Emprove® Quality Management Dossier

Documentation to support risk assessment

For demonstration purposes only and should not be used for any qualification and/or registration activities.

120079
ESHMUNO®Q

Table of Contents

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1 Supply Chain Information

Supply chain information

120079 ESHMUNO® Q

Valid for the following package size(s):
120079.0010; 120079.0100; 120079.0500; 120079.5000

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, Werk Gernsheim, Mainzer Str. 41, 64579 Gernsheim, Germany.

Testing & Release:
Testing and release is performed at Merck KGaA, Werk Gernsheim, Mainzer Str. 41, 64579 Gernsheim, 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
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Sigma-Aldrich Corporation
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EMD Millipore Corporation
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[redacted]
Quality Services

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Date: 19-Feb-2019

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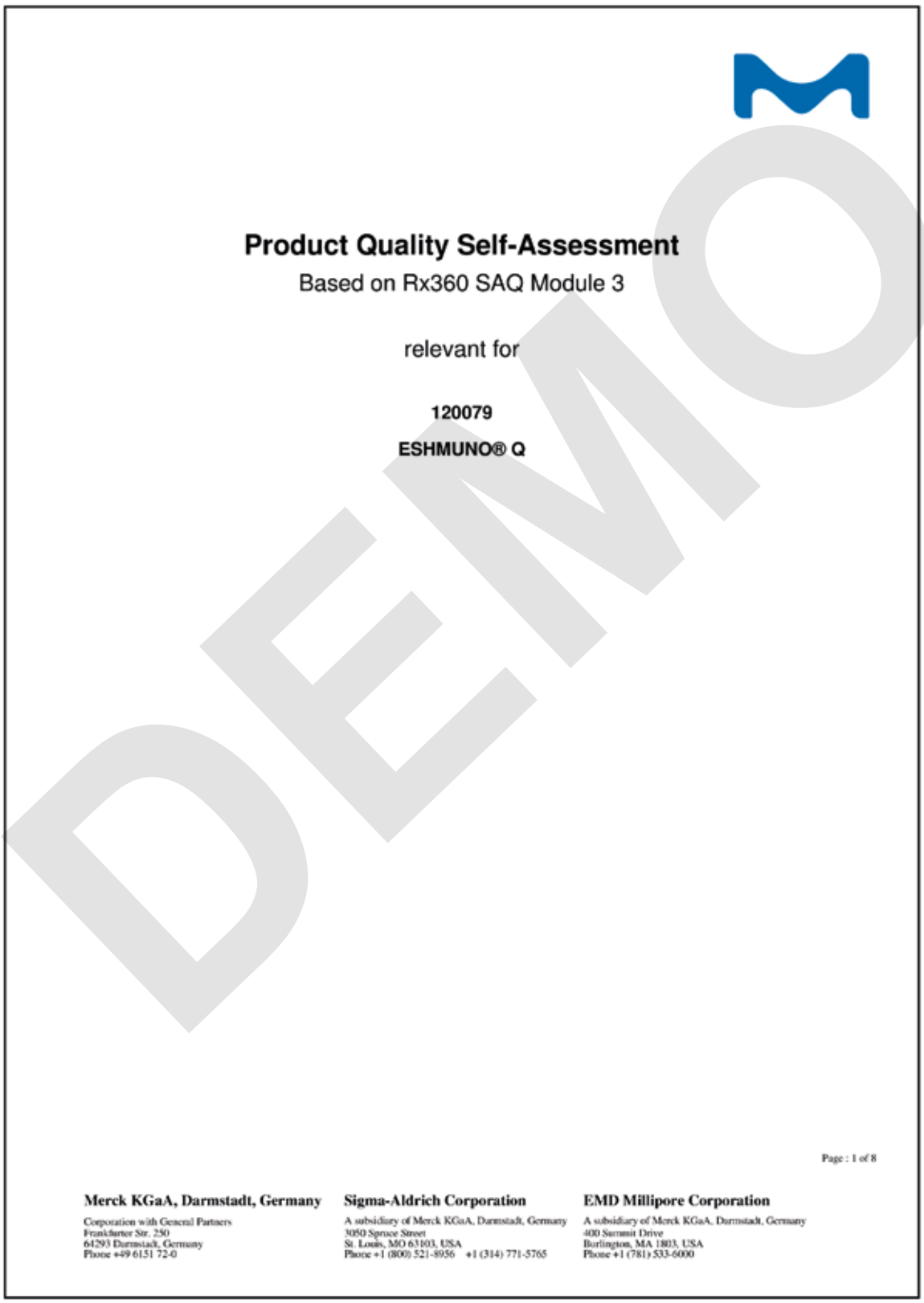
2 Product Quality Self-Assessment



Product Quality Self-Assessment

Based on Rx360 SAQ Module 3

relevant for

120079

ESHMUNO® Q

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Contents

I. General Information

1. This Product Quality Self-Assessment (Product-QSA) provides Quality Management System information specific to this product.
2. This Product-QSA is associated with following documents:
   a. The Company-wide Self-Assessment for its overall quality system
   b. The respective Site Quality Self-Assessment (Site-QSA)

II. Quality Management System (QMS)

1. Are you considered original manufacturer of the listed product ? yes
2. Which GMP standards are applied for the product? [illegible]

III. Documentation - General

1. Is there a conformance statement, quality policy or certificate for GMP requirements ? [illegible]
2. Is there a Certificate of Suitability to the Monographs of the European Pharmacopeia (CEP) for the above-mentioned product ? no
3. Is there a Drug Master File (DMF) for the above-mentioned product ? no
4. Do you perform annual reports for the aforementioned product ? yes
5. Is the product EXCIPACT certified ? no

IV. Documentation Requirements - Customer Documentation

1. If applicable, can you provide the following declarations on request ?
   a. Aflatoxines yes
   b. Allergenes yes
   c. Animal Origin(BSE/TSE) yes
   d. cGMP certificate no
   e. GMO yes
   f. Ionizing Irradiation yes
   g. Manufacturing description / Flowchart yes
   h. Melamine yes
   i. Supply Chain Information yes

V. Computerized Systems

1. Are appropriate qualification and validation procedures available for your computerized system ? yes

2.	Do you perform risk assessment for your computerised system ?	yes
3.	Do your computer systems that could impact quality have controls for operation, maintenance and prevention of unauthorised access ?	yes
4.	Do you have an approved master plan of the validation of the computerised system ?	yes
5.	Do you document changes and deviations of validated systems ?	yes

VI. Personnel - Training

1.	Are employees working in production rooms given periodic medical check-ups ?	yes
2.	Is it ensured that no person with an infectious disease will come in contact with the product ?	yes
3.	Do you have a job training program ?	yes
4.	Do your training procedures identify training needs by job function ?	yes
5.	Is your personnel trained under GMP requirements ?	yes
6.	Do you have training records and is training completed prior to performing job- relative activities ?	yes

VII. Manufacturing Information - Equipment Utilities

1.	Is the product manufactured on dedicated equipment?	yes, product group specific equipment
2.	Are there cleaning procedures for non-dedicated equipment to remove the previous product in place?	yes
3.	Has production equipment been qualified?	yes
4.	Has validation been performed for cleaning procedures, as applicable?	no
5.	If NO to 4., is there data to show that cleaning procedures for non-dedicated equipment is adequate to remove the previous product?	yes
6.	What type of water is involved in manufacturing and cleaning?	
	a. Purified Water / PW (EP and USP grade)	yes
	b. Highly Purified Water / HPW (EP grade)	no
	c. Water for Injection / WFI (EP and USP grade)	no
	d. Potable water	no
	e. Distilled water	no
	f. Deionized water	no
7.	What method is used to purify water ?	
	a. Reverse Osmosis	yes
	b. Ultra-Filtration	no
	c. Ion Exchange	no

8.	Is production performed in aseptic environment ?	[redacted]

VIII. Manufacturing Information - General

1.	If applicable, is production and handling of highly sensitizing materials (such as penicillins or cephalosporins) conducted in closed equipment separate from that used for product manufacture?	[redacted]
2.	If applicable, are dedicated production areas or appropriate cleaning activities implemented within the site for material of high pharmacological activity (e.g. certain steroids), toxicity (e.g. cytotoxic anti-cancer agents) or highly toxic non-pharmaceutical materials (e.g. herbicides or pesticides) to avoid cross-contamination ?	[redacted]
3.	Is the product manufactured batchwise or continuously ?	[redacted]
4.	How do you define a homogeneous batch ?	[redacted]
5.	Are solvents excluded from or consistently removed (i.e., to ICH Q3C limits) during the manufacturing process ?	[redacted]
6.	Are residual solvents reported per ICH Q3C, i.e., listed in the specification and CoA ?	[redacted]
7.	Can one batch be traced back to a. its starting material ? b. its IPC (in-process control) ? c. its release control ? d. the bulk material ?	[redacted]
8.	Do the written procedures cover reprocessing?	[redacted]
9.	Are adequate in-process controls performed?	[redacted]
10.	Are the in-process controls supervised by the Quality Unit(s)?	[redacted]

IX. Filling Information

1.	With the respect to the product in question, do you perform filling ?	[redacted]
2.	Is there a hygiene monitoring program in the filling area for products manufactured under GMP ?	[redacted]
3.	Is there an HVAC system in the filling room/s ?	[redacted]
4.	Is filling performed in an aseptic environment ?	[redacted]
5.	Is the filling line dedicated ?	[redacted]
6.	Is there data to show that cleaning procedures (e.g. cleaning validation) for non-dedicated equipment is adequate to remove the previous product ?	[redacted]

X. Environmental Conditions

1. Do you monitor and document environmental conditions (e.g. air handling, temperature or sanitary conditions) in the following areas:
   a. Filling ?
   b. Finished good warehouse ?

XI. Labeling/Packaging Information

1. Is access to labels and printed materials controlled and recorded ?
2. Does this include label reconciliation/discarding ?
3. Is the original manufacturer name listed on every packaging unit ?

XII. Quality / Laboratory Control

1. Is written information about laboratory instruments available for :
   a. Qualification instructions and records?
   b. Calibration instructions and records?
   c. Maintenance instructions and records?
   d. Recording, reporting, and storing of raw data?
2. Do you perform stability studies for the final product ?
3. Do you perform full testing on your raw materials ?
4. Is there a reference to compliance to pharmacopoeia given in the product name ?
5. Which volume of pharmacopoeia is used for lot release ?
6. Do you perform all testing listed on the CoA in-house ?
7. Is the preparation of standards and controls documented ?
8. Is there an approved procedure for handling the investigation and documentation of out of specification (OOS) ?
9. Is there a documented review (double-check) of data by a second individual ?
10. Is validation of non-compendial analytical procedures a standard requirement for this article ?

XIII. Sampling

1. Do you store and ship samples in the same methods as provided product ?
2. Do you pull samples in a statistically significant method to provide adequate representation of a product batch ?

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

Product Quality Self-Assessment

We herewith certify that the information provided in response to the questions posed are accurate and complete.

[redacted]

Quality Services

Name and Function

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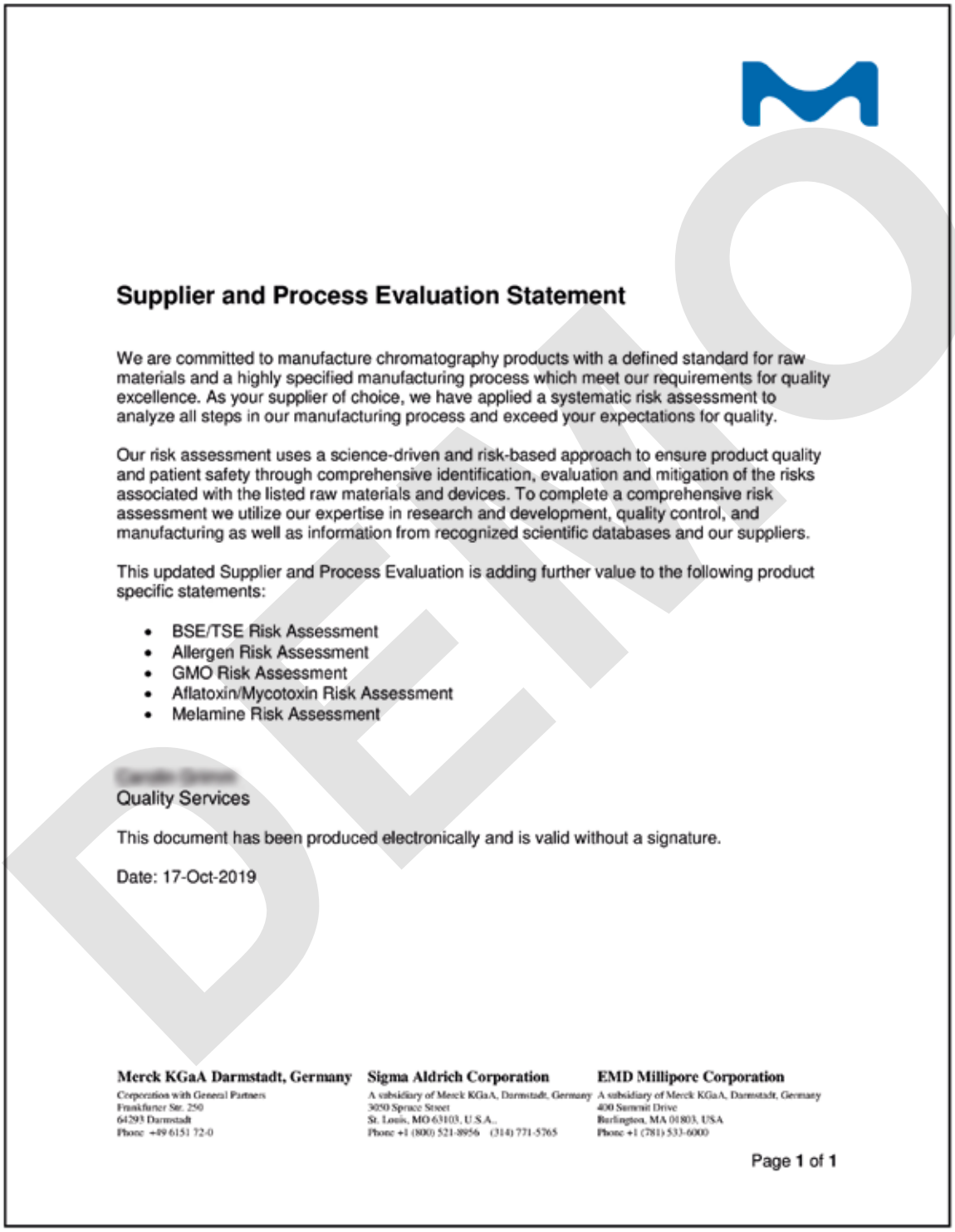
3 Supplier and Process Evaluation Statement



Supplier and Process Evaluation Statement

We are committed to manufacture chromatography products with a defined standard for raw materials and a highly specified manufacturing process which meet our requirements for quality excellence. As your supplier of choice, we have applied a systematic risk assessment to analyze all steps in our manufacturing process and exceed your expectations for quality.

Our risk assessment uses a science-driven and risk-based approach to ensure product quality and patient safety through comprehensive identification, evaluation and mitigation of the risks associated with the listed raw materials and devices. To complete a comprehensive risk assessment we utilize our expertise in research and development, quality control, and manufacturing as well as information from recognized scientific databases and our suppliers.

This updated Supplier and Process Evaluation is adding further value to the following product specific statements:

- BSE/TSE Risk Assessment
- Allergen Risk Assessment
- GMO Risk Assessment
- Aflatoxin/Mycotoxin Risk Assessment
- Melamine Risk Assessment

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Date: 17-Oct-2019

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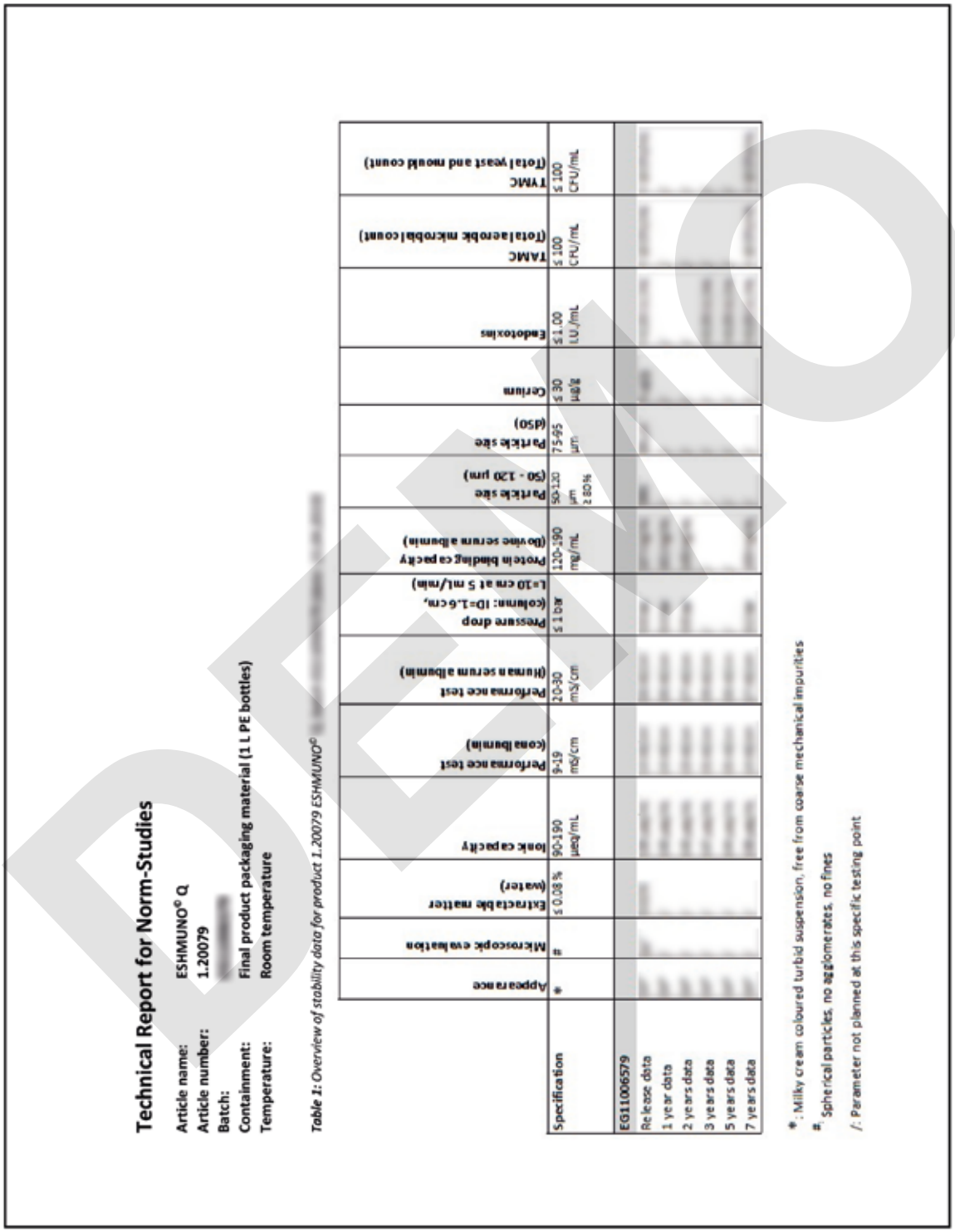
4 Stability data



Technical Report for Norm-Studies

Article name: ESHMUNO® Q
Article number: 1.20079
Batch: [redacted]
Containment: Final product packaging material (1 L PE bottles)
Temperature: Room temperature

Table 1: Overview of stability data for product 1.20079 ESHMUNO®

	Appearance	Microscopic evaluation	Extractable matter (water)	Ionic capacity	Performance test (conductivity)	Performance test (Human serum albumin)	Pressure drop (column: ID=1.6 cm, L=10 cm at 5 ml/min)	Protein binding capacity (bovine serum albumin)	Particle size (50 - 120 µm)	Particle size (d50)	Cerium	Endotoxins	TAMC (Total aerobic microbial count)	TYMC (Total yeast and mould count)
Specification	*	#	≤ 0.08 %	90-190 µeq/mL	9-19 mS/cm	20-30 mS/cm	≤ 1 bar	120-190 mg/mL	50-120 µm 2 80 %	75-95 µm	≤ 30 µg/g	≤ 1.00 LU/mL	≤ 100 CFU/mL	≤ 100 CFU/mL
EG11006579														
Release data	[redacted]													
1 year data														
2 years data														
3 years data														
5 years data														
7 years data														

*: Milky cream coloured turbid suspension, free from coarse mechanical impurities

#: Spherical particles, no agglomerates, no fines

/: Parameter not planned at this specific testing point

Technical Report for Norm-Studies

Article name: ESHMUNO® Q
Article number: 1.20079
Batch: [redacted]
Containment: Final product packaging material (1 L PE bottles)
Temperature: Room temperature

Table 1: Overview of stability data for product 1.20079 ESHMUNO® [redacted]

	Appearance	Microscopic evaluation	Extractable matter (water)	Ionic capacity	Performance test (conalbumin)	Performance test (Human serum albumin)	Pressure drop (column: ID=1.6cm, L=10 cm at 5 ml/min)	Protein binding capacity (Bovine serum albumin)	Particle size (50 - 120 µm)	Particle size (d50)	Certrim	Endotoxins	TAMC (Total aerobic microbial count)	TYMC (Total yeast and mould count)
Specification	*	#	≤ 0.08 %	90-190 µeq/mL	9-19 mS/cm	20-30 mS/cm	≤ 1 bar	120-190 mg/mL	50-120 µm ≥ 80 %	75-95 µm	≤ 30 µg/g	≤ 1.00 I.U./mL	≤ 100 CFU/mL	≤ 100 CFU/mL
TA20960079														
Release data	[redacted]													
1 year data	[redacted]													
2 years data	[redacted]													

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Technical Report for Norm-Studies

Article name: ESHMUNO® Q
Article number: 1.20079
Batch number: [redacted]
Containment: Final product packaging material (1 L PE bottles)
Temperature: Room temperature

Table 1: Overview of stability data for product 1.20079 ESHMUNO® [redacted]

	Appearance	Microscopic evaluation	Extractable matter (water)	Ionic capacity	Performance test (conductivity)	Performance test (human serum albumin)	Pressure drop (column: ID=1.6 cm, L=10 cm at 5 mL/min)	Protein binding capacity (bovine serum albumin)	Particle size (50 - 120 µm)	Particle size (d50)	Certain	Endotoxins	TAMC (Total aerobic microbial count)	TYMC (Total yeast and mould count)	
Specification	*	#	≤ 0.08 %	90-190 µeq/mL	9-19 mS/cm	20-80 mS/cm	≤ 1 bar	120-190 mg/mL	50-120 µm ≥ 80%	75-95 µm	≤ 30 µg/g	≤ 1.00 LU/mL	≤ 100 CFU/mL	≤ 100 CFU/mL	
TA2100379															
Release data			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
1 year data			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
2 years data			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

*: Milky cream coloured turbid suspension, free from coarse mechanical impurities

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/: Parameter not planned at this specific testing point

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VM_ED6023EN 12/2019