILITY

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Variability in raw materials can impact the upstream performance and product yield. Variability in filter performance can cause process interruptions and deviations.

More Information

DOWNSTREAM

Variability in raw materials can impact the downstream performance, product yield and quality. Variability in filter performance can cause process interruptions and deviations.

More Information

FORMULATION/FINAL FILTRATION

Variability in raw materials can impact final formulation, product quality and drug product stability. Variability in filter performance can cause process interruptions and deviations.

More Information

HIGH LEVELS OF RESIDUAL SOLVENTS

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

DOWNSTREAM

Residual solvents can cause negative impact in the downstream process and affect product quality by interacting with the protein.

More Information

FORMULATION/FINAL FILTRATION

Residual solvents can lead to out of specification results of the final drug product and can cause patient risk.

More Information

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Unknown particles might impact the upstream process and can have un-expected effects like filter clogging etc.

More Information

DOWNSTREAM

Unknown particles might impact the downstream process and can have unexpected effects like filter clogging etc.

More Information

FORMULATION/FINAL FILTRATION

Any unexpected particulate matters in the final formulation are of high risk and need to be explained to regulatory authorities.

More Information

COMPROMISED QUALITY DUE TO UNKNOWN EXTRACTABLES

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

The upstream performance and yield can be impacted by extractables from filter and single use components.

More Information ▶

DOWNSTREAM

The downstream performance and yield can be impacted by extractables from filter and single use components.

More Information ▶

FORMULATION/FINAL FILTRATION

Extractables from filters and single use components need to be well characterized and understood to comply with regulatory expectations and ensure patient safety.

More Information ▶

UNSUITABLE (NOT BIOCOMPATIBLE) MATERIALS

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Usage of inappropriate chemical grades can lead to lack of documentation needed for drug approval.

Using filters and single use components where the materials of construction are not biocompatible can negatively affect patient safety.

More Information ▶

DOWNSTREAM

Usage of inappropriate chemical grades can lead to lack of documentation needed for drug approval.

Using filters and single use components where the materials of construction are not biocompatible can negatively affect patient safety.

More Information ▶

FORMULATION/FINAL FILTRATION

Usage of inappropriate chemical grades can lead to lack of documentation/compliance needed for drug approval.

Using filters and single use components where the materials of construction are not biocompatible can negatively affect patient safety.

More Information ▶

UNKNOWN SUPPLY CHAIN

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Security of supply and supply chain transparency are key attributes when qualifying raw materials, filters and single use components.

More Information

DOWNSTREAM

Security of supply and supply chain transparency are key attributes when qualifying raw materials, filters and single use components.

More Information

FORMULATION/FINAL FILTRATION

Security of supply and supply chain transparency are key attributes when qualifying raw materials, filters and single use components.

More Information

PROCESS COMPATIBILITY

IN WHICH PROCESS STEP DO YOU FACE THIS RISK?

UPSTREAM

Filters and single use components must be able to perform as required under the specified sterilization and operating conditions.

More Information

DOWNSTREAM

Filters and single use components must be able to perform as required under the specified sterilization and operating conditions.

More Information

FORMULATION/FINAL FILTRATION

Filters and single use components must be able to perform as required under the specified sterilization and operating conditions.

More Information

THE EMPROVE® PROGRAM

YOUR FAST TRACK THROUGH REGULATORY CHALLENGES

The Emprove® Program is focused on resolving challenges in (Bio)-pharmaceutical development.

Our portfolio includes comprehensive documentation of the latest regulatory requirements for more than **400 raw and starting materials**, as well as a **selection of filters and single-use components**. In addition, it even anticipates industry expectations for further recommendations.

Simplifying your processes with the Emprove® Program:

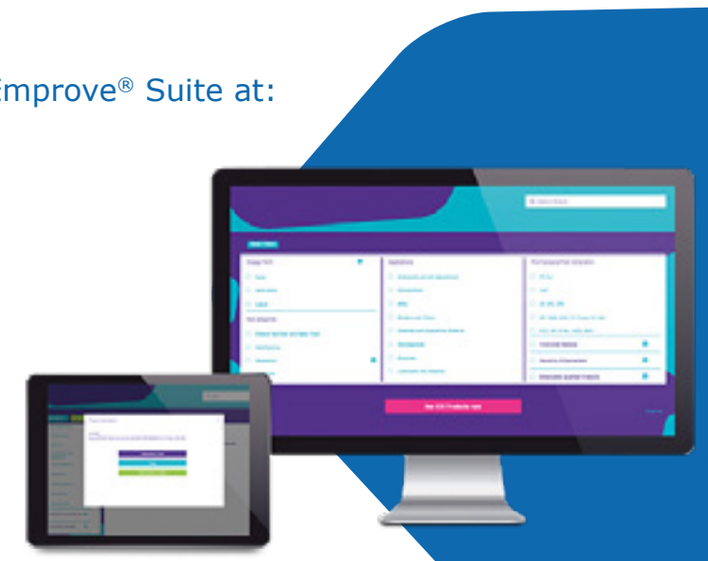
- Accelerating approval preparation
- Facilitating qualification processes
- Supporting risk assessment, management and mitigation
- Increasing supply chain transparency
- Saving time and money

For an overview of products available with Emprove® documentation visit:

Emprove® Program Website

Gain 24/7 online access to all your dossiers with our Emprove® Suite at:

Emprove® Suite Website



CONTACT

MATERIAL QUALIFICATION, RISK ASSESSMENT AND PROCESS OPTIMIZATION SUPPORT

We offer extensive support to find the tailor-made Emprove® Program solution for your manufacturing process. Please contact us directly for comprehensive consultation and recommendations.

Further information and research:

Emprove® Program Website

Emprove® Suite login to download your Dossier

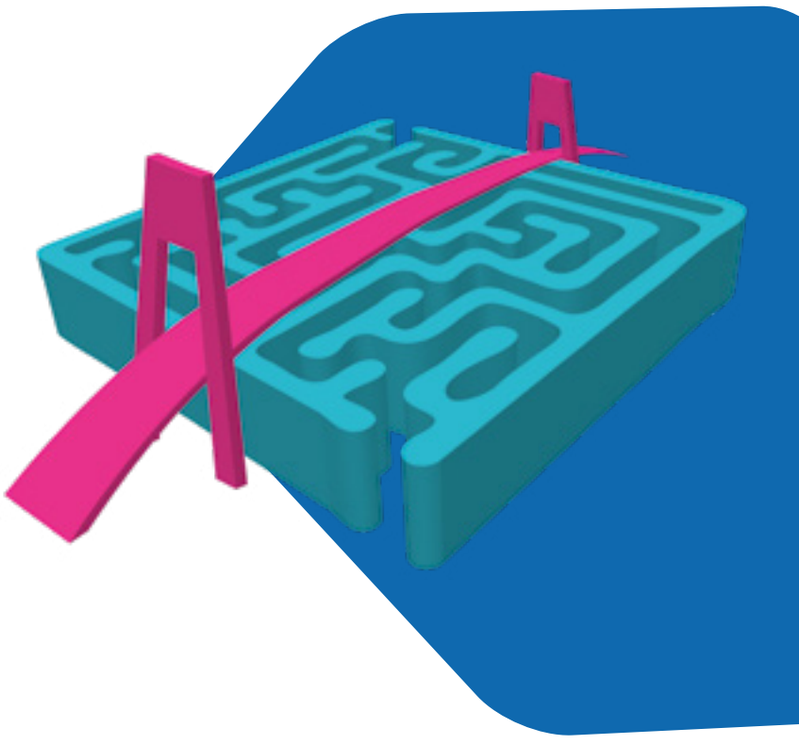
DEMO: Quality Management Dossier

DEMO: Operational Excellence Dossier

CONTACT:

Contact us directly

We are looking forward to supporting your business.



OUR SUPPORT TO MITIGATE YOUR RISK OF INCREASED MICROBIAL LOAD

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Microbiology parameters (TAMC, TYMC)[(TAMC = total aerobic microbial count; TYMC = total combined yeast/moulds count)] are part of the product specification for all Emprove® Expert products. The specification is shown in chapter „3.2.S.1.3 General Properties" of the Emprove® Material Qualification Dossiers. 3 example CoAs from representative product-scale batches (incl. TAMC and TYMC values) are shown in chapter „3.2.S.4.4 Batch Analysis" of the Emprove® Material Qualification Dossiers.

See Demo Version

QUALITY MANAGEMENT

Stability studies (see Emprove® Quality Management Dossiers Chapter 4: Stability Studies) for the Emprove® Expert product portfolio include microbiology parameters TAMC and TYMC. If these parameters are not part of the stability study parameters, then an internal risk assessment is available, e.g. highly concentrated solvents or microbicidal stability studies.

See Demo Version

OPERATIONAL EXCELLENCE

To meet quality control requirements, the analytical procedures for our inhouse test method are included in the Operational Excellence Dossier (Chapter 3: Analytical Procedure).

See Demo Version

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OUR SUPPORT TO MITIGATE YOUR RISK OF INCREASED MICROBIAL LOAD

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MATERIAL QUALIFICATION

1. Lot release microbial retention testing of sterilizing grade filters is performed on samples of filters as indicated in the specification table.
2. Lot release endotoxin testing after sterilization is performed on samples of filters, gold certified mobius assemblies and connectors as indicated in the specification table.
3. The original validation of the sterilizing grade filter's ability to remove bacteria under hydraulic stress are in the specification table and the test summary and results section.
4. Integrity testing (air diffusion and bubble point) of sterilizing grade filters is commonly used to confirm the retention capability of the membrane. The integrity test specifications are listed in the specification table.

See Demo Version

QUALITY MANAGEMENT

1. Details on the microbial retention testing to ensures the filter will be able to retain bacteria for the entire shelf life are provided in the shelf life testing requirements and results section.
2. Filters and single use components that are sold pre-sterilized by gamma irradiation had the gamma irradiation cycle validated as detailed in the Quality Management Dossier in the gamma irradiation section.

See Demo Version

OUR SUPPORT TO MITIGATE YOUR RISK OF HIGH LEVELS OF ENDOTOXINS

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

The endotoxin parameter is part of the product specification for all Emprove® Expert products. The specification is shown in chapter „3.2.S.1.3 General Properties" of the Emprove® Material Qualification Dossiers.
3 example CoAs from representative product-scale batches (incl. endotoxins) are shown in chapter „3.2.S.4.4 Batch Analysis" of the Emprove® Material Qualification Dossiers.

See Demo Version

QUALITY MANAGEMENT

Endotoxins as quality indicating parameter is monitored during stability studies („Chapter 4: Stability Studies").

See Demo Version

OPERATIONAL EXCELLENCE

To meet quality control requirements analytical procedure for our inhouse test method are included in the Operational Excellence Dossier (Chapter 3: Analytical Procedure).

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OUR SUPPORT TO MITIGATE YOUR RISK OF HIGH LEVELS OF ENDOTOXINS

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

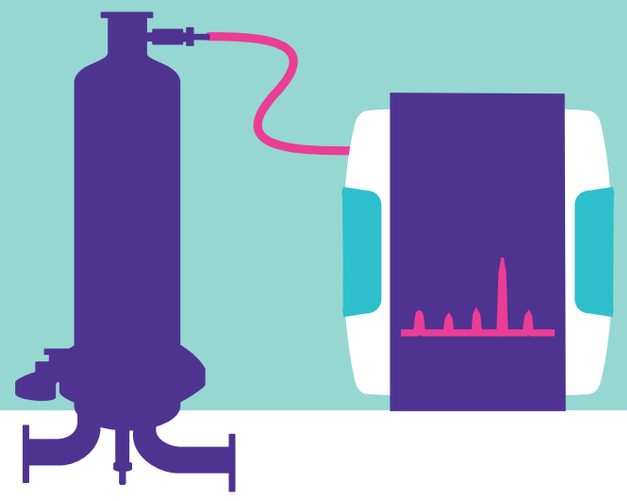
As indicated in the quality information section under specifications in the Material Qualification Dossier, filters and single use components are evaluated for endotoxin as part of lot release according to USP <85>, EP 2.6.14 & JP 4.01. The original validation testing for endotoxin is also included in the test summary and results under bacterial endotoxin.

See Demo Version

QUALITY MANAGEMENT

Details on endotoxin testing to ensures filters and single use component meet the endotoxin lot release criteria for the entire shelf life are provided in the shelf life testing requirements and results section.

See Demo Version



HIGH LEVELS OF ELEMENTAL IMPURITIES

OUR SUPPORT TO MITIGATE YOUR RISK OF HIGH LEVELS OF ELEMENTAL IMPURITIES

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Reference to ICH Q3D within specification footer "Elemental impurity specification have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated." Once an element (metal) is "likely to be present", the corresponding element is specified and tested for every subsequent batch via a validated test method. Part of specification as footer (s.o.), metals that are "likely to be present" are part of specification (Material Qualification Dossier 3.2.S.1.3 General Properties); metals that are "likely to be present" are part of example CoAs (Material Qualification Dossier 3.2.S.4.4 Batch Analysis).

See Demo Version

OPERATIONAL EXCELLENCE

In-depth EI information as part of Operational Excellence Dossier (Chapter 1: Elemental Impurity Information), in case element(s) are intentionally added this/these metals are named in Operational Excellence Dossier.

See Demo Version

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HIGH LEVELS OF ELEMENTAL IMPURITIES

OUR SUPPORT TO MITIGATE YOUR RISK OF HIGH LEVELS OF ELEMENTAL IMPURITIES

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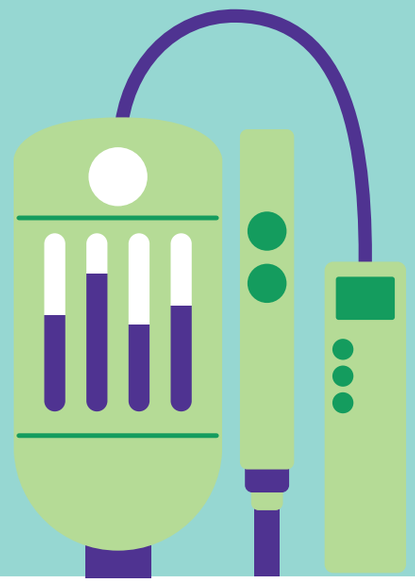
OPERATIONAL EXCELLENCE

Elemental impurities as per ICH Q3D are included in the extractables report:
1. Results summary
2. Elemental substances by ICP-MS

See Demo Version



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OUR SUPPORT TO MITIGATE YOUR RISK OF BATCH-TO-BATCH VARIABILITY

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EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Batch-to-batch consistency is evaluated within 3 examples CoAs (Material Qualification Dossier 3.2.S.4.4 Batch Analysis).

See Demo Version

OPERATIONAL EXCELLENCE

Dedicated product quality report (Operational Excellence Dossier Chapter 2: Product Quality Report) showing consistency of manufacturing process “quality-inducing parameter” values for all batched produced in one year.

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OUR SUPPORT TO MITIGATE YOUR RISK OF BATCH-TO-BATCH VARIABILITY

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

The lot release testing that is performed is detailed in the Quality Information under Specifications in the Material Qualification Dossier. These tests include an in process integrity test, water flow rate and pressure drop, endotoxin and hydraulic stress. These tests are part of the quality checks in place to ensure consistent performance. The original validation of this criteria is detailed in the test summary and results section.

See Demo Version

QUALITY MANAGEMENT

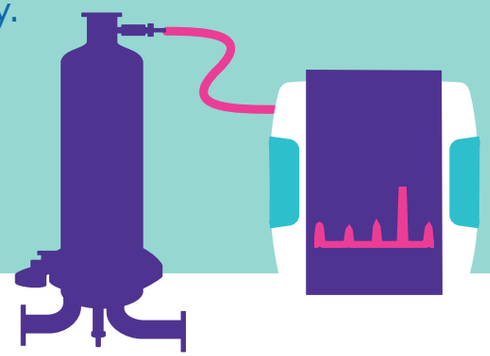
The quality self assessment section in the Quality Management Dossier details quality procedures in place that contribute to batch to batch consistency

See Demo Version

OPERATIONAL EXCELLENCE

Extractables profiles assessed from multiple lots following BPOG and USP 665 methodologies are provided to support batch-to-batch consistency.

See Demo Version



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OUR SUPPORT TO MITIGATE YOUR RISK OF HIGH LEVELS OF RESIDUAL SOLVENTS

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MATERIAL QUALIFICATION

Partially solvents are part of specification (Material Qualification Dossier 3.2.S.1.3 General Properties) and of example CoAs (Material Qualification Dossier 3.2.S.4.4 Batch Analysis). Our justification of specification mentions accordance to ICH Q3C: Material Qualification Dossier 3.2.S.4.5 Justification of Specification. Statement within the chapter: „The specification of our product has been developed in accordance with the requirements of the declared pharmacopoeia including ICH Q3C for residual solvents and with respect to the requirements of customers in different application fields."

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OUR SUPPORT TO MITIGATE YOUR RISK OF PARTICULATE CONTAMI-NATION

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EMPROVE® DOSSIERS FILTERS AND SINGLE USE

OPERATIONAL EXCELLENCE

„Technically unavoidable particle information“ in Operational Excellence Dossier Chapter 4: Technically Unavoidable Particle Proifle, based on the „IPEC Federation TUPP Guide 2015“.

See Demo Version

Contact ▶ Emprove® Program ▶

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OUR SUPPORT TO MITIGATE YOUR RISK OF PARTICULATE CONTAMI-NATION

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

The Material Qualification Dossier details in the quality information section under specifications the particulate testing that was done according to USP <788>. For sterilizing grade filters , particulate and non fiber release testing was performed as part of the validation as detailed in the Test Summaries and Results section.

For single use assemblies, particulate testing per USP <788> is performed as part of lot release for gold assemblies and quarterly for silver assemblies as detailed in the Release Criteria Section. USP <788> testing was also performed as part of validation as detailed in the Test Summary and Results section.

See Demo Version

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COMPROMISED QUALITY DUE TO UNKNOWN EXTRACTABLES

OUR SUPPORT TO MITIGATE YOUR RISK OF INSECURE PRODUCT STABILITY AND -QUALITY

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Flush volumes to meet TOC (total organic carbon) and conductivity WFI specifications according to USP <643> and USP <645> are provided in the Material Qualification Dossier for filters in the product quality section under release criteria. The initial validation to meet this specification is detailed in the test summaries and results section under TOC and conductivity.

See Demo Version

QUALITY MANAGEMENT

As part of the shelf life testing for filters detailed in the Quality Management Dossier in the shelf life testing and results section, samples are tested to ensure they meet the flushing requirements to meet TOC and conductivity WFI specifications according to USP <643> and USP <645>.

See Demo Version

OPERATIONAL EXCELLENCE

Extractables profiles assessed from multiple lots following BPOG methodologies are provided to support batch-to-batch consistency. BPOG publication of extractables protocol: standardised extractables testing protocol for single use systems in biomanufacturing, pharmaceutical engineering, Nov 2014.

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UNSUITABLE (NOT BIOCOMPATIBLE) MATERIALS

OUR SUPPORT TO MITIGATE YOUR RISK OF UNSUITABLE (NOT BIO-COMPATIBLE) MATERIALS

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Quality standards are applied to our material grades. A GMP-statement for excipient-GMP (for Emprove® Expert / Essential products) is given in the Material Qualification Dossier, chapter 3.2.S.2.1 Manufacturer. GMP statement (for Emprove® Expert / Essential products; Material Qualification Dossier 3.2.S.2.1 Manufacturer).
It is explained why our specification is set up the way it is (Material Qualification Dossier 3.2.S.4.5 Justification of Specification). Following certificates also certify suitability (EXCiPACT™ certificate; ISO 9001 certificate (Material Qualification Dossier 3.2.S.2.1 Manufacturer) BST/TSE, allergen, mycotoxin/aflatoxin, GMO, melamine, halal (if applicable), kosher (if applicable)(Material Qualification Dossier 3.2.S.3.2 Impurities).

See Demo Version

QUALITY MANAGEMENT

Further information on applied quality levels can be found in the product quality self-assessment: (Quality Management Dossie Chapter 2: Product Quality Self-Assessment). For the excipient grade chemicals (Emprove® Essential/Expert) stability studies according to ICH Q1A are conducted; stability data can be found in Quality Management Dossie Chapter 4 - Stability Data.

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UNSUITABLE (NOT BIOCOMPATIBLE) MATERIALS

OUR SUPPORT TO MITIGATE YOUR RISK OF UNSUITABLE (NOT BIO-COMPATIBLE) MATERIALS

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

The Material Qualification Dossier details the following to support material suitability in the general properties under materials of construction, the quality information under specifications and the test summary and results under material toxicity:

1. Material of construction
2. Biocomaptibility testing (Class VI USP <88>, Cytotoxicity ISO 10993, USP <87>, physiochemical test for plastics (USP <661>)
3. FDA indirect food additivie requirement according to 21 CFR 177-182 (filters only).
4. Regulatory/allergan statements are in the regulatory information section (animal origin, BPA, melamine, latex, GMO, DEHP, plant/vegetable origin)

See Demo Version

OUR SUPPORT TO MITIGATE YOUR RISK OF UNKNOWN SUPPLY CHAIN

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

If Merck (incl. subsidiaries) is the original manufacturer, the information is given in the chapter („Material Qualification Dossier 3.2.S.2.1 Manufacturer"). If Merck KGaA (incl. subsidiaries) is not the original manufacturer, we link to the electronical original manufacturer tracing (eOMT), outside the Emprove® dossiers to ensure supply chain transparency.

See Demo Version

QUALITY MANAGEMENT

Detailed supply chain information is given on: original manufacturer (either Merck KGaA or link to eOMT), site of quality release, site of downfilling, site of labeling and site of warehousing prior to global distribution network (Quality Management Dossier Chapter 1: Supply Chain Information). Original manufacturer (if not us) are thoroughly evaluated: (Quality Management Dossier Chapter 3: Supplier Audit Report Summary).

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OUR SUPPORT TO MITIGATE YOUR RISK OF UNKNOWN SUPPLY CHAIN

EMPROVE® DOSSIERS CHEMICALS

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

The following information in the Material Qualification Dossier in the manufacturing information section provides details regarding the supply chain:

1. Change control policy
2. Manufacturing location

See Demo Version

QUALITY MANAGEMENT

The following information in the Quality Management Dossier addresses the robustness of the supply chain:

1. Quality self-assessment in the quality self assessment section
2. ISO certification in the ISO 9001 section
3. Chain of custody of raw materials in the chain of custody sections

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OUR SUPPORT TO MITIGATE YOUR RISK OF PROCESS COMPATIBILITY

EMPROVE® DOSSIERS FILTERS AND SINGLE USE

MATERIAL QUALIFICATION

Process compatibility claims (pressure claims, sterilization claims, temperature claims) are listed in the Material Qualification Dossier under quality information in the specification section. The original validation of these claims are listed in the test summaries and results section.

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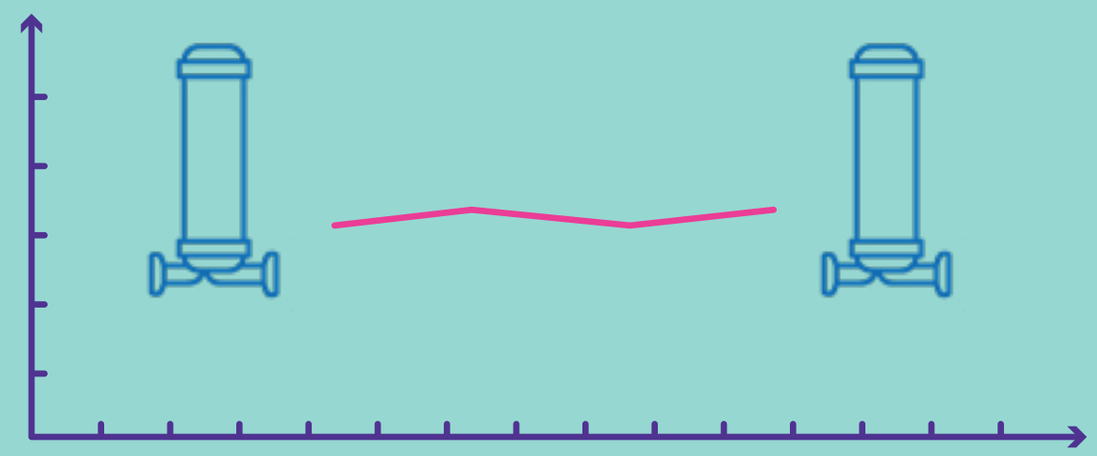

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RELATED DOSSIER CONTENT

General Properties

Batch Analysis

DOSSIER OVERVIEW

Visit Website

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Specification

1.01816.0000 Ammonium sulfate EMPROVE® EXPERT ACS,NF

	Spec. Values	
Assay (alkalimetric)	99.5 - 100.5	%
Identity	passes test	
Insoluble matter	≤ 0.001	%
pH-value (5 %; water; 25 °C)	5.0 - 6.0	
Chloride (Cl)	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.0010	%
Phosphate (PO_4)	≤ 0.0005	%
Heavy metals (ACS)	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%
Cr (Chromium)	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%
Pt (Platinum) (*)	≤ 0.0001	%
Zn (Zinc)	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process	
Residue on ignition (as sulfate)	≤ 0.005	%
Loss on Drying (105 °C)	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test	
E.coli (absent in 1 g)	passes test	
Staphylococcus aureus (absent in 1 g)	passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test	
Candida albicans (absent in 1 g)	passes test	
Endotoxins	≤ 2.5	I.U./g

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated (*).
Corresponds to bio ACS,NF

Claudia Wiegand
Responsible laboratory manager quality control

This document has been produced electronically and is valid without a signature.

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SALSA Version 020708 /000000000001 Date: 01.04.2019

Visit Website

RELATED DOSSIER CONTENT

General Properties

Batch Analysis

DOSSIER OVERVIEW

Visit Website

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Certificate of Analysis

1.01816.0000 Ammonium sulfate suitable for the biopharmaceutical production EMPROVE® bio ACS,NF
Batch AM1135916

	Spec. Values		Batch Values	
Assay (alkalimetric)	99.5 - 100.5	%	100.0	%
Identity	passes test		passes test	
Insoluble matter	≤ 0.001	%	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0		5.2	
Chloride (Cl)	≤ 0.0002	%	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.001	%	≤ 0.001	%
Phosphate (PO_4)	≤ 0.0005	%	≤ 0.0005	%
Heavy metals (as Pb)	≤ 0.0005	%	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%	≤ 0.0001	%
Cr (Chromium) (*)	≤ 0.000075	%	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%	≤ 0.0002	%
Zn (Zinc)	≤ 0.0001	%	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process		excluded by manufacturing process	
Residue on ignition (as sulphate)	≤ 0.005	%	≤ 0.005	%
Loss on Drying (105°C)	≤ 0.1	%	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test		passes test	
E.coli (absent in 1 g)	passes test		passes test	
Staphylococcus aureus (absent in 1 g)	passes test		passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test		passes test	
Candida albicans (absent in 1 g)	passes test		passes test	
Endotoxins	≤ 2.5	I.U./g	≤ 2.5	I.U./g

* specified acc. to EMEA/CHMP/SWP/4446/2000. Other residues of metal catalysts or metal reagents acc. to this guideline are not likely to be present.
Corresponds to bio ACS,NF

Date of examination (DD.MM.YYYY) 07.03.2017
Minimum shelf life (DD.MM.YYYY) 31.03.2022

Claudia Wiegand
Responsible laboratory manager quality control

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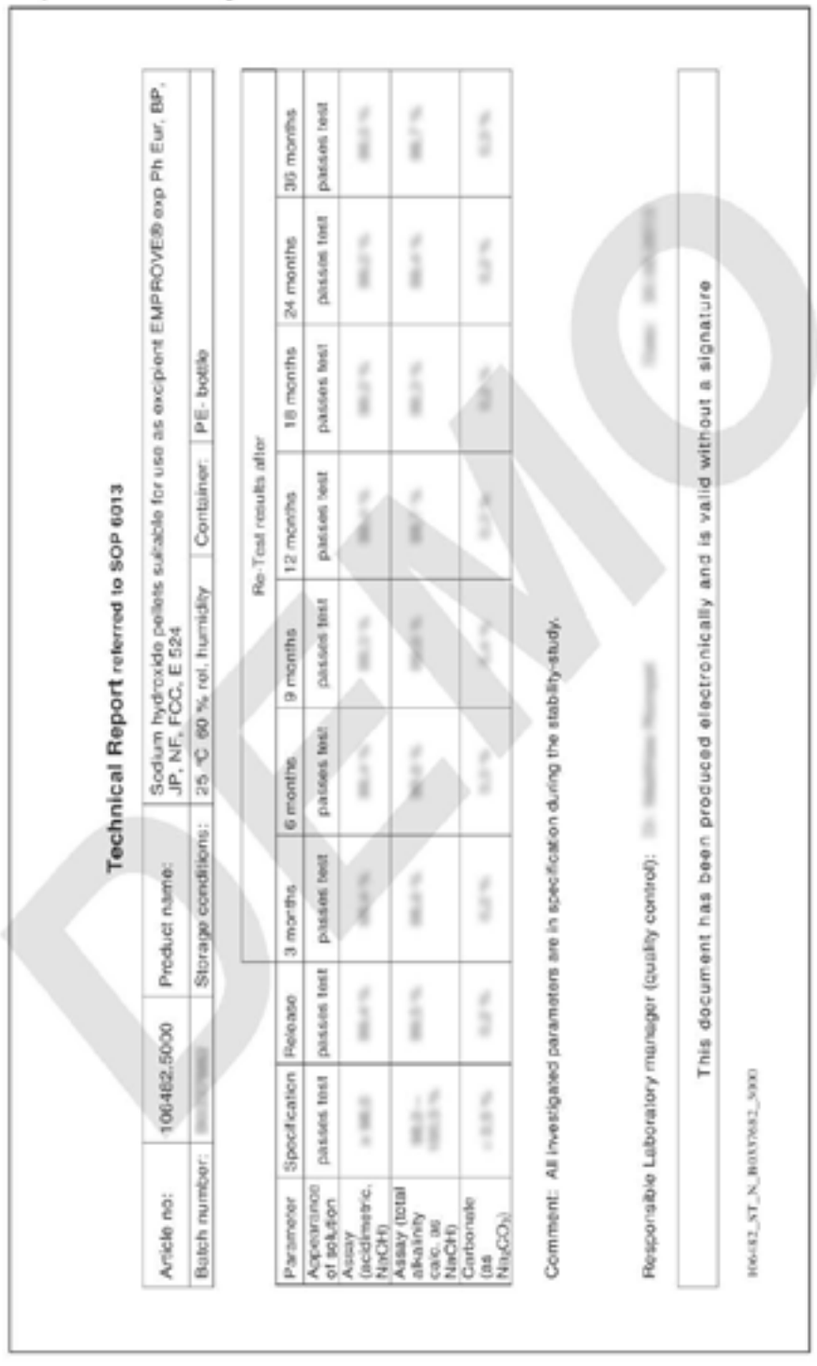

Technical Report referred to SOP 6013

Article no:	106462.5000	Product name:	Sodium hydroxide pellets suitable for use as excipient EMPROVE® exp Ph Eur, BP, JP, NF, FCC, E 524
Batch number:	[redacted]	Storage conditions:	25 °C/ 60 % rel. humidity	Container:	PE- bottle

Parameter	Specification	Release	Re-Test results after			
			3 months	6 months	9 months	12 months	18 months	24 months	36 months
Appearance of solution	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test
Assay (acidimetric, NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assay (total alkalinity calc. as NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carbonate (as Na_2CO_3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comment: All investigated parameters are in specification during the stability-study.

Responsible Laboratory manager (quality control): [redacted]

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Merck KGaA, Darmstadt, Germany

Ammonium sulfate EMPROVE® EXPERT ACS, NF		Monograph
Item No. 101816	CAS 7783-20-2	[redacted]

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Bacterial Retention and Sterilization 3 Forward Cycles of 30 Minutes at 135 °C and 1000 mbar (15 psid) Differential Pressure

Test Summary

Tests were performed to confirm that cartridge filters with Millipore Express® SHC membrane (Standard Area) completely retain a 10^7 cfu per cm^2 challenge of *Brevudimonas diminuta* after steaming-in-place for 3 forward cycles of 30 minutes at 135°C and 1000 mbar (15 psid) differential pressure. Cartridges were challenged according to ASTM F838 methodology. The number of organisms in the filtrate was determined, and cartridge integrity (diffusion and bubble point) was measured.

Results

After steaming-in-place for a minimum of 3 forward Steam in Place (SIP) cycles of 30 minutes at 135°C and 1000 mbar (15 psid), all cartridge filters with Millipore Express® SHC membrane (Standard Area) completely retained a *Brevudimonas diminuta* challenge of 10^7 cfu per cm^2 of filter area. The acceptance criterion is zero organisms in the filtrate.

Full test results are shown in Appendix II.

Bacterial Retention and Sterilization 5 Forward Cycles of 30 Minutes at 135 °C

Test Summary

Tests were performed to confirm that cartridge filters with Millipore Express® SHC membrane (High Area) completely retain a 10^7 cfu per cm^2 challenge of *Brevudimonas diminuta* after steaming-in-place for 5 forward cycles of 30 minutes at 135°C. Cartridges were challenged according to ASTM F838 methodology. The number of organisms in the filtrate was determined, and cartridge integrity (diffusion) was measured.

Results

After steaming-in-place for 5 forward cycles of 30 minutes at 135°C all cartridge filters with Millipore Express® SHC membrane (High Area) completely retained a *Brevudimonas diminuta* challenge of 10^7 cfu per cm^2 of filter area. The acceptance criterion is zero organisms in the filtrate.

Full test results are shown in Appendix II.

Bacterial Endotoxin

Test Summary

Bacterial Endotoxin testing was conducted on one Millipore Express® SHF and one Millipore Express® SHC cartridge at an independent laboratory according to USP <85> Bacterial Endotoxin Test. The test results determine the level of endotoxins contained within the Millipore Express® SHF or SHC cartridge filter.

Results

The geometric mean endpoint concentration of the test articles was <0.06 EU/mL and each contained <0.06 EU/mL of beacterial endotoxin. The bacterial endotoxin testing and limits meet the requirements of USP <85>, EP 2.6.14 and JP 4.01.

Independent laboratory certificates are shown in Appendix I.

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Bacterial Endotoxin

Integrity Testing

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Bacterial Endotoxin

Integrity Testing

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Integrity Testing (Air Diffusion and Bubble Point)

Test Summary

The results from integrity tests are used to determine the ability of Millipore Express® SHF or SHC cartridge filters to perform as intended. Millipore Express® SHF and SHC cartridge filter integrity was measured by performing bubble point and diffusion tests, as outlined below. By correlating the integrity test values to Millipore Express® SHF or SHC cartridge filter bacterial retention, the integrity test is utilized to monitor the Millipore Express® SHF or SHC cartridge filters' sterilizing capability after exposure to various hydraulic and thermal stresses.

Bubble Point Value
Bubble point was determined for the water-wetted filter using an automatic integrity tester.

Diffusion Values
The gas flow rate was measured in the forward direction at the specification pressure using air and water as the wetting fluid.

Results

All Millipore Express® SHF and SHC cartridge filters met the bubble point specifications of >4 bar (58 psi) and the following diffusion specifications:

Device Length (in.)	Diffusion Specification at 2.76 bar (40 psi) (cc/min)
Millipore Express® SHF Cartridge Filter	
5	≤ 16.4
10	≤ 30.0
20	≤ 60.0
30	≤ 90.0
Millipore Express® SHC Cartridge Filter	
5	≤ 13.3
10	≤ 28.2
20	≤ 56.3
30	≤ 84.5

Test results are below.

Device Length (in.)	Number of Lots Tested	Number of Devices Tested	Diffusion Range (cc/min)	Bubble Point Range (psi)
Millipore Express® SHF Cartridge Filter				
5	1	2	9.0 - 10.0	80.2 - 84.3
10	6	48	19.9 - 27.7	71.0 - 88.0
Millipore Express® SHC Cartridge Filter				
5	1	2	7.0 - 7.7	84.1 - 85.0
10	1	22	17.4 - 21.6	81.1 - 87.8

Full test results are shown in Appendix II.

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Shelf Life Testing

Gamma Irradiation

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Shelf Life Testing Requirements and Results

Cartridge and Autoclaveable Capsule Filters

Emprove® Quality Management Dossier
Shelf Life Information Data Sheet
Product Family: Millipore Express® PES PP

Shelf Life Information		
Shelf Life: 60 months		
Expiration Date: N/A		
Storage Conditions: 15°C-30°C		

Performance Tests	Specification	Data Range
Flow Delta P	≤ 1.7psi	
Diffusion	≤ 30.0cc/min @ 40psi	
Bubble Point	≥ 50.0psi	
Retention	No passage of B. diminuta at >1 x 10^7 cfu/cm^2 (Pass / Fail)	
Minimum Hydraulic Stress	≤ 30.0cc/min @ 40psi	
LAL Endotoxin Test	<0.25 EU/ml	
USP WFI Oxidizable	Pass / Fail	
TOC	<500ppb	
Conductivity	<1.3uS/cm	

Not all products listed have undergone stability testing to determine the products' shelf lives. The design of the stability schedule is such that only select product(s) within a product family are tested. The design assumes that the products selected are representative of the family as they utilize the same materials of construction, production processes, and packaging components as the products within the family.

The product(s) above does not have a published expiration date or shelf life claim. The shelf life stated above is a guideline based upon available product stability data which is constantly updated as new data is made available. It is not a guarantee or a claim designating the time prior to which a lot of the product will remain within the shelf life specification if stored under the defined conditions, and after which it must not be put into use. It is not an expiration date or a Use-By-Date. Further, as this is not a product claim, updates to product shelf lives do not require customer notification.

For firms that must establish expiration dates or Use-By-Dates for this product(s) utilized in a cGMP manufacturing environments, it is recommended that the firms assign a default Use-By-Date based on their internal procedures/practices.

Melissa Sheerin

Melissa Sheerin
Shelf Life Engineer
Separations and Instruments Technology Cluster

MilliporeSigma

A business of Merck KGaA, Darmstadt, Germany

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Gamma Irradiation

Certain Millipore Express® SHC and Millipore Express® SHF Opticap® XL and XLT Capsule Devices can be sterilized by gamma irradiation. These items can be identified in the Catalong Numbers table of this document. The following testing and processes are in place to ensure that the devices will perform as intended after gamma irradiation.

We utilize a contract sterilizer providing gamma irradiation processing services. The contract sterilizer operates under a quality system that is in compliance with 21 CFR Part 820 and applicable sections of 21 CFR part 211. In addition, it is registered to the ISO 13485:2003 and EN ISO 13485:2012 Quality Standards, and adheres to the requirements of ISO 11137-2:2006 (Gamma) and ISO 11135-1:2007 (EO). Current certification expires December 2018. We perform audits of this facility every two years.

Testing Requirements and Results

Test Summary

A validation was performed to substantiate 25 – 40 kGy as a sterilization dose (SAL of 10^{-6}) for Opticap® XL and XLT capsule filters using the ANSI/AAMI/ISO 11137-2:2006 VDmax method. This requires the demonstration that the product bioburden is less than 1000 cfu.

[redacted]

capsules.

Acceptance Criteria

Bacteriostasis/Fungistasis:

Bacteriostasis/Fungistasis testing must show growth on irradiated product. This is a control on the sterility test that demonstrates that growth can be detected.

Initial Bioburden:

The overall average of 30 units (10 from each of 3 lots) must be less than 1000 cfu for the tested products.

Post-Gamma Sterility:

If there are 0 or 1 positives after sterility testing, then radiation sterilization at 25 kGy is substantiated, and that product can be claimed to be sterile. If there are 3 or more positives after sterility testing, then that product has failed the qualification.

If there are 2 positives after sterility testing for either product, then another 10 units from lot 2 need to be submitted to the verification dose and tested again for sterility. If there is 1 or more positives after the second set of sterility tests, then the product has failed the qualification and the VDmax method cannot be used.

If the product fails the qualification but the positive sterility test result can be attributed to an incorrect estimation of bioburden, an error in sterility testing, or an error in dose delivery then a corrective action will be documented and the qualification can be repeated.

RELATED DOSSIER CONTENT

Shelf Life Testing

Gamma Irradiation

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RELATED DOSSIER CONTENT

General Properties

Batch Analysis

DOSSIER OVERVIEW

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Specification

1.01816.0000 Ammonium sulfate EMPROVE® EXPERT ACS,NF

	Spec. Values	
Assay (alkalimetric)	99.5 - 100.5	%
Identity	passes test	
Insoluble matter	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0	
Chloride (Cl)	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.0010	%
Phosphate (PO_4)	≤ 0.0005	%
Heavy metals (ACS)	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%
Cr (Chromium)	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%
Pt (Platinum) (*)	≤ 0.0001	%
Zn (Zinc)	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process	
Residue on ignition (as sulfate)	≤ 0.005	%
Loss on Drying (105 °C)	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test	
E.coli (absent in 1 g)	passes test	
Staphylococcus aureus (absent in 1 g)	passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test	
Candida albicans (absent in 1 g)	passes test	
Endotoxins	≤ 2.5	I.U./g

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated (*).
Corresponds to bio ACS,NF

Claudia Wiegand
Responsible laboratory manager quality control

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RELATED DOSSIER CONTENT

General Properties

Batch Analysis

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Certificate of Analysis

1.01816.0000 Ammonium sulfate suitable for the biopharmaceutical production EMPROVE® bio ACS,NF
Batch AM1135916

	Spec. Values		Batch Values	
Assay (alkalimetric)	99.5 - 100.5	%	100.0	%
Identity	passes test		passes test	
Insoluble matter	≤ 0.001	%	≤ 0.001	%
pH-value (5 %; water; 25 °C)	5.0 - 6.0		5.2	
Chloride (Cl)	≤ 0.0002	%	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.001	%	≤ 0.001	%
Phosphate (PO_4)	≤ 0.0005	%	≤ 0.0005	%
Heavy metals (as Pb)	≤ 0.0005	%	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%	≤ 0.0001	%
Cr (Chromium) (*)	≤ 0.000075	%	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%	≤ 0.0002	%
Zn (Zinc)	≤ 0.0001	%	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process		excluded by manufacturing process	
Residue on ignition (as sulphate)	≤ 0.005	%	≤ 0.005	%
Loss on Drying (105°C)	≤ 0.1	%	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test		passes test	
E.coli (absent in 1 g)	passes test		passes test	
Staphylococcus aureus (absent in 1 g)	passes test		passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test		passes test	
Candida albicans (absent in 1 g)	passes test		passes test	
Endotoxins	≤ 2.5	I.U./g	≤ 2.5	I.U./g

* specified acc. to EMEA/CHMP/SWP/4446/2000. Other residues of metal catalysts or metal reagents acc. to this guideline are not likely to be present.
Corresponds to bio ACS,NF

Date of examination (DD.MM.YYYY) 07.03.2017
Minimum shelf life (DD.MM.YYYY) 31.03.2022

Claudia Wiegand
Responsible laboratory manager quality control

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RELATED DOSSIER CONTENT

Stability Studies

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Chapter 4: Stability data

Technical Report referred to SOP 6013

Article no:	106482.5000	Product name:	Sodium hydroxide pellets suitable for use as excipient EMPROVE® exp Ph Eur, BP, JP, NF, FCC, E 524		
Batch number:	[redacted]	Storage conditions:	25 °C 60 % rel. humidity	Container:	PE- bottle

			Re-Test results after						
Parameter	Specification	Release	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Appearance of solution	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test
Assay (acidimetric, NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assay (total alkalinity calc. as NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carbonate (as Na_2CO_3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comment: All investigated parameters are in specification during the stability-study.

Responsible Laboratory manager (quality control): [redacted] Date: [redacted]

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Chapter 3: Analytical Procedure

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Merck KGaA, Darmstadt, Germany

Ammonium sulfate EMPROVE® EXPERT ACS, NF		Monograph [redacted]
Item No. 101816	CAS 7783-20-2	

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Release Criteria

Bacterial Retention	Quantitative retention of 10^7 CFU/cm² *Brevundimonas diminuta* ATCC® 19146 per ASTM® methodology.
USP Bacterial Endotoxin	Aqueous extraction contains < 0.25 EU/mL per 10 in. filter as determined by the Limulus Amebocyte Lysate (LAL) test, meeting requirements of USP <85>, EP 2.6.14 and JP 4.01..
Bubble Point at 23°	≥ 4000 mbar (58.0 psi) air with water
Air Diffusion	Through a water wet membrane at ambient temperature at 2.8 bar (40 psi): Millipore Express® SHF Membrane ≤ 16.4 cc/min per 5 in. cartridge ≤ 30.0 cc/min per 10 in. cartridge Millipore Express® SHC Membrane Standard Area ≤ 13.3 cc/min per 5 in. cartridge ≤ 28.2 cc/min per 10 in. cartridge High Area ≤ 56.4 cc/min per 10 in. cartridge
Water Flow Rate & Pressure Drop	See table below
Hydraulic Stress	Maintains integrity after sterilization and a forward stress to 100 psi (6.9 bar) and a reverse stress to 30 psi (2.1 bar).
Oxidizable Substances	Autoclaved cartridge effluent meets the requirements for USP sterile water for injection after a water flush of: Millipore Express® SHF Membrane: 1.0 L (per 5 or 10 in. cartridge) Millipore Express® SHC Membrane (Standard Area only): 2.0 L (per 5 or 10 in. cartridge)
Total Organic Carbon (TOC) and Conductivity	Samples exhibited < 500 ppb TOC per USP <643> and less than 1.3 µS/cm conductivity per USP <645> after sterilization and a water flush of: Millipore Express® SHF Membrane 5.5 L per 5 in. cartridge at 25°C 10 L per 10 in. cartridge at 25°C Millipore Express® SHC Membrane 9.5 L per 5 in. cartridge at 25°C 20 L per 10 in. cartridge at 25°C

Length (in.)	Flow Rate Lpm (gpm)	Pressure Drop mbar (psi)
Millipore Express® SHF Membrane		
5	7.6 (2.0)	≤ 214 (3.1)
10	7.6 (2.0)	≤ 120 (1.7)
Millipore Express® SHC Membrane		
5	7.6 (2.0)	≤ 421 (6.1)
10	7.6 (2.0)	≤ 200 (2.9)

Bacterial Retention and Sterilization 3 Forward Cycles of 30 Minutes at 135 °C and 1000 mbar (15 psid) Differential Pressure

Test Summary

Tests were performed to confirm that cartridge filters with Millipore Express® SHC membrane (Standard Area) completely retain a 10^7 cfu per cm^2 challenge of *Brevudimonas diminuta* after steaming-in-place for 3 forward cycles of 30 minutes at 135°C and 1000 mbar (15 psid) differential pressure. Cartridges were challenged according to ASTM F838 methodology. The number of organisms in the filtrate was determined, and cartridge integrity (diffusion and bubble point) was measured.

Results

After steaming-in-place for a minimum of 3 forward Steam in Place (SIP) cycles of 30 minutes at 135°C and 1000 mbar (15 psid), all cartridge filters with Millipore Express® SHC membrane (Standard Area) completely retained a *Brevudimonas diminuta* challenge of 10^7 cfu per cm^2 of filter area. The acceptance criterion is zero organisms in the filtrate.

Full test results are shown in Appendix II.

Bacterial Retention and Sterilization 5 Forward Cycles of 30 Minutes at 135 °C

Test Summary

Tests were performed to confirm that cartridge filters with Millipore Express® SHC membrane (High Area) completely retain a 10^7 cfu per cm^2 challenge of *Brevudimonas diminuta* after steaming-in-place for 5 forward cycles of 30 minutes at 135°C. Cartridges were challenged according to ASTM F838 methodology. The number of organisms in the filtrate was determined, and cartridge integrity (diffusion) was measured.

Results

After steaming-in-place for 5 forward cycles of 30 minutes at 135°C all cartridge filters with Millipore Express® SHC membrane (High Area) completely retained a *Brevudimonas diminuta* challenge of 10^7 cfu per cm^2 of filter area. The acceptance criterion is zero organisms in the filtrate.

Full test results are shown in Appendix II.

Bacterial Endotoxin

Test Summary

Bacterial Endotoxin testing was conducted on one Millipore Express® SHF and one Millipore Express® SHC cartridge at an independent laboratory according to USP <85> Bacterial Endotoxin Test. The test results determine the level of endotoxins contained within the Millipore Express® SHF or SHC cartridge filter.

Results

The geometric mean endpoint concentration of the test articles was <0.06 EU/mL and each contained <0.06 EU/mL of beacterial endotoxin. The bacterial endotoxin testing and limits meet the requirements of USP <85>, EP 2.6.14 and JP 4.01.

Independent laboratory certificates are shown in Appendix I.

RELATED DOSSIER CONTENT

Release Criteria

Bacterial Endotoxin

DOSSIER OVERVIEW

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Shelf Life Testing Requirements and Results

Cartridge and Autoclaveable Capsule Filters

Emprove® Quality Management Dossier
Shelf Life Information Data Sheet
Product Family: Millipore Express® PES PP

Shelf Life Information		
Shelf Life: 60 months		
Expiration Date: N/A		
Storage Conditions: 15ºC-30ºC		

Performance Tests	Specification	Data Range
Flow Delta P	≤ 1.7psi	
Diffusion	≤ 30.0cc/min @ 40psi	
Bubble Point	≥ 50.0psi	
Retention	No passage of B. diminuta at >1 x 10⁷ cfu/cm² (Pass / Fail)	
Minimum Hydraulic Stress	≤ 30.0cc/min @ 40psi	
LAL Endotoxin Test	<0.25 EU/ml	
USP WFI Oxidizable	Pass / Fail	
TOC	<500ppb	
Conductivity	<1.3uS/cm	

Not all products listed have undergone stability testing to determine the products' shelf lives. The design of the stability schedule is such that only select product(s) within a product family are tested. The design assumes that the products selected are representative of the family as they utilize the same materials of construction, production processes, and packaging components as the products within the family.

The product(s) above does not have a published expiration date or shelf life claim. The shelf life stated above is a guideline based upon available product stability data which is constantly updated as new data is made available. It is not a guarantee or a claim designating the time prior to which a lot of the product will remain within the shelf life specification if stored under the defined conditions, and after which it must not be put into use. It is not an expiration date or a Use-By-Date. Further, as this is not a product claim, updates to product shelf lives do not require customer notification.

For firms that must establish expiration dates or Use-By-Dates for this product(s) utilized in a cGMP manufacturing environments, it is recommended that the firms assign a default Use-By-Date based on their internal procedures/practices.

Melissa Sheerin

Melissa Sheerin
Shelf Life Engineer
Separations and Instruments Technology Cluster

MilliporeSigma

A business of Merck KGaA, Darmstadt, Germany

RELATED DOSSIER CONTENT

Shelf Life Testing

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Emprove® Program

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Specification

1.01816.0000 Ammonium sulfate EMPROVE® EXPERT ACS,NF

	Spec. Values	
Assay (alkalimetric)	99.5 - 100.5	%
Identity	passes test	
Insoluble matter	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0	
Chloride (Cl)	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.0010	%
Phosphate (PO_4)	≤ 0.0005	%
Heavy metals (ACS)	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%
Cr (Chromium)	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%
Pt (Platinum) (*)	≤ 0.0001	%
Zn (Zinc)	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process	
Residue on ignition (as sulfate)	≤ 0.005	%
Loss on Drying (105 °C)	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test	
E.coli (absent in 1 g)	passes test	
Staphylococcus aureus (absent in 1 g)	passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test	
Candida albicans (absent in 1 g)	passes test	
Endotoxins	≤ 2.5	I.U./g

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated (*).
Corresponds to Ph. ACS,NF

Claudia Wiegand
Responsible laboratory manager quality control

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Certificate of Analysis

1.01816.0000 Ammonium sulfate suitable for the biopharmaceutical production EMPROVE® bio ACS,NF
Batch AM1135916

	Spec. Values		Batch Values	
Assay (alkalimetric)	99.5 - 100.5	%	100.0	%
Identity	passes test		passes test	
Insoluble matter	≤ 0.001	%	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0		5.2	
Chloride (Cl)	≤ 0.0002	%	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.001	%	≤ 0.001	%
Phosphate (PO_4)	≤ 0.0005	%	≤ 0.0005	%
Heavy metals (as Pb)	≤ 0.0005	%	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%	≤ 0.0001	%
Cr (Chromium) (*)	≤ 0.000075	%	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%	≤ 0.0002	%
Zn (Zinc)	≤ 0.0001	%	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process		excluded by manufacturing process	
Residue on ignition (as sulphate)	≤ 0.005	%	≤ 0.005	%
Loss on Drying (105°C)	≤ 0.1	%	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test		passes test	
E.coli (absent in 1 g)	passes test		passes test	
Staphylococcus aureus (absent in 1 g)	passes test		passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test		passes test	
Candida albicans (absent in 1 g)	passes test		passes test	
Endotoxins	≤ 2.5	I.U./g	≤ 2.5	I.U./g

* specified acc. to EMEA/CHMP/SWP/4446/2000. Other residues of metal catalysts or metal reagents acc. to this guideline are not likely to be present.
Corresponds to bio ACS,NF

Date of examination (DD.MM.YYYY) 07.03.2017
Minimum shelf life (DD.MM.YYYY) 31.03.2022

Claudia Wiegand
Responsible laboratory manager quality control

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Elemental Impurity Information

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Chapter 1: Elemental Impurity Information

I. Introduction

The guideline ICH Q3D presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. The risk assessment should be based on scientific knowledge and principles. According to ICH Q3D, information for this risk assessment includes, among others, information supplied by drug substance and/or excipient manufacturers.

This information is intended to provide data to support this risk assessment. This document shall help to identify potential elemental impurities derived from intentionally added catalysts and inorganic reagents. "Additionally it presents information about potential elemental impurities that may be present in drug substances and/or excipients".

II. Intentionally added elements during the manufacturing process

Test

Platinum (Pt) is used in the manufacturing process of the above mentioned product. Platinum is included in the specification and controlled accordingly in the final product.

No other elements listed in classes 1 – 3 according to ICH Q3D are used in the manufacturing steps that are outlined in the manufacturing procedure for the above mentioned item.

The flow diagram of the manufacturing procedure please find in the EMPROVE® Material Qualification Dossier on our website.

III. Elemental Impurity Profile

To show the typical elemental impurity profile for the above mentioned product an elemental impurity screen has been performed on the batches as shown on the next page.

RELATED DOSSIER CONTENT

Materials of Construction

DOSSIER OVERVIEW

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General Properties

Millipore Express® SHF (Sterile High Flux) cartridge filters are sterilizing-grade normal flow filters with pleated 0.2 µm polyethersulfone membrane and polysulfone and polypropylene components. Millipore Express® SHC (Sterile High Capacity) cartridge filters are sterilizing-grade normal flow filters with pleated Millipore Express® SHF membrane with an on-board 0.5 µm polyethersulfone membrane prefilter and polysulfone, polyethersulfone and polypropylene components.

Cartridges with Millipore Express® SHF or SHC membrane provide high flow rates, low extractables, and broad chemical compatibility. These cartridge filters are recommended for the removal of particles and bacterial organisms from a wide range of aqueous solutions.

All cartridge bonds are thermoplastic; no adhesives are used. Each Millipore Express® SHF and SHC filter is integrity tested and visually inspected prior to shipment. Each filter is labeled with the filter type, catalog number, lot number, pore size, and logo.

Materials of Construction

Component	Materials of Construction
Filter membrane	Hydrophilic polyethersulfone (PES)
Film Edge	Polypropylene
Supports	Polypropylene
Cage and end caps	Polypropylene
Core	Polysulfone (standard area cartridges)
	Polyethersulfone (high area cartridges)
O-rings	Silicone, Ethylene Propylene Diene Monomer (EPDM) or Fluoroelastomer

Dimensions (nominal)

Cartridge	Filtration Area m^2 (ft^2)	Maximum Length cm (in.)	Maximum Diameter cm (in.)	Hold Up Volume	
				mL	Conditions
Millipore Express® SHF					
5 in. Cartridge	0.29 (3.1)	12.5 (5)	6.9 (2.7)	--	90 psi for 1 min
Per 10 in. Cartridge	0.54 (5.8)	25.4 (10)	6.9 (2.7)	20	
Millipore Express® SHC Standard Area					
5 in. Cartridge	0.23 (2.5)	12.5 (5)	6.9 (2.7)	--	90 psi for 1 min
Per 10 in. Cartridge	0.49 (5.3)	25.4 (10)	6.9 (2.7)	50	
Millipore Express® SHC High Area					
Per 10 in. Cartridge	1.0 (10.8)	25.4 (10)	6.9 (2.7)	92	75 psi for 1 min

Conclusion

The extractables from our filter devices are part of our filter device validation. All filter components have been tested as per USP <88>, Biological reactivity tests, in vivo. The test reports and certificates for these tests can be viewed in the Material Qualification Dossiers for these devices. USP <88>, Biological reactivity tests, in vivo [5] testing also uses very aggressive time and temperature protocols and extraction solutions. The extracts from Opticap® XL 10 Autoclavable Capsule Filter with Millipore Express® SHC membrane have been shown to be non-toxic.

Guidance for Industry and BPOG have mandated the general extractables requirements [3,4] in an effort to determine the amount and identity of the extractables through a standard approach. There are no acceptance criteria established by regulatory agencies with respect to the quantity of the extractables. It is the responsibility of the end user to utilize information from this dossier to assess the risk in their manufacturing process to ensure that the materials used are appropriate and meet the defined specifications for the toxicological risk to the final drug product safety.

The results from this extraction study in addition to the leachables screening results, should be used in determining the list of target compounds for which the safety threshold must be established. One of the approaches to safety thresholds is per ICH M7 recommendations. Other references are as listed [9,10].

The extractables data from this report should be used in relation to the specific manufacturing process and final drug product formulation. It should also include the cumulative use of the unit in the complete manufacturing flow.

RELATED DOSSIER CONTENT

Conclusion

Elemental substances

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Elemental substances by ICP-MS

Elemental substances were detected via inductively coupled plasma mass spectrometry (ICP/MS) of extracts in WFI and 0.1 M H_3PO_4. Elements tested, determined level of detection and limit of quantitation as well as results for method control exemplary for WFI, 30 min as example are listed below. No observation is above the limit as expected in the BPOG protocol.

Observed ICP/MS Elemental Amounts above Limit of Quantitation for Opticap® XL 10 Autoclavable Capsule Filter with Millipore Express® SHC membrane

Extraction Solvent	Element	ICH Classification	Amount [mg/filter]		
			30 min	1 Day	7 Days
WFI	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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Elemental substances

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Certificate of Analysis

1.01816.0000 Ammonium sulfate suitable for the biopharmaceutical production EMPROVE® bio ACS,NF
Batch AM1135916

	Spec. Values		Batch Values	
Assay (alkalimetric)	99.5 - 100.5	%	100.0	%
Identity	passes test		passes test	
Insoluble matter	≤ 0.001	%	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0		5.2	
Chloride (Cl)	≤ 0.0002	%	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.001	%	≤ 0.001	%
Phosphate (PO_4)	≤ 0.0005	%	≤ 0.0005	%
Heavy metals (as Pb)	≤ 0.0005	%	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%	≤ 0.0001	%
Cr (Chromium) (*)	≤ 0.000075	%	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%	≤ 0.0002	%
Zn (Zinc)	≤ 0.0001	%	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process		excluded by manufacturing process	
Residue on ignition (as sulphate)	≤ 0.005	%	≤ 0.005	%
Loss on Drying (105°C)	≤ 0.1	%	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test		passes test	
E.coli (absent in 1 g)	passes test		passes test	
Staphylococcus aureus (absent in 1 g)	passes test		passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test		passes test	
Candida albicans (absent in 1 g)	passes test		passes test	
Endotoxins	≤ 2.5	I.U./g	≤ 2.5	I.U./g

* specified acc. to EMEA/CHMP/SWP/4446/2000. Other residues of metal catalysts or metal reagents acc. to this guideline are not likely to be present.
Corresponds to bio ACS,NF

Date of examination (DD.MM.YYYY) 07.03.2017
Minimum shelf life (DD.MM.YYYY) 31.03.2022

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106482 Sodium hydroxide pellets EMPROVE® ESSENTIAL Ph Eur,BP,FCC,JP,NF,E 524

Product Quality Report Summary

This report is based on the analytical results of a minimum of 5 batches released during the reporting period [redacted]

Based on the analytical results, the batches tested and released during the reporting period, show a consistently high quality of the product.
Yes ☒ / No ☐

The parameters "total alkalinity", "assay", "carbonate" and "potassium" deliver continuous quantitative values (no limit test) and provide valuable information for the control of the manufacturing process. Therefore trend analyses were conducted for these parameters.
Yes ☒ / No ☐

The consistent operation of the manufacturing process is demonstrated in the period under review based on the following aspects:

- All parameters are within the specification limits
  Yes ☒ / No ☐
- During ongoing stability studies no out of specification results have been confirmed.
  Yes ☒ / No ☐
- In the period under review no material changes regarding this product were performed.
  A material change includes a significant change in any of the following:

  a) Route of synthesis
  b) Specification (if not due to compendial changes)
  c) Nature of the starting materials (BSE/TSE-Status)
  d) Manufacturing site
  e) Part number
  f) Significant change to package configuration

  Yes (no material changes) ☒ / No (material changes) ☐

Quality assessment
In summary, it is confirmed, that for the product 106482 all specified requirements are met. The product corresponds to the requirements of the declared pharmacopoeias and directives referred in the Specification.

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Product Quality

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Release Criteria

Bacterial Retention	Quantitative retention of 10^7 CFU/cm² *Brevundimonas diminuta* ATCC® 19146 per ASTM® methodology.
USP Bacterial Endotoxin	Aqueous extraction contains < 0.25 EU/mL per 10 in. filter as determined by the Limulus Amebocyte Lysate (LAL) test, meeting requirements of USP <85>, EP 2.6.14 and JP 4.01..
Bubble Point at 23°	≥ 4000 mbar (58.0 psi) air with water
Air Diffusion	Through a water wet membrane at ambient temperature at 2.8 bar (40 psi): Millipore Express® SHF Membrane ≤ 16.4 cc/min per 5 in. cartridge ≤ 30.0 cc/min per 10 in. cartridge Millipore Express® SHC Membrane Standard Area ≤ 13.3 cc/min per 5 in. cartridge ≤ 28.2 cc/min per 10 in. cartridge High Area ≤ 56.4 cc/min per 10 in. cartridge
Water Flow Rate & Pressure Drop	See table below
Hydraulic Stress	Maintains integrity after sterilization and a forward stress to 100 psi (6.9 bar) and a reverse stress to 30 psi (2.1 bar).
Oxidizable Substances	Autoclaved cartridge effluent meets the requirements for USP sterile water for injection after a water flush of: Millipore Express® SHF Membrane: 1.0 L (per 5 or 10 in. cartridge) Millipore Express® SHC Membrane (Standard Area only): 2.0 L (per 5 or 10 in. cartridge)
Total Organic Carbon (TOC) and Conductivity	Samples exhibited < 500 ppb TOC per USP <643> and less than 1.3 µS/cm conductivity per USP <645> after sterilization and a water flush of: Millipore Express® SHF Membrane 5.5 L per 5 in. cartridge at 25°C 10 L per 10 in. cartridge at 25°C Millipore Express® SHC Membrane 9.5 L per 5 in. cartridge at 25°C 20 L per 10 in. cartridge at 25°C

Length (in.)	Flow Rate Lpm (gpm)	Pressure Drop mbar (psi)
Millipore Express® SHF Membrane		
5	7.6 (2.0)	≤ 214 (3.1)
10	7.6 (2.0)	≤ 120 (1.7)
Millipore Express® SHC Membrane		
5	7.6 (2.0)	≤ 421 (6.1)
10	7.6 (2.0)	≤ 200 (2.9)

Water Flow Rate & Pressure Drop

Test Summary

The water flow rate/pressure drop was determined for the Millipore Express® SHF and SHC cartridge filters over a range of flow rates from 1 gpm to 20 gpm (3.8 Lpm to 75.7 Lpm).

Differential pressure versus water flow rate readings were recorded for cartridges. The results indicate the water pressure drop of the filters.

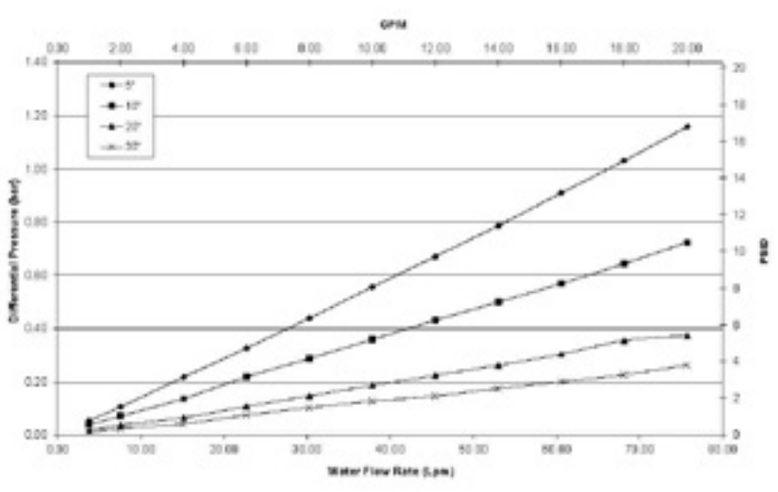
Results

All Millipore Express® SHF and SHC cartridge filters met specifications. Results are normalized to a water temperature of 23°C.

Flow Rate and Pressure Drop Specifications

Device Length (in.)	Flow Rate Lpm (gpm)	Pressure Drop mbar (psi)
Millipore Express® SHF Cartridge Filter		
5	7.6 (2.0)	≤ 214 (3.1)
10	7.6 (2.0)	≤ 120 (1.7)
Millipore Express® SHC Cartridge Filter		
5	7.6 (2.0)	≤ 421 (6.1)
10	7.6 (2.0)	≤ 200 (2.9)

Flow Rate vs Pressure Drop
Millipore Express® SHF Cartridge Filters
0.2 µm (CGEP)



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Test Summaries and Results

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Results Summary

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Results Summary

Following is a summary of extractable compounds identified in this study. The estimated concentrations are the highest concentration observed per model solvent. The table does not include the results for Ion Chromatography (IC), Total Organic Carbon (TOC), Nonvolatile Residue (NVR), pH or Conductivity. Those results are presented in the results section of this report.

Opticap® XL 10 Autoclavable Capsule Filter with Millipore Express® SHC membrane Extractable Test Result Summary

Solvent	Extractable	Retention Time (minute)	Estimated Concentration		Analytical Method
			(mg/filter)	(µg/cm²)	
WFI	N-Methyl-2-pyrrolidone	14.46	4.2	0.86	DI-GC/MS
	[illegible]	11.34	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	1.6	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	0.29	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	ICP-MS
0.1 M H_3PO_4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0.5 N NaOH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Specification

1.01816.0000 Ammonium sulfate EMPROVE® EXPERT ACS,NF

	Spec. Values	
Assay (alkalimetric)	99.5 - 100.5	%
Identity	passes test	
Insoluble matter	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0	
Chloride (Cl)	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.0010	%
Phosphate (PO_4)	≤ 0.0005	%
Heavy metals (ACS)	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%
Cr (Chromium)	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%
Pt (Platinum) (*)	≤ 0.0001	%
Zn (Zinc)	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process	
Residue on ignition (as sulfate)	≤ 0.005	%
Loss on Drying (105 °C)	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test	
E.coli (absent in 1 g)	passes test	
Staphylococcus aureus (absent in 1 g)	passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test	
Candida albicans (absent in 1 g)	passes test	
Endotoxins	≤ 2.5	I.U./g

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). Class 1-3 elements are not likely to be present above the ICH Q3D option 1 limit, unless specified and indicated (*).
Corresponds to bio ACS,NF

Claudia Wiegand
Responsible laboratory manager quality control

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101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Certificate of Analysis

1.01816.0000 Ammonium sulfate suitable for the biopharmaceutical production EMPROVE® bio ACS,NF

Batch AM1122916

	Spec. Values		Batch Values	
Assay (alkalimetric)	99.5 - 100.5	%	100.1	%
Identity	passes test		passes test	
Insoluble matter	≤ 0.001	%	≤ 0.001	%
pH-value (5 %; water, 25 °C)	5.0 - 6.0		5.2	
Chloride (Cl)	≤ 0.0002	%	≤ 0.0002	%
Nitrate (NO_3)	≤ 0.001	%	≤ 0.001	%
Phosphate (PO_4)	≤ 0.0005	%	≤ 0.0005	%
Heavy metals (as Pb)	≤ 0.0005	%	≤ 0.0005	%
Al (Aluminium)	≤ 0.000075	%	≤ 0.000075	%
As (Arsenic)	≤ 0.00002	%	≤ 0.00002	%
Ca (Calcium)	≤ 0.001	%	≤ 0.001	%
Cd (Cadmium)	≤ 0.0001	%	≤ 0.0001	%
Cr (Chromium) (*)	≤ 0.000075	%	≤ 0.000075	%
Cu (Copper)	≤ 0.0001	%	≤ 0.0001	%
Fe (Iron)	≤ 0.0002	%	≤ 0.0002	%
Mg (Magnesium)	≤ 0.0005	%	≤ 0.0005	%
Pb (Lead)	≤ 0.0002	%	≤ 0.0002	%
Zn (Zinc)	≤ 0.0001	%	≤ 0.0001	%
Residual solvents (ICH Q3C)	excluded by manufacturing process		excluded by manufacturing process	
Residue on ignition (as sulphate)	≤ 0.005	%	≤ 0.005	%
Loss on Drying (105°C)	≤ 0.1	%	≤ 0.1	%
Total aerobic microbial count	≤ 1000	CFU/g	≤ 1000	CFU/g
Total yeast and mould count	≤ 10	CFU/g	≤ 10	CFU/g
Salmonella species (absent in 10 g)	passes test		passes test	
E.coli (absent in 1 g)	passes test		passes test	
Staphylococcus aureus (absent in 1 g)	passes test		passes test	
Pseudomonas aeruginosa (absent in 1 g)	passes test		passes test	
Candida albicans (absent in 1 g)	passes test		passes test	
Endotoxins	≤ 2.5	I.U./g	≤ 2.5	I.U./g

* specified acc. to EMEA/CHMP/SWP/4446/2000. Other residues of metal catalysts or metal reagents acc. to this guideline are not likely to be present.
Corresponds to bio ACS,NF

Date of examination (DD.MM.YYYY) 03.03.2017
Minimum shelf life (DD.MM.YYYY) 31.03.2022

Claudia Wiegand
Responsible laboratory manager quality control

Merck KGaA, Frankfurter Straße 250, 64293 Darmstadt (Germany): +49 6151 72-0
EMD Millipore Corporation - a subsidiary of Merck KGaA, Darmstadt, Germany
400 Summit Drive, Burlington, MA 01803, USA, Phone +1 (781) 533-6000

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3.2.S.4.5 Justification of Specification

The specification of our product has been developed in accordance with the requirements of the declared pharmacopoeia including ICH Q3C for Residual Solvents and with respect to the requirements of customers in different application fields.

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). In case elements have been identified as likely to be present they are added to the specification with a suitable limit and indicated.

The parameter Platinum (Pt) is specified due to recognized impurity of the manufacturing process. All other specified parameters, resulting from the history of the product based on former declared regulations and customer requirements, are not relevant for the control of the product's pharmaceutical quality.

3.2.S.5 Reference Standards of Materials

3.2.S.5.1 Reference Standards of Materials:

Not applicable, no standard material required.

3.2.S.6 Container Closure System

3.2.S.6.1 Container Closure System:

The packing materials with which the article comes into contact are:

- DPES (double polyethylene sack) liner (in secondary packing: corrugated cardboard box)
- Polyethylene bottle/container
- PE bag system with integrated humidity regulation in PE drum; material in direct contact: PE, complying to pharmacopoeial requirements

Income packaging materials are subjected to acceptance inspection in the package-testing laboratory. The materials are selected at Merck KGaA according to special criteria with regard to suitability for the application. In addition, the materials are inspected for physical condition upon receipt.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The minimum shelf life of product has been defined based on the chemical behaviour of material and on experience in handling and storing material at Merck KGaA, Darmstadt, Germany.

3.2.S.7.2 Postapproval Stability Protocol and Stability Comment

If stored at declared storage conditions and in original closed containers, the minimum shelf life applies as indicated in our certificate of analysis
Ongoing stability studies are performed considering the product’s shelf life duration in line with "T
IPEC Excipient Stability Program Guide" 2010.

RELATED DOSSIER CONTENT

TUPP

DOSSIER OVERVIEW

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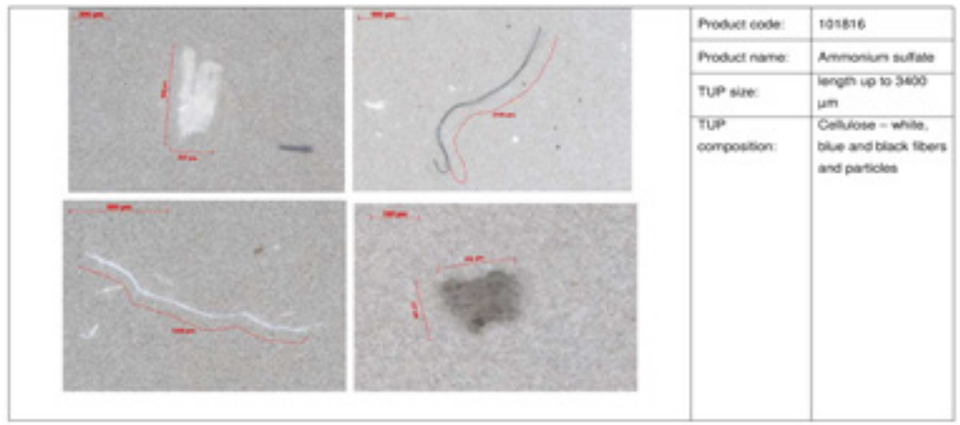
101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF



Product code:	101816
Product name:	Ammonium sulfate
TUP size:	length up to 3400 µm
TUP composition:	Cellulose – white, blue and black fibers and particles

Version 1.1 4 / 14

Product code:	101816
Product name:	Ammonium sulfate
TUP size:	length up to 300 µm
TUP composition:	Silicates (with and without paraffin and with iron) – black particles

Version 1.1 5 / 14

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RELATED DOSSIER CONTENT

Specifications

Particulates/Non-Fibe

DOSSIER OVERVIEW

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Specifications

Design Criteria

Non-Fiber Releasing	Millipore Express® SHF and SHC membrane meets the criteria for a non-fiber releasing filter as defined in 21 CFR 210.3 (b)(6).
Alcohol Reference Test	≥ 1280 mbar (18.5 psi) 70/30 water/IPA with nitrogen at 23°C
Component Material Toxicity	Component Materials meet the criteria of the USP <88> Reactivity Test for Class VI Plastics. These products meet the requirements of the USP<88> Safety Test, utilizing a 0.9% sodium chloride extraction. This product is non-cytotoxic per ISO(R) 10993-5.
Indirect Food Additive	All component materials meet the FDA Indirect Food Additive requirements cited in 21 CFR 177-182.
Sterilization	Millipore Express® SHF and SHC cartridge filters may be autoclaved for up to 25 cycles of 60 minutes at 126°C.
	Millipore Express® SHF cartridge filters may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar)
	Millipore Express® SHC cartridge filters Standard Area may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar) or 3 forward cycles at ≤ 15 psi (1 bar) High Area may be steamed in place for 30 minutes at 135 °C for up to 5 forward cycles at ≤ 5 psi (340 mbar)
Maximum Differential Pressure	Forward: 6.9 bar (100 psi) at 25°C 1.70 bar (25 psi) at 80°C 1 bar (15 psi) at 135°C (Millipore Express® SHC cartridge filters) 0.34 bar (5 psi) at 135°C (Millipore Express® SHF cartridge filters) Reverse: 2.1 bar (30 psi) at 25°C 0.07 bar (1 psi) at 135°C

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Particulates/Non-Fiber Releasing

Test Summary

Testing was performed to show that Millipore Express® SHF and SHC cartridge filters do not release particles into the filtrate during use. Three lots of Millipore Express® SHF 10 inch cartridges (1 device from each lot) were autoclaved for one cycle of 60 minutes at 126 °C then flushed with a total of 10 liters of 0.1 µm filtered water at a flow rate of 1 liter per minute. A portion of the filtrate (intervals of 500 mL) was monitored for size and quantity of particles.

Results

The Millipore Express® SHF and SHC cartridge filters meet the requirements listed in the table below. The results meet the requirements of USP <788> and also meet the requirements for a non-fiber releasing filter as defined in 21 CFR 210.3 (b)(6). PDA Technical Report No. 26 states in section 4.2: "Filter flush effluent is considered compliant upon meeting compendial guidelines for particulate matter in injections. Using these criteria, filters are also considered qualified as non-fiber releasing."

Subvisible Particulate testing specification limits meet the requirements of USP <788>, EP 2.9.19, JP 6.07, ICH Q4B (Annex 3, R1), and WHO 5.7.1.

Particle Size Range (µm)	Combined Specification Maximum Particles/mL
≥ 10	20
≥ 25	2

Full test results are shown in Appendix II.

RELATED DOSSIER CONTENT

Specifications

Particulates/Non-Fibe

DOSSIER OVERVIEW

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Release Criteria

Bacterial Retention	Quantitative retention of 10^7 CFU/cm^2 *Brevundimonas diminuta* ATCC® 19146 per ASTM® methodology.
USP Bacterial Endotoxin	Aqueous extraction contains < 0.25 EU/mL per 10 in. filter as determined by the Limulus Amebocyte Lysate (LAL) test, meeting requirements of USP <85>, EP 2.6.14 and JP 4.01..
Bubble Point at 23°	≥ 4000 mbar (58.0 psi) air with water
Air Diffusion	Through a water wet membrane at ambient temperature at 2.8 bar (40 psi): Millipore Express® SHF Membrane ≤ 16.4 cc/min per 5 in. cartridge ≤ 30.0 cc/min per 10 in. cartridge Millipore Express® SHC Membrane Standard Area ≤ 13.3 cc/min per 5 in. cartridge ≤ 28.2 cc/min per 10 in. cartridge High Area ≤ 56.4 cc/min per 10 in. cartridge
Water Flow Rate & Pressure Drop	See table below
Hydraulic Stress	Maintains integrity after sterilization and a forward stress to 100 psi (6.9 bar) and a reverse stress to 30 psi (2.1 bar).
Oxidizable Substances	Autoclaved cartridge effluent meets the requirements for USP sterile water for injection after a water flush of: Millipore Express® SHF Membrane: 1.0 L (per 5 or 10 in. cartridge) Millipore Express® SHC Membrane (Standard Area only): 2.0 L (per 5 or 10 in. cartridge)
Total Organic Carbon (TOC) and Conductivity	Samples exhibited < 500 ppb TOC per USP <643> and less than 1.3 µS/cm conductivity per USP <645> after sterilization and a water flush of: Millipore Express® SHF Membrane 5.5 L per 5 in. cartridge at 25°C 10 L per 10 in. cartridge at 25°C Millipore Express® SHC Membrane 9.5 L per 5 in. cartridge at 25°C 20 L per 10 in. cartridge at 25°C

Length (in.)	Flow Rate Lpm (gpm)	Pressure Drop mbar (psi)
Millipore Express® SHF Membrane		
5	7.6 (2.0)	≤ 214 (3.1)
10	7.6 (2.0)	≤ 120 (1.7)
Millipore Express® SHC Membrane		
5	7.6 (2.0)	≤ 421 (6.1)
10	7.6 (2.0)	≤ 200 (2.9)

RELATED DOSSIER CONTENT

Release Criteria

TOC and Conductivity

Oxidizable Substances

DOSSIER OVERVIEW

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Total Organic Carbon (TOC) and Conductivity

Test Summary

Flushing tests were performed to monitor the reduction of total organic carbon (TOC) and conductivity with flush volume. Millipore Express® SHF and SHC cartridge filters were autoclaved for one cycle of 60 minutes at 126°C prior to flushing. The filters were flushed with purified water at various flow rates according to filter size. The filter effluent was sampled and tested for conductivity and TOC.

Results

The specification for WFI quality water, according to USP <1231> Water for Pharmaceutical Purposes, is < 500 ppb TOC per USP <643> and < 1.3 µS/cm conductivity per USP <645> at 25° C (see below for specifications at different temperatures) at flush volumes listed below. Flush results on the individual filters are summarized in the following graphs.

Conductivity Specifications Adjusted for Temperature

Temperature (°C)	Conductivity Requirement (µS/cm)
15	1.0
20	1.1
25	1.3
30	1.4

Cartridge Length (in.)	Flush Volume Specification (L)	
	Millipore Express® SHF Membrane	Millipore Express® SHC Membrane
5	5.5	9.5
10	10	20
20	20	40
30	30	60

RELATED DOSSIER CONTENT

Release Criteria

TOC and Conductivity

Oxidizable Substances

DOSSIER OVERVIEW

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Oxidizable Substances

Test Summary

USP Oxidizable Substances Tests were performed to determine the presence or absence of oxidizable substances contained in the Millipore Express® SHF and SHC cartridge filters. Cartridges were autoclaved for one cycle of 60 minutes at 126°C. The filters were then flushed at a flow rate of 200 mL/min with purified water. The filter effluent was collected in 200 mL aliquots which were then tested for oxidizable substances per current USP methodology.

Results

Flush Volume Specifications

Cartridge Length (in.)	Flush Volume Specification (mL)	
	Millipore Express® SHF Membrane	Millipore Express® SHC Membrane
5	1000	2000
10	1000	2000
20	2000	4000
30	3000	6000

All Millipore Express® SHF cartridge filters did not show the presence of any oxidizable substances (passing result) after a flush of 600 mL per cartridge filter.

All Millipore Express® SHC cartridge filters did not show the presence of any oxidizable substances (passing result) after a flush of 800 mL per cartridge filter.

Full test results are shown in Appendix II.

Shelf Life Testing Requirements and Results

Cartridge and Autoclaveable Capsule Filters

Emprove® Quality Management Dossier
Shelf Life Information Data Sheet
Product Family: Millipore Express® PES PP

Shelf Life Information
Shelf Life: 60 months
Expiration Date: N/A
Storage Conditions: 15°C-30°C

Performance Tests	Specification	Data Range
Flow Delta P	≤ 1.7psi	
Diffusion	≤ 30.0cc/min @ 40psi	
Bubble Point	≥ 50.0psi	
Retention	No passage of B. diminuta at >1 x 10^7 cfu/cm^2 (Pass / Fail)	
Minimum Hydraulic Stress	≤ 20.0cc/min @ 40psi	
LAL Endotoxin Test	<0.25 EU/ml	
USP WFI Oxidizable	Pass / Fail	
TOC	<500ppb	
Conductivity	<1.3uS/cm	

Not all products listed have undergone stability testing to determine the products' shelf lives. The design of the stability schedule is such that only select product(s) within a product family are tested. The design assumes that the products selected are representative of the family as they utilize the same materials of construction, production processes, and packaging components as the products within the family.

The product(s) above does not have a published expiration date or shelf life claim. The shelf life stated above is a guideline based upon available product stability data which is constantly updated as new data is made available. It is not a guarantee or a claim designating the time prior to which a lot of the product will remain within the shelf life specification if stored under the defined conditions, and after which it must not be put into use. It is not an expiration date or a Use-By-Date. Further, as this is not a product claim, updates to product shelf lives do not require customer notification.

For firms that must establish expiration dates or Use-By-Dates for this product(s) utilized in a cGMP manufacturing environments, it is recommended that the firms assign a default Use-By-Date based on their internal procedures/practices.

Melissa Sheerin

Melissa Sheerin
Shelf Life Engineer
Separations and Instruments Technology Cluster

MilliporeSigma

A business of Merck KGaA, Darmstadt, Germany

RELATED DOSSIER CONTENT

Shelf Life Testing

DOSSIER OVERVIEW

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RELATED DOSSIER CONTENT

Results Summary

DOSSIER OVERVIEW

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Results Summary

Following is a summary of extractable compounds identified in this study. The estimated concentrations are the highest concentration observed per model solvent. The table does not include the results for Ion Chromatography (IC), Total Organic Carbon (TOC), Nonvolatile Residue (NVR), pH or Conductivity. Those results are presented in the results section of this report.

Opticap® XL 10 Autoclavable Capsule Filter with Millipore Express® SHC membrane Extractable Test Result Summary

Solvent	Extractable	Retention Time (minute)	Estimated Concentration		Analytical Method
			(mg/filter)	(µg/cm²)	
WFI	N-Methyl-2-pyrrolidone	14.46	4.2	0.86	DI-GC/MS
	[illegible]	11.34	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	1.6	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	0.29	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	ICP-MS
0.1 M H_3PO_4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0.5 N NaOH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Visit Website

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer

original manufacturer see below

address:
Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany

Please find attached a DIN ISO 9001 Certificate and a description of our QA-System applied at Merck KGaA, Darmstadt in the following pages.

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

3.2.S.4.5 Justification of Specification

The specification of our product has been developed in accordance with the requirements of the declared pharmacopoeia including ICH Q3C for Residual Solvents and with respect to the requirements of customers in different application fields.

Elemental impurity specifications have been set considering ICH Q3D (Guideline for Elemental Impurities). In case elements have been identified as likely to be present they are added to the specification with a suitable limit and indicated.

The parameter Platinum (Pt) is specified due to recognized impurity of the manufacturing process. All other specified parameters, resulting from the history of the product based on former declared regulations and customer requirements, are not relevant for the control of the product's pharmaceutical quality.

3.2.S.5 Reference Standards of Materials

3.2.S.5.1 Reference Standards of Materials:

Not applicable, no standard material required.

3.2.S.6 Container Closure System

3.2.S.6.1 Container Closure System:

The packing materials with which the article comes into contact are:

- DPES (double polyethylene sack) liner (in secondary packing: corrugated cardboard box)
- Polyethylene bottle/container
- PE bag system with integrated humidity regulation in PE drum; material in direct contact: PE, complying to pharmacopoeial requirements

Income packaging materials are subjected to acceptance inspection in the package-testing laboratory. The materials are selected at Merck KGaA according to special criteria with regard to suitability for the application. In addition, the materials are inspected for physical condition upon receipt.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The minimum shelf life of product has been defined based on the chemical behaviour of material and on experience in handling and storing material at Merck KGaA, Darmstadt, Germany.

3.2.S.7.2 Postapproval Stability Protocol and Stability Comment

If stored at declared storage conditions and in original closed containers, the minimum shelf life applies as indicated in our certificate of analysis
Ongoing stability studies are performed considering the product's shelf life duration in line with "The IPEC Excipient Stability Program Guide" 2010.

3.2.S.2.3 Control of Materials

Raw materials:

The raw materials are suitable controlled before used in the production process.
The specification and amount of the raw materials used in the process is confidential as it presents detailed production know-how.

3.2.S.2.4 Control of Critical Steps and Intermediates

In-Process Controls:

The manufacturing process is performed under conditions such that the quality of the product is at all times in accordance with the specification.
The detailed in-process controls in this process are confidential as they represent detailed production know-how.

3.2.S.2.5 Process Validation and/or Evaluation

Description not necessary because the manufacturing process includes no aseptic processing and sterilization.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and other Characteristics

According to pharmacopoeia

3.2.S.3.2 Impurities

The specification of our product has been developed in accordance with the requirements of the declared pharmacopoeia including ICH Q3C for Residual Solvents and with respect to the requirements of customers in different application fields.

Elemental impurity specifications have been set considering ICH Q3D (Guidelines for Elemental Impurities).

In accordance with the current IPEC Federation „Technically Unavoidable Particle Profile (TUPP) Guide", for this product technically unavoidable particles been identified and evaluated. Detailed information is available in the Operational Excellence Dossier.

Chapter 2: Product quality self-assessment

Product Quality Self-Assessment

Based on Rx360 SAQ Module 3

relevant for

101816

Ammonium sulfate EMPROVE® EXPERT ACS,NF

Merck KGaA, Darmstadt, Germany
Corporation with General Partners
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3050 Spruce Street
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EMD Millipore Corporation
A subsidiary of Merck KGaA, Darmstadt, Germany
400 Summit Drive
Burlington, MA 1803, USA

Chapter 4: Stability data

Technical Report referred to SOP 6013

Article no:	106482.5000	Product name:	Sodium hydroxide pellets suitable for use as excipient EMPROVE® exp Ph Eur, BP, JP, NF, FCC, E 524
Batch number:	[redacted]	Storage conditions:	25 °C/ 60 % rel. humidity	Container:	PE- bottle

Parameter	Specification	Release	Re-Test results after			
			3 months	6 months	9 months	12 months	18 months	24 months	36 months
Appearance of solution	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test	passes test
Assay (acidimetric, NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assay (total alkalinity calc. as NaOH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carbonate (as Na_2CO_3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comment: All investigated parameters are in specification during the stability-study.

Responsible Laboratory manager (quality control): [redacted]

This document has been produced electronically and is valid without a signature

[redacted]

RELATED DOSSIER CONTENT

Materials of Construction

Specifications

Material Toxicity

DOSSIER OVERVIEW

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General Properties

Millipore Express® SHF (Sterile High Flux) cartridge filters are sterilizing-grade normal flow filters with pleated 0.2 µm polyethersulfone membrane and polysulfone and polypropylene components. Millipore Express® SHC (Sterile High Capacity) cartridge filters are sterilizing-grade normal flow filters with pleated Millipore Express® SHF membrane with an on-board 0.5 µm polyethersulfone membrane prefilter and polysulfone, polyethersulfone and polypropylene components.

Cartridges with Millipore Express® SHF or SHC membrane provide high flow rates, low extractables, and broad chemical compatibility. These cartridge filters are recommended for the removal of particles and bacterial organisms from a wide range of aqueous solutions.

All cartridge bonds are thermoplastic; no adhesives are used. Each Millipore Express® SHF and SHC filter is integrity tested and visually inspected prior to shipment. Each filter is labeled with the filter type, catalog number, lot number, pore size, and logo.

Materials of Construction

Component	Materials of Construction
Filter membrane	Hydrophilic polyethersulfone (PES)
Film Edge	Polypropylene
Supports	Polypropylene
Cage and end caps	Polypropylene
Core	Polysulfone (standard area cartridges)
	Polyethersulfone (high area cartridges)
O-rings	Silicone, Ethylene Propylene Diene Monomer (EPDM) or Fluoroelastomer

Dimensions (nominal)

Cartridge	Filtration Area m^2 (ft^2)	Maximum Length cm (in.)	Maximum Diameter cm (in.)	Hold Up Volume	
				mL	Conditions
Millipore Express® SHF					
5 in. Cartridge	0.29 (3.1)	12.5 (5)	6.9 (2.7)	--	90 psi for 1 min
Per 10 in. Cartridge	0.54 (5.8)	25.4 (10)	6.9 (2.7)	20	
Millipore Express® SHC Standard Area					
5 in. Cartridge	0.23 (2.5)	12.5 (5)	6.9 (2.7)	--	90 psi for 1 min
Per 10 in. Cartridge	0.49 (5.3)	25.4 (10)	6.9 (2.7)	50	
Millipore Express® SHC High Area					
Per 10 in. Cartridge	1.0 (10.8)	25.4 (10)	6.9 (2.7)	92	75 psi for 1 min

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RELATED DOSSIER CONTENT

Materials of Construction

Specifications

Material Toxicity

DOSSIER OVERVIEW

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Specifications

Design Criteria

Non-Fiber Releasing	Millipore Express® SHF and SHC membrane meets the criteria for a non-fiber releasing filter as defined in 21 CFR 210.3 (b)(6).
Alcohol Reference Test	≥ 1280 mbar (18.5 psi) 70/30 water/IPA with nitrogen at 23°C
Component Material Toxicity	Component Materials meet the criteria of the USP <88> Reactivity Test for Class VI Plastics. These products meet the requirements of the USP<88> Safety Test, utilizing a 0.9% sodium chloride extraction. This product is non-cytotoxic per ISO(R) 10993-5.
Indirect Food Additive	All component materials meet the FDA Indirect Food Additive requirements cited in 21 CFR 177-182.
Sterilization	Millipore Express® SHF and SHC cartridge filters may be autoclaved for up to 25 cycles of 60 minutes at 126°C.
	Millipore Express® SHF cartridge filters may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar)
	Millipore Express® SHC cartridge filters
	Standard Area may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar) or 3 forward cycles at ≤ 15 psi (1 bar) High Area may be steamed in place for 30 minutes at 135 °C for up to 5 forward cycles at ≤ 5 psi (340 mbar)
Maximum Differential Pressure	Forward: 6.9 bar (100 psi) at 25°C 1.70 bar (25 psi) at 80°C 1 bar (15 psi) at 135°C (Millipore Express® SHC cartridge filters) 0.34 bar (5 psi) at 135°C (Millipore Express® SHF cartridge filters) Reverse: 2.1 bar (30 psi) at 25°C 0.07 bar (1 psi) at 135°C

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Component Material Toxicity

USP <88> Biological Reactivity Tests for Class VI Plastics

Test Summary

Systemic and intracutaneous extract injections as well as intramuscular implantations were performed by an independent laboratory to determine the toxicity of Millipore Express® SHF and SHC cartridge filters and their suitability for contact with parenterals. All the components from Millipore Express® SHF and SHC cartridge filters were autoclaved at 126°C for one cycle of 60 minutes then submitted for USP Class VI testing.

This study was conducted based on the USP 27, NF 22, 2004, <88> Biological Reactivity tests, *In Vivo*.

Results

Millipore Express® SHF and SHC cartridge filters are non-toxic per USP Class VI biological Tests for Plastics. The test articles meet the requirements of USP 27, NF 22, 2004 for the Biological Test for Plastics, Class VI-70°C.

Independent laboratory certificates are shown in Appendix I.

USP <88> Safety Test

Test Summary

The USP <88> Safety Test was conducted by an independent laboratory to confirm that Millipore Express® SHF and SHC cartridge filters are nontoxic. Millipore Express® SHF and SHC cartridge filters were autoclaved at 126°C for one cycle of 60 minutes prior to submission for testing. The test articles were extracted in 0.9% USP Sodium Chloride for Injection at no less than 85°C for one hour.

This study was conducted based on the United States Pharmacopeia 26, National Formulary 21, 2003.

Results

Millipore Express® SHF and SHC cartridge filters are nontoxic per the USP <88> Safety Test. The test articles meet the requirements of USP 26, NF 21, 2003, Safety Test.

Independent laboratory certificates are shown in Appendix I.

ISO® 10993-5 Cytotoxicity Test

Test Summary

The ISO® 10993-5 Cytotoxicity Test was conducted at an independent laboratory to confirm that Millipore Express® SHF and SHC cartridge filters are non-cytotoxic. One Millipore Express® SHC cartridge filter was tested after one autoclave cycle of 60 minutes at 126°C.

This study was conducted based on the procedure described in the International Organization for Standardization, Biological Evaluation of Medical Devices – Part 5: Tests for In Vitro Cytotoxicity, ISO® 10993-5, 1999. Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials, ISO® 10993-12, 2002.

Results

Millipore Express® SHF and SHC cartridge filters are considered non-cytotoxic and me
the requirements of the Elution Test, ISO® 10993-5.

Independent laboratory certificates are shown in Appendix I.

RELATED DOSSIER CONTENT

Materials of Construction

Specifications

Material Toxicity

DOSSIER OVERVIEW

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3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer

original manufacturer see below

address:
Merck KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany

Please find attached a DIN ISO 9001 Certificate and a description of our QA-System applied at Merck KGaA, Darmstadt in the following pages.

RELATED DOSSIER CONTENT

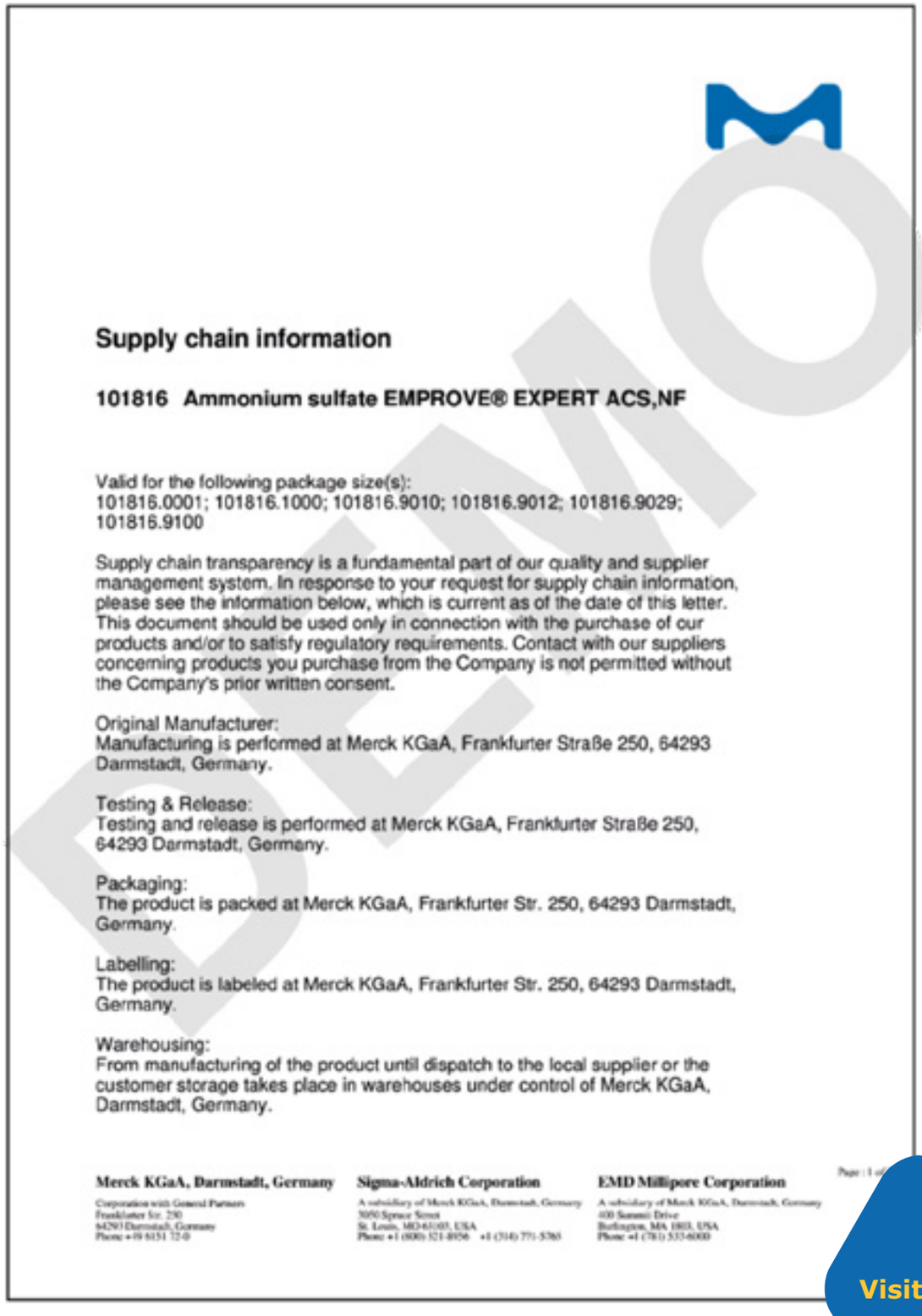
Supply Chain

Supplier Audit

DOSSIER OVERVIEW

Visit Website

Chapter 1: Supply chain information



Supply chain information

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

Valid for the following package size(s):
101816.0001; 101816.1000; 101816.9010; 101816.9012; 101816.9029; 101816.9100

Supply chain transparency is a fundamental part of our quality and supplier management system. In response to your request for supply chain information, please see the information below, which is current as of the date of this letter. This document should be used only in connection with the purchase of our products and/or to satisfy regulatory requirements. Contact with our suppliers concerning products you purchase from the Company is not permitted without the Company's prior written consent.

Original Manufacturer:
Manufacturing is performed at Merck KGaA, Frankfurter Straße 250, 64293 Darmstadt, Germany.

Testing & Release:
Testing and release is performed at Merck KGaA, Frankfurter Straße 250, 64293 Darmstadt, Germany.

Packaging:
The product is packed at Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany.

Labelling:
The product is labeled at Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany.

Warehousing:
From manufacturing of the product until dispatch to the local supplier or the customer storage takes place in warehouses under control of Merck KGaA, Darmstadt, Germany.

Merck KGaA, Darmstadt, Germany
Corporation with General Partners
Frankfurter Str. 250
64293 Darmstadt, Germany
Phone +49 6151 72-0

Sigma-Aldrich Corporation
A subsidiary of Merck KGaA, Darmstadt, Germany
3050 Spruce Street
St. Louis, MO 63103, USA
Phone +1 (800) 521-8956 +1 (314) 771-5765

EMD Millipore Corporation
A subsidiary of Merck KGaA, Darmstadt, Germany
400 Summit Drive
Burlington, MA 1803, USA
Phone +1 (781) 533-6000

Visit Website

101816 Ammonium sulfate EMPROVE® EXPERT ACS,NF

3. Is the sampling method in your facility validated and/or qualified?

4. Do you have suitably equipped sampling areas for the following :
   a. Incoming goods ?
   b. Key raw materials ?
   c. Semi-finished products ?
   d. Finished products ?
   e. Packaging materials ?
   f. Rejected materials?

XIV. Materials Management

1. Are returnable shipping containers used for this article ?
2. If YES to 1., are dedicated Containers used for this article ?

XV. Revision

1. Content Revision Number
2. Template Number

XVI. Survey Contact Information

For further questions, please contact your local sales representative at the office nearest you. For up to date contact information, contact your local business partner

3.2.S.2.3 Control of Materials

Raw materials:

The raw materials are suitable controlled before used in the production process.
The specification and amount of the raw materials used in the process is confidential as it presents detailed production know-how.

3.2.S.2.4 Control of Critical Steps and Intermediates

In-Process Controls:

The manufacturing process is performed under conditions such that the quality of the product is at all times in accordance with the specification.
The detailed in-process controls in this process are confidential as they represent detailed production know-how.

3.2.S.2.5 Process Validation and/or Evaluation

Description not necessary because the manufacturing process includes no aseptic processing and sterilization.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and other Characteristics

According to pharmacopoeia

3.2.S.3.2 Impurities

The specification of our product has been developed in accordance with the requirements of the declared pharmacopoeia including ICH Q3C for Residual Solvents and with respect to the requirements of customers in different application fields.

Elemental impurity specifications have been set considering ICH Q3D (Guidelines for Elemental Impurities).

In accordance with the current IPEC Federation „Technically Unavoidable Particle Profile (TUPP) Guide", for this product technically unavoidable particles been identified and evaluated. Detailed information is available in the Operational Excellence Dossier.

Manufacturing Information

Country of Origin	U.S.A.
Manufacturing Location	Jaffrey, NH
Standard Warranty	The applicable warranty for the products listed in this publication may be found at www.millipore.com/terms (within the "Terms and Conditions of Sale" applicable to your purchase transaction).
Change Notification Policy	Our worldwide change notification policy and supporting management procedures assure that customers are notified in a timely manner of a modification to a process or product that may have potential impact on their product, process, documentation, or procedures. We are responsible for controlling changes, assessing the expected impact of changes, and providing assurance that products are maintained in a validated state. An internal procedure to determine whether a change is considered notifiable is followed. A customer notification is typically provided for changes to the following: • Certificates of Quality or product labeling • Company name or acquisition • Critical manufacturing process steps which impacts the published product specifications or may affect the intended use of the product. • Critical raw materials or manufacturers which impacts the published product specifications or may affect the intended use of the product. • Discontinuation of a product • Manufacturing location • Primary Packaging • Physical product dimensions • Published product specifications and/or product claims A customer notification is typically NOT required for the following: • Change in raw material distributor (not manufacturer) • Data acquisition to production equipment • "Like in kind" changes (such as replacement for preventative maintenance, repairs, or recalibration) • Procedural changes that do not affect product performance or claims • Upgrade within manufacturing to a higher clean room classification The changes listed above are not all-inclusive, and every change is evaluated on a case-by-case basis to determine notification requirements and impact to our customers.

RELATED DOSSIER CONTENT

Manufacturing Information

DOSSIER OVERVIEW

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Quality Self Assessments

Divisional Quality Self-Assessment

RELATED DOSSIER CONTENT

Quality Self-Assessment

ISO 9001

Chain of Custody

DOSSIER OVERVIEW

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ISO 9001 Certification

Corporate Quality (EQ-Q) provides strategy and governance related to ISO Quality systems. Evidence for the support of all legal entities of the Merck KGaA Group in terms of Quality Management is the Group ISO 9001 certificate which covers minimum requirements and which is permanently monitored with regard to compliance with the applicable standards. EMD Millipore manufacturing sites are included in this matrix certificate and comply with all indicated requirements.

IQNet

THE INTERNATIONAL CERTIFICATION NETWORK

CERTIFICATE

IQNet and
DQS GmbH Deutsche Gesellschaft zur Zertifizierung von Managementsystemen

hereby certify that the company

Merck KGaA

Frankfurter Straße 250
64293 Darmstadt
Germany

with the organizational units/sites as listed in the annex

has implemented and maintains a **Quality Management System**.

Scope:
Development, manufacture and distribution of basic chemicals, special chemical products and analytical systems.

Through an audit, documented in a report, it was verified that the management system fulfills the requirements of the following standard:

ISO 9001 : 2008

Date of revision	2016-11-24
Valid from	2014-11-24
Valid until	2017-11-23
Date of certification	2016-11-24

Registration number: DE-005356 QM08

IQNet

Michael Drechsel
President of IQNet

Frank Graichen
Managing Director of DQS GmbH

DQS

IQNet Partners**:
AENOR Spain AFNOR Certification France AIB-Vincotte International Belgium APCER Portugal CCC Cyprus CISQ Italy CQC China CQM China CQS Czech Republic Cro Cert Croatia DQS Holding GmbH Germany FCAV Brazil FONDONORMA Venezuela ICONTEC Colombia IMNC Mexico Inspecta Certification Finland INTECO Costa Rica IRAM Argentina JQA Japan KFQ Korea MIRTEC Greece MSZT Hungary Nemko AS Norway NSAI Ireland PCBC Poland Quality Austria Austria RR Russia SIGE Mexico SII Israel SIQ Slovenia SIRIM QAS International Malaysia SQS Switzerland SRAC Romania TEST St Petersburg Russia TSE Turkey YUQS Serbia
IQNet is represented in the USA by: AFNOR Certification, CISQ, DQS Holding GmbH and NSAI Inc.

* This attestation is directly linked to the IQNet Partner's original certificate and shall not be used as a stand-alone document
** The list of IQNet partners is valid at the time of issue of this certificate. Updated information is available under www.iqnet-certification.com

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Chain of Custody

Handling of Materials Entering into the Manufacturing Area

Controls are in place regarding the handing of materials entering into controlled manufacturing areas. The packaging of material entering the controlled areas is cleaned with an appropriate lint free cloth and 70/30% IPA/Water. If material is double bagged, the outer bag is removed prior to entry into the area. Access to controlled areas is restricted to certain types of packaging.

All bins and carts used for transferring product into the controlled environment are wiped down with low lint wipes and 70/30% IPA/water spray.

Tools used in the repair or maintenance of processing equipment are cleaned with 70/30% IPA/water spray and wipes prior to usage in the controlled environment.

There is an established visual inspection guideline for this product. Each device is 100% visually inspected during bagging and again during final packaging.

Gowning

All entrants to any manufacturing area must be properly gowned. This gowning includes hair nets, beard covers (where applicable), smocks, safety glasses with side shields, and shoe coverings (disposable or reusable shoe covers). Clothing worn by manufacturing personnel must be clean to minimize the potential introduction of contaminants to the controlled environment. Also any clothes with holes, frayed edges or which drag on the floor are not allowed.

Cleaning of Manufacturing Area

Trained employees conduct an aggressive, active and complete cleaning of the manufacturing areas. These activities include the cleaning of product work surfaces, processing equipment and furniture. These cleanings are conducted on a daily, weekly and quarterly frequency as predefined in the procedure and are done to minimize viable and non-viable particulates within in the manufacturing areas. The daily cleaning of processing equipment is conducted at the start of each shift as well as the start of each new lot. This cleaning of the equipment is performed regardless of whether equipment is scheduled to be used that day. The cleanings are performed using 70/30% IPA/Water and lint free wipes to further mitigate particulates within the manufacturing space.

Supplier Management

Suppliers are categorized based on an internal management procedure (MP) to determine whether the supplier is a non-critical, essential, or critical supplier. Criteria for determination includes (but is not limited to) impact of a raw material/product failure, raw material complexity, and location of manufacture.

Based on categorization, the suppliers are assessed according to this MP. The supplier categorization dictates supplier audit frequency, ISO certification requirements, Quality agreement and change control requirements. Critical raw material suppliers are audited every two years. A supplier must meet all requirements of the assessment process to be approved.

A Supplier Rating System is used to track supplier performance for criteria such as quality acceptance rate, on-time delivery, corrective action responsiveness, and production impact. An annual review of the supplier base is conducted to review supplier performance metrics, audit requirements, and a re-evaluation of the categorization.

RELATED DOSSIER CONTENT

Quality Self-Assessment

ISO 9001

Chain Of Custody

DOSSIER OVERVIEW

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RELATED DOSSIER CONTENT

Specifications

DOSSIER OVERVIEW

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Specifications

Design Criteria

Non-Fiber Releasing	Millipore Express® SHF and SHC membrane meets the criteria for a non-fiber releasing filter as defined in 21 CFR 210.3 (b)(6).
Alcohol Reference Test	≥ 1280 mbar (18.5 psi) 70/30 water/IPA with nitrogen at 23°C
Component Material Toxicity	Component Materials meet the criteria of the USP <88> Reactivity Test for Class VI Plastics. These products meet the requirements of the USP<88> Safety Test, utilizing a 0.9% sodium chloride extraction. This product is non-cytotoxic per ISO(R) 10993-5.
Indirect Food Additive	All component materials meet the FDA Indirect Food Additive requirements cited in 21 CFR 177-182.
Sterilization	Millipore Express® SHF and SHC cartridge filters may be autoclaved for up to 25 cycles of 60 minutes at 126°C.
	Millipore Express® SHF cartridge filters may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar)
	Millipore Express® SHC cartridge filters Standard Area may be steamed in place for 30 minutes at 135°C for up to: 25 forward cycles at ≤ 5 psi (340 mbar) or 22 forward cycles at ≤ 5 psi (340 mbar) and 3 reverse cycles at < 1 psi (69 mbar) or 3 forward cycles at ≤ 15 psi (1 bar) High Area may be steamed in place for 30 minutes at 135 °C for up to 5 forward cycles at ≤ 5 psi (340 mbar)
Maximum Differential Pressure	Forward: 6.9 bar (100 psi) at 25°C 1.70 bar (25 psi) at 80°C 1 bar (15 psi) at 135°C (Millipore Express® SHC cartridge filters) 0.34 bar (5 psi) at 135°C (Millipore Express® SHF cartridge filters) Reverse: 2.1 bar (30 psi) at 25°C 0.07 bar (1 psi) at 135°C

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