Process Validation Protocol

patheon
by Thermo Fisher Scientific

Title: ***MabThera 100mg/10mL and MabThera 500mg/50mL***
Sterile Area 6, Xtrema line

Date: 27/03/2023

Control No: ***P800AB01***

Client: ***Roche***

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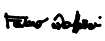
Date and signature:	28-Mar-2023		*Electronically signed by: Fabio Zaffaroni* *Reason: Reviewer of the GxP document* *Date: Mar 28, 2023 09:46 GMT+2*
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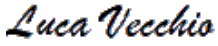
Date and signature:	28-Mar-2023		*Electronically signed by: Luca Vecchio* *Reason: Reviewer of the GxP document* *Date: Mar 28, 2023 11:06 GMT+2*

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1 PURPOSE

The present document is the Process Validation Protocol for:

Name:	**MabThera 100mg/10mL and MabThera 500mg/50mL**
Type:	**Liquid (vials)**
Owner:	**Roche**
Manufacturer:	**Patheon Italia S.p.A., part of Thermo Fisher Scientific** **Monza Production Plant** **Via Stucchi, 110**
Batch size:	**MabThera 100mg/10mL – approx. 250 L, corresponding to about 23'764 vials (theoretical)** **MabThera 100mg/10mL – approx. 250 L, corresponding to about 23'764 vials (theoretical)** **MabThera 500mg/50mL – approx. 250 L, corresponding to about 4'892 vials (theoretical)** **MabThera 100mg/10mL – approx. 747 L, corresponding to about 71'000 vials (theoretical)**

The present document is related to the manufacturing of 4 (four) PPQ validation batches of MabThera 100 mg/10 mL vial (nominal minimum batch size: approx. 250 L of Bulk Drug Product; nominal maximum batch size: approx. 747 L of Bulk Drug Product) and MabThera 500 mg/ 50mL vial (nominal minimum batch size: approx. 250 L of Bulk Drug Product; nominal maximum batch size: approx. 747 L of Bulk Drug Product) in Xtrema line of Sterile Area 6 department, Patheon Monza (Italy), part of Thermo Fisher Scientific.

Purpose of this *prospective process validation* is to establish documented evidence providing a high degree of assurance that the manufacturing process of **MabThera 100 mg and 500 mg** is robust and reproducible and will consistently produce a product in the two SKUs which meets its pre-determined specifications and quality attributes.

Purpose of the present protocol is to define the program of the validation activities, in particular:

- sampling;
- critical process parameters;
- controls and analysis to be performed;
- data collection procedure;
- acceptance criteria;
- responsibilities in conducting the activities.

Background

Rituximab is a monoclonal antibody that binds CD20 protein on the surface of leukemia and lymphoma cells.

The trade name for Rituximab is MabThera. The product is currently manufactured by F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) and globally commercialized for the treatment of adults with the following blood cancers: previously untreated and relapsed/refractory follicular lymphoma, previously untreated diffuse large B-cell lymphoma, and previously untreated and relapsed/refractory chronic lymphocytic leukemia. MabThera is also approved for the treatment of adults in auto-immune diseases: severe active rheumatoid arthritis, pemphigus vulgaris and severe active granulomatosis with polyangiitis and microscopic polyangiitis (GPA/MPA).

The manufacture of two (2) different dosages is foreseen for MabThera drug product:

1. MabThera 100 mg (100 mg / vial of concentrate for solution for infusion): the solution is filled in 10 mL glass vial type I and then sealed with 20 mm coated stoppers and flip-off aluminum seals;
2. MabThera 500 mg (500 mg / vial of concentrate for solution for infusion): the solution is filled in 50 mL glass vial type I and then sealed with 20 mm coated stoppers and flip-off aluminum seals.

MabThera manufacturing process of both dosage strengths (100 mg/vial and 500 mg/vial) is transferred from the donor site Roche (Mannheim plant, Germany) to the receiving site Patheon Monza (Thermo Fisher Scientific), in Sterile Area 6 (ST6) at the commercial scale of approximately 250 - 747 L bulk volume.

Preliminary Activities in Patheon Monza

The project was introduced and managed in Patheon Monza Quality System according to the new product introduction (NPI) change control QR# 191938 “Introduction of MabThera 100 mg and 500 mg in Sterile Area 6” [1].

The following batches were manufactured to support the introduction of MabThera 100 mg and 500 mg in Patheon Monza site:

- 2 non-GMP surrogate batches at maximum batch size, approx. 1000 L (1 for each SKU) – Surrogate trial protocol TT237A011 [2], Surrogate trial repot TT237D011 [3];
- 1 non-GMP engineering batch at minimum batch size, approx. 250 L (split in two parts, ~125 L used to fill the MabThera 500mg in 50 mL vials and ~125 L used to fill MabThera 100 mg in 10 mL vials) – Engineering trial protocol TT237B011 and related Addendum 1 [4], Engineering trial report TT237C011 [5].

The next step of the technology transfer is to validate the manufacturing process in the Patheon Monza manufacturing plant, part of Thermo Fisher Scientific.

Process Validation Approach

A three-stage approach is followed by Patheon Monza for process validation as required by FDA/EMA. Details regarding Stage 1, Stage 2 and Stage 3 approach are fully described in the Patheon Monza Process Validation Master Plan (VMP) Q001AA10 [6] and briefly summarized here below.

According to the Process Validation Master Plan Q001AA10 [6], *Eudralex Vol. 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15, 2015, and to Qualification and Validation* and to *FDA Guidance for Industry – Process Validation: General principles and Practices, 2011*, the process validation is considered as a lifecycle approach with three distinct stages, each with an intended objective:

- Process Design (Stage 1): the stage where a process is developed, critical quality attributes are identified, critical parameters defined, control strategy developed, and process ranges confirmed. This stage is when the design space is determined and scale up work is performed. Prior to commencing Process Qualification, each process must have at least one batch tested according to validation criteria to help provide assurance that the process is capable of success during the process qualification stage. Stage 1 is part of the Technology Transfer (TTP237/01 [7]) and is not covered by the present document.

- Process Qualification (Stage 2): this stage is to demonstrate that the manufacturing or packaging process is a capable and reproducible commercial production process. Stage 2 is covered by the present document. In particular:
  - 4 (four) GMP PPQ validation batches will be produced to validate MabThera 100 mg and MabThera 500 mg manufacturing process.

  Process Validation activities are designed and executed according to the requirements and approach described in Patheon Process Validation Master Plan Q001AA10 [6].

- Continued Process Verification (Stage 3): during routine commercial supply, this is the stage where the process is demonstrated to remain in a state of control. Stage 3 is covered by the dedicated Patheon Monza SOP-000031006 *"Continued Process Verification - CPV"* [8], and it is outside of the scope of this document.

As part of the Stage 2 activities, the purpose of this process validation protocol is to establish documented evidence providing a high degree of assurance that the manufacturing process of MabThera 100 mg and MabThera 500 mg will consistently produce a product in the two SKUs which meets its pre-determined specifications and critical quality attributes.

1.1 VALIDATION STRATEGY

According to Patheon Process Validation Master Plan Q001AA10 [6] and current regulatory authority guidelines (FDA and EMA) the required number of validation batches was determined based on a risk assessment of the manufacturing process, considering:

1. product knowledge;
2. process knowledge;
3. control strategy.

The risk associated with each parameter is described below.

Product Knowledge Risk Level

Table 1 Product Knowledge Risk Levels.

Risk Level	Product Knowledge
High	Product CQAs to reduce risk to patients not established or demonstrates risk of failure.
Medium	Product CQAs to reduce risk to patients have been established and moderate risk of failure of CQAs.
Low	Product CQAs established and show low risk for patient impact when product meets CQAs.

The product Critical Quality Attributes (CQAs) relevant to MabThera drug product manufacturing have already been defined by Roche and listed in the Attachment #2 of the present protocol: there is no impact on patient safety if the CQAs are met. Two surrogate batches at maximum batch size (one for each SKU), and one engineering batch (split in two parts, ~125 L used to fill the MabThera 500 mg in 50mL vials and ~125 L used to fill MabThera 100mg in 10mL vials) were already manufactured at Patheon Monza with compliant results increasing the level of confidence.
Furthermore, it is specified that the same product is already commercial in both dosage strengths. Therefore, it is possible to rely on a deep product knowledge supported by the donor site Roche, Mannheim.
For the above-mentioned reasons, the risk level associated with the Product knowledge can be considered **low**.

Process Knowledge Risk Level

Table 2 Process Knowledge Risk Levels.

Risk level	Process knowledge
High	Limited process development (1-2 batches), lack of similar processes, no development report or a report with minimal data, limited process knowledge, no data at commercial scale.
Medium	Moderate development (3-4 batches), some experience with similar products, development report, experience at commercial scale.
Low	Significant product history (5+ batches), similar processes well understood, comprehensive development report, performance history from other suppliers on equivalent equipment.

Two surrogate batches at maximum batch size (one for each SKU) were manufactured according to TT237A011 [2] with the aim to evaluate setup, machinability and perform a preliminary process characterization. Outcome is summarized in report TT237D011 [3].

One engineering batch (split in two parts, ~125 L used to fill the MabThera 500 mg in 50 mL vials and ~125 L used to fill MabThera 100 mg in 1 0mL vials) was successfully manufactured according to TT237B011 [4] to consistently simulate the overall process flow (from F/T tanks thawing to final cold storage at 2-8°C of drug product, including simulation of some process holding time challenges), establish suitable ranges for site-specific critical process parameters (CPPs) and guarantee Critical Quality attributes (CQAs), perform a fine tuning of filling and crimping parameters. Outcome is summarized in report TT237C011 [5].

For what above, the risk level associated with process knowledge is considered **Medium**.

Control Strategy Risk Level

Table 3 Control Strategy Risk Levels.

Risk level	Control strategy
High	Lack of proven control strategies across all aspects
Medium	Some control strategies which are well developed and others which are under development or have moderate strategy for most aspects
Low	Developed or proven control strategies for all aspects

During the manufacturing of MabThera 100 mg and MabThera 500 mg PPQ batches an extended sampling plan, including samples for validation purpose only, will be performed to demonstrate control of the product quality attributes during the manufacturing process: IPCs will be in place as well in the future commercial manufacturing.
For the above-mentioned reasons, the risk level associated with the control strategy can be considered **low**.

Conclusions

The overall risk rating is evaluated based on the following considerations:

Table 4 Overall risk rating and recommended number of PPQ batches.

Overall Risk Rating	Typical Criteria	Recommended number of PV Batches
Severe	All factors have high risk ratings	Not ready for PV
High	2 factors high or 2 medium and 1 high	10
Moderate	3 factors medium or 1 high, 1 medium, 1 low	5
Low	1-2 medium and others low	3
Minimal	All low risk	1 - 3

Based on the above evaluations, the overall risk level is defined in following table:

Table 5 Current risk level for MabThera 100 mg and MabThera 500 mg.

Risk element	Risk level	Overall risk	Number of PPQ batches for MabThera 100mg	Number of PPQ batches for MabThera 500mg
Product	Low	Low	3	3
Process	Medium			
Control strategy	Low			

The overall risk rating for MabThera 100 mg and MabThera 500 mg manufacturing is considered **low**. Therefore, **3 (three) consecutive batches per each SKU** are deemed enough to cover the process validation.

However, as multiple strengths/batch sizes of the same product are manufactured, and the solution preparation of the bulk drug product is identical among the two SKUs, the following **matrix approach** that foresees a bracketing will be applied:

Table 6 MabThera PPQ batches – Validation strategy.

Drug product description	Batch size	Patheon Batch number	Process validation batches	Approximate batch size
MabThera 100mg	Minimum	B0002	PPQ #1	~250 L
MabThera 100mg	Minimum	B0003	PPQ #2	~250 L
MabThera 100mg	Maximum	B0001	PPQ #3 (*)	~747 L
MabThera 500mg	Minimum	B0001	PPQ #4 (*)	~250 L

(*) Batch subjected to holding times challenge.

It is specified that the matrix approach detailed in **Table 6** is supported by Roche's Quality and Technical regulatory experts, leveraging the following:

- primary packaging material configuration, fill volume: lowest fill volume is considered worst case regarding potential leachables from the rubber stopper and glass (volume to surface ratio);
- batch size: according to previous validation studies performed at Roche Mannheim for the same product (VAL-0126370 and VAL-0123449), the batch size had no negative influence on the product quality.

Further details are provided in the MEMO (Attachment 8 of the present protocol).

2 SCOPE

The phases of the process which take place at Patheon Monza plant, and which will be subject to validation, are the following:

- Receipt of freeze/thaw (F/T) tanks containing partially formulated bulk drug substance and storage in Patheon Monza warehouse at ≤ -20°C;
- Thawing of MabThera Bulk Drug Substance (BDS) through dedicated thawing stations;
- Temporary storage of F/T tanks at room temperature and at 2-8°C (storage at 2-8°C during commercial manufacturing is optional);
- Polysorbate stock solution and pH adjustment solution preparation in 2L, 5L, and 10L glass bottles;
- Preparation of buffer solution in Stainless Steel (SS) buffer tank;
- Pooling of the BDS contained in the F/T tanks into a SS compounding tank by means of a peristaltic pump;
- Buffer solution transfer to SS compounding tank by using nitrogen pressure through disposable tubing;
- Formulated bulk mixing in the SS compounding tank;
- Bioburden reduction filtration of the formulated bulk drug product from the compounding tank into the SS storage tank by nitrogen pressure through a disposable line equipped with 1 (one) 0.22 µm bioburden reduction filter;
- Post-use integrity test on bioburden reduction filter[1];
- Storage of the formulated bulk drug solution into the SS storage tank at room temperature and then at 2-8°C (storage at 2-8°C during commercial manufacturing is optional);
- Transfer of the storage tank from the solution preparation room to the filling room, near the isolator, using an electric transpallet;
- Pre-use post sterilization integrity test (in-line) of both the sterilizing filters to be performed through bubble point test and according to filters' supplier certificate;
- Sterilizing filtration of the formulated bulk drug product through 2 (two) 0.22 µm sterilizing filters by nitrogen pressure (pressure monitoring in place);
- Vials filling driven by peristaltic pumps;
- Post-use post sterilization integrity test (off-line) on the second sterilizing filter (the filter closest to the filling bag);

[1] Pre-use integrity test is performed by the supplier.

- Vials stoppering and crimping;
- Semi-finished bulk drug product storage at 2-8 °C before visual inspection;
- For MabThera 100 mg: 100% Automatic Visual Inspection (AVI) and Manual Visual Inspection (MVI) for ejects;
- For MabThera 500 mg: 100% Manual Visual Inspection;
- Finished bulk Drug Product storage at 2-8°C.

A flow chart of the manufacturing process is shown in Section 4 (Process description).

Other aspects related to the manufacturing process validation, e.g. equipment qualification, cleaning validation, etc., are covered by separate protocols and reports, available on site and referenced in the product Validation Master Plan Q486AA01 [9].

3 RESPONSIBILITIES

Validation – Patheon Monza

- Ensure that the validation activities are conducted according to the present protocol;
- Provide support to the Production and Quality Control personnel in executing the protocol; including sampling and in-process controls;
- Prepare the Process Validation Report;
- Archive approved Protocol and Report.

Technology Transfer – Patheon Monza

- Review this Protocol before execution;
- Define the manufacturing instructions for validation batches;
- Assess any deviations to the protocol and define corrective actions;
- Review the Process Validation Report.

Production – Patheon Monza

- Review this Protocol before execution;
- Participate in writing the manufacturing instructions for validation batches;
- Provide the resources (area, equipment, personnel) necessary to manufacture the batches and to execute the protocol;
- Perform the required in-process controls, as stated in this protocol;
- Provide the resources necessary to collect samples, as stated in the Protocol;
- Execute any corrective actions to resolve deviations, as required;
- Review the Process Validation Report.

Quality System & Compliance – Patheon Monza

- Review this Protocol before execution for GMP conformance;
- Participate in writing the manufacturing instructions for validation batches;
- Review the Process Validation Report for GMP conformance.

Quality Control (QC) – Patheon Monza

- Review this Protocol before execution;
- Review the appropriate analytical methods and confirm instrument calibration status;
- Provide the resources necessary to analyze samples during protocol execution, as defined by this Protocol;
- Provide Validation department with the results of all the tests performed;
- Review the Process Validation Report.

Qualified Person – Patheon Monza

- Approve this Protocol prior to execution, according to GMP and DLvo 219/06;
- Approve the Process Validation Report, according to GMP and DLvo 219/06.

Roche

- Approve the present Protocol before execution;
- Review and approve the manufacturing instructions for validation batches;
- Provide Certificate of Analysis for the Bulk Drug Substance provided;
- Perform testing activities as per Protocol;
- Approve the Process Validation Report.

4 PROCESS DESCRIPTION

4.1 MANUFACTURING PROCEDURE

The manufacturing instructions to be followed during the production of the validation batches are contained in the relevant Master Batch Records dedicated to:

- MabThera 100 mg, code 352518 ver.1 var 01 (ST6 manufacturing) [10];
- MabThera 100 mg, code 363303 ver.1 var 01 (visual inspection) [11];
- MabThera 500 mg, code 352519 ver.1 var 01 (ST6 manufacturing) [12];
- MabThera 500 mg, code 363304 ver.1 var 01 (visual inspection) [13].

The formulated composition of the bulk drug product and vial unit formulas for MabThera 100 mg and MabThera 500 mg are showed in following **Table *7***.

Table 7 MabThera 100 mg and MabThera 500 mg compositions.

Ingredient	Function	Concentration (mg/mL)	MabThera 500 mg Unit formula (mg/vial)	MabThera 100 mg Unit formula (mg/vial)
Rituximab	Active Ingredient	10	500	100
Sodium citrate dihydrate	Buffering Agent	7.35	367.5	73.5
Sodium chloride	Tonicity	9.0	450	90
Polysorbate 80	Surfactant	0.7	35.0	7.0
1N hydrochloride acid or 1N sodium hydroxyde	pH adjustment	q.s.ad pH 6.5	q.s.ad pH 6.5	q.s.ad pH 6.5
Water For Injection (WFI)	Solvent	q.s. to ~250L (min. batch size) q.s. to ~747L (max. batch size)	q.s. to 50 mL	q.s. to 10 mL
Density: 1.01 g/mL at room temperature (RT)				
Viscosity: 0.8 cP at 25 ºC and 1.4 cP at 5 ºC				

The Bill of Materials (BOM) to be used for the manufacturing of PPQ batches is shown in the following tables.

Table 8 Bill of Materials for MabThera 100 mg manufacturing process.

Patheon Monza code	Description	Amount For SKU 100mg – BS min	Amount For SKU 100mg – BS max	Unit
241582	VIAL 22mm 10mL BB	27392	81650	Pc
273438	STOPPER 20mm D713 RTS	28000	84000	Pc
273433	SEAL 20mm RED	32500	84500	Pc
102706	RITUXIMAB DS 300L TANK US (SAMSUNG)	46.55	139.08	kg
102557	Sodium chloride EMPROVE Ph,Eur,BP,JP,USP	8840	8840	G
102558	Sodium citrate dihydrate EMPROVE	7220	7220	G
102627	TWEEN 80 HP-LQ-(MH)	690	690	G
101377	SODIO IDROSSIDO EP USP JP	40	40	G
101269	AC.CLORIDRICO 37% MULTICOMPENDIAL	394.2	394.2	G
273492	SGS04049 ASMBL TUB	2	2	Pc
273469	DPTE-BetaBag PU Sterile 190-30L	3	3	Pc
273698	DPTE-BETABAG PU STERILE 105-30L	14	14	Pc
273501	SGS04044 ASMBL TUB	2	2	Pc
273498	SGS03744 ASMBL TUB	5	5	Pc
273496	SGS04047 ASMBL BB FILT	1	1	Pc
273503	SGS03875 ASMBL PUPSIT FILT	1	1	Pc
274103	SGS06884 ASMBL TUB	1	1	Pc
274138	SGS03665 ASMBL FILL NO CLAMP	1	1	Pc
273746	20mL Novasemptum syringes	8	8	Pc
271723	SINGLE SAMPLING UNIT 250ML - Novaseptum Bag	12	12	Pc
273719	SGS04719 SAMPLING MANIFOLD	10	10	Pc

Table 9 Bill of Materials for MabThera 500mg manufacturing process.

Patheon Monza code	Description	Amount For SKU 500mg – BS min	Unit
241584	VIAL 42.5mm 50mL BB	5626	Pc
273438	STOPPER 20mm D713 RTS	8000	Pc
273434	SEAL 20mm GREY	6500	Pc
102706	RITUXIMAB DS 300L TANK US (SAMSUNG)	46.55	kg
102557	Sodium chloride EMPROVE Ph,Eur,BP,JP,USP	8840	G
102558	Sodium citrate dihydrate EMPROVE	7220	G
102627	TWEEN 80 HP-LQ-(MH)	690	G
101377	SODIO IDROSSIDO EP USP JP	40	G
101269	AC.CLORIDRICO 37% MULTICOMPENDIAL	394.2	G
273492	SGS04049 ASMBL TUB	2	Pc
273469	DPTE-BetaBag PU Sterile 190-30L	3	Pc
273698	DPTE-BETABAG PU STERILE 105-30L	14	Pc
273501	SGS04044 ASMBL TUB	2	Pc
273498	SGS03744 ASMBL TUB	5	Pc
273496	SGS04047 ASMBL BB FILT	1	Pc
273503	SGS03875 ASMBL PUPSIT FILT	1	Pc
274130	SGS03667 ASMBL FILL	1	Pc
273746	20mL Novasemptum syringes	8	Pc
271723	SINGLE SAMPLING UNIT 250ML - Novaseptum Bag	12	Pc
273719	SGS04719 SAMPLING MANIFOLD	10	Pc

Primary packaging components

Primary packaging materials to be used in MabThera 100 mg and MabThera 500 mg drug products manufacturing are listed here below:

Table 10 Primary packaging components.

Material	Description	Supplier	Manufacturer	Patheon Monza code	Patheon Specification number
Vials	Vial 22 mm 10 mL BB	Schott	Schott	241582	SPKGP0682
Vials	Vial 42.5 mm 50 mL BB	Schott	Schott	241584	SPKGP0685
Stoppers	Stopper 20 mm D713	Daiyko	Daiyko	273438	SPKGP0683
Seals	Seals 20mm RED	Datwyler	Datwyler	273433	SPKGP0684
Seals	Seals 20 mm GREY	Datwyler	Datwyler	273434	SPKGP0684

Vials, stoppers, and seals are the primary packaging materials that will be used for both MabThera dosage strengths commercial manufacturing and technology transfer batches. Stopper type is the same for the two dosage strengths, whereas the vials' size and the color of the seals are dedicated to the specific dosage volume/SKU:

- 10 mL vial type and red seals are dedicated to 100 mg/vial dosage;
- 50 mL vial type and grey seals are dedicated to 500 mg/vial dosage.

Secondary packaging (Bulk packaging)

Secondary packaging materials to be used in MabThera 100 mg and MabThera 500 mg drug products manufacturing are listed here below.

It is clarified that Patheon Monza will not perform a secondary packaging process: secondary packaging materials will be used to pack and ship the finished product to Roche.

Table 11 Secondary packaging components.

Description	Dosage	Description	Supplier	Patheon Monza code	Patheon Specification number
Alveare A-PET 358x268x30.2mm 130pz	MabThera 100 mg	To collect 10 mL finish product vials, in case of incomplete boxes to prevent vials from slipping	Bachmann Forning AG Hochdorf - Switzerland	261545	SM 0017 T
Alveare A-PET 358x268x38.5mm 35pz	MabThera 500 mg	To collect 50 mL finish product vials, in case of incomplete boxes to prevent vials from slipping		261543	SM 0019 T
Space filler	MabThera 500 mg	To be used for 50mL Akylux boxes only	Comimbal SRL	261554	SM 0014 FR
Akylux black	MabThera 100 mg and MabThera 500 mg	To collect 10 mL and 50 mL vials for the shipping. The boxes are the same in which empty vials are supplied by Schott	Schott	N.A. (*)	N.A.

(*) Same boxes in which are supplied the empty vials by the supplier.

4.2 SUMMARIZED MANUFACTURING INSTRUCTIONS

A brief summary of the manufacturing procedure for **MabThera 100 mg and MabThera 500 mg** is described below.

In section 4.3 the process is illustrated as flow diagram, showing the materials used, the process steps and the in-process controls (IPC) foreseen for the manufacturing and the execution of the PPQ validation batches.

Further details are given in the relevant Manufacturing Instructions ("Batch Record").

It is specified that all the improvements identified during engineering runs and reported in the engineering report [5] have been implemented for the manufacturing of the validation batches.

4.2.1 BDS Receipt and Storage

Roche will supply Patheon Monza the Bulk Drug Substance (BDS) in Stainless Steel Freeze/Thaw (F/T) tanks in the dimension of 300 L or 120 L from the following suppliers:

- 300 L US, supplied by Samsung 10174175 (South Korea) – main source;
- 120 L/ 300 L US, supplied by Vacaville (United States) – secondary source.

F/T tanks will be shipped by Roche at ≤ -20°C. Upon receival at Patheon Monza, F/T tanks will be stored at ≤ -25°C ± 5 °C (set point – 25 °C) in a dedicated walk-in cell (FRC422). The F/T tank shipment will be under Roche responsibility.

It is specified that F/T tanks handling among different areas of the Patheon Monza facility (managed by SOP-000233649 [23]) will involve the use of a dedicated trolley, in order to facilitate the transport.

For PPQ validation campaign, 2 (two) 300 L US F/T tanks will be used. BDS allocation for PPQ manufacturing is foreseen as follows.

Table 12 BDS allocation for PPQ batches.

PPQ	Batch size	Allocated F/T tank
MabThera 100mg	Min.	Tank 2
MabThera 100mg	Min.	Tank 2
MabThera 100mg	Max.	Tank 1
MabThera 500mg	Min.	Tank 1 + Tank 2

It is specified that F/T tank identified as n°1 was already used during the manufacturing of the engineering runs. Further details are provided in the dedicated engineering report [5].

4.2.2 Dispensing: BDS Thawing Step

The F/T tanks will be moved from the warehouse to the dedicated thawing room 2204 according to the packing list to be provided by the client.
The thawing of the F/T tanks will be performed at room temperature, using two (2) dedicated thawing/freezing stations 620w NR (station 1: TWU001 SN S452788 and station 2: TWU002 SN S453427), supplied by Zeta. Each F/T tank can undergo a maximum of 3 (three) F/T cycles, according to Roche documentation RPT-0305064 [24]. The minimum and maximum volume of BDS needed in the F/T tanks to launch the refreezing and thawing cycles are 50 – 300 L for 300L F/T tanks and 30 – 103 L for 120 L tanks.

The tanks will be connected to a silicone oil (heat exchange medium) supplied through dedicated tubing. Moreover, two recirculation disposable assemblies (SGS04049) will be connected in series to the F/T tanks before starting the thawing, in order to allow the recirculation of the product during the thawing step, by means of a peristaltic pump (630EnN/R). The connection between the two recirculation disposable assemblies will be performed under Laminar Air Flow (LAF) and using Lynx Steam Through Connectors (STC).
The estimated time for the thawing step of 300 L tanks is approximately 19 hours (including 7 hours without product recirculation and 10 hours with product recirculation); while the estimated time for the thawing step of 120L tanks is approximately 12 hours (E1295AN01 [30], E1295BN01 [31]). At the end of the thawing cycle the BDS temperature is kept at 2-8°C. The total thawing duration will be calculated and reported in the MBR.
After the sampling activities at the end of thawing (and before the holding time challenge, when planned), the peristaltic pump will be inverted to empty the recirculation tubes from any BDS residuals.
Upon thawing completion, an optional storage of F/T at 2-8°C will be allowed - in case of need - during routine manufacturing. At Roche side, F/T tanks storage holding time (HT) at 2-8°C is defined as cumulative 60 days; while F/T tanks storage HT at room temperature is defined as cumulative 48 hours.

TIR/TOR challenge of F/T tanks

For the PPQ campaign described in this protocol, a TIR/TOR challenge will be performed using Tank n°1 in order to validate the allowed contact time at room temperature per each usage and the cumulative (entire life cycle of the F/T tank) allowed storage time at 2-8 °C to be applied during future commercial manufacturing. In detail, a target of approximately 16 hours at room temperature and a target of approximately 15 days at 2-8°C will be challenged. Further details regarding holding time challenge at room temperature and at 2-8°C are reported in the section 5.2.3.

To perform sampling for the holding time challenge, the peristaltic pump will be activated and after the sampling activities, the peristaltic pump will be inverted to let the emptying of the recirculation tube.

Then, the F/T tanks will be moved from dispensing to Sterile Area 6 in the solution preparation room of the Xtrema line (room 823), wiping with IPA to pharmaceutical Grade D to Grade C (as per SOP-000233649 [23]).

Sampling activities foreseen for BDS thawing step

At the completion of thawing, F/T tanks will be sampled according to Table A1 of Sampling and testing Plan. In detail, the following test items will be assessed:

- Identity, only for Tank 2 which will be used for the first time;
- Leachable;
- Endotoxins and Bioburden for microbial control.

In addition, samples for Endotoxins method validation and Bioburden method validation will be collected from the first three PPQ batches produced.

Considering that F/T tanks will be subjected to room temperature and 2-8 °C multiple times along the validation campaign, samples for microbial control (Bioburden and Endotoxin) will be collected at the end of each hold step (either intended for validation purposes – as planned for Tank 1 – or not).

Figure 1 Sampling during BDS thawing step of Tank 1.

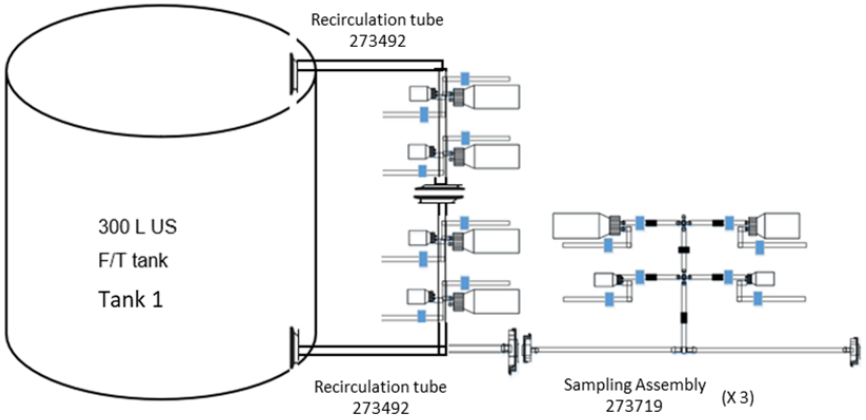
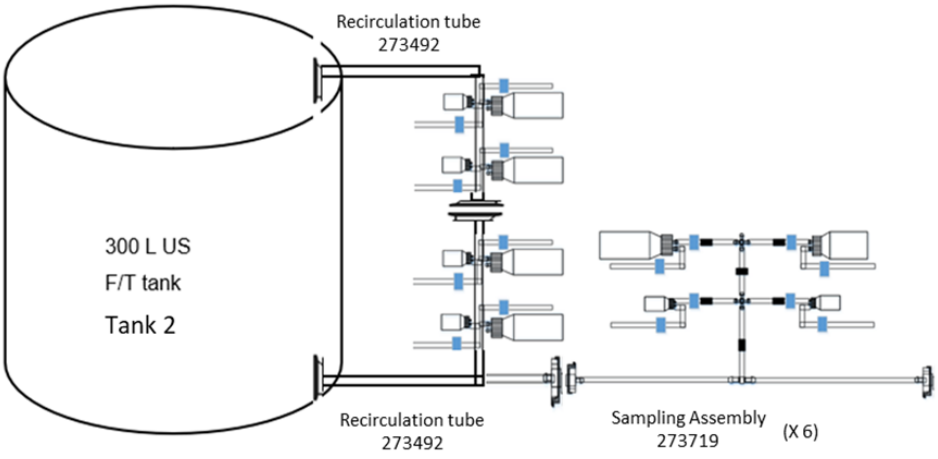


Figure 2 Sampling during BDS thawing step of Tank 2.



4.2.3 Dispensing of Excipients

For the MabThera process, excipients for buffer preparation will be weighed directly into a plastic bag in dispensing department according to the Bill of Materials (BOM) and delivered to Sterile Area 6, IMA line. Water for injection (WFI) and nitrogen will be supplied by Patheon Monza.
BOM, manufacturing instructions and process parameters to be recorded, will be captured in the relevant master batch records [10] [11] [12] [13].

4.2.4 Preparation of primary packaging components

Glass vials

Schott vials (Patheon Monza code 241582 for MabThera 100 mg, and Patheon Monza code 241584 for MabThera 500 mg) will be used.
The vials will be delivered in filling room 843 from dispensing department to be washed. The vials will be manually fed into the Washer Vega8 (LFL013). Vials will be conveyed to a rotative carousel where they will be washed with WFI and air-blown with compressed air, filtered through a 0.22 µm pore size filter. After the washing process, vials will go into the depyrogenation tunnel 1250FL DH (TST010). After exit the tunnel, the vials will access into the isolator and the filling machine.

Stoppers

The stoppers (Patheon Monza code 273438, both for MabThera 100 mg and MabThera 500 mg) are provided by West and delivered to Patheon Monza (4000 stoppers/bag) ready for sterilization. The packaging configuration foresees a double bag packaging, constituted of an internal bag with a rapid transfer port (RTP port GLC DPTE-BetaBag 190/25L) and an external polyethylene (PE) bag. Stoppers will be sterilized and dried in autoclave (ATC-025 and ATC-026) in Patheon Sterile Area 6 using an appropriate validated cycle (SOP-000111043 [25]). After that, the autoclaved bags will be connected to the isolator via the RTP port.

Seals

Seals (Patheon Monza code 273433 for MabThera 100 mg and Patheon Monza code 273434 for MabThera 500 mg) will be directly loaded to the crimping machine and applied to the stoppered vials by crimping machine ALU400 SA5017 (CPL013) without being treated prior to use by Patheon Monza.

4.2.5 Buffer Preparation

The buffer solution will be prepared in a 1100 L SS tank (RTR342) placed in position RP02 in grade C area of Sterile Area 6 solution preparation room, Xtrema line (temperature= 18 °C - 23°C). Concentration of each component in the formulated bulk is reported in the table below (**Table 13**).

Table 13 Excipients concentration for buffer preparation.

Description	Starting concentration	Final concentration in the 1100L buffer tank
Sodium citrate dihydrate	N.A.	7.35 mg/mL
Sodium chloride	N.A.	9.0 mg/mL
Polysorbate 80 stock solution	N.A.	0.7 mg/mL
Sodium hydroxide (pH adjuster)	1 N	q.s.ad pH 6.5
Hydrochloric acid (pH adjuster)	1 N	q.s.ad pH 6.5
Water for injection (WFI)	N.A.	N.A.

Final buffer formulation composition is reported in **Table 14**. Particularly, each excipient quantity is reported in order to manufacture 991.0 (±1%) kg of buffer (as per standard manufacturing process at the donor site, Roche Mannheim).

The amount of buffer to be added will be adjusted based on the concentration of the Bulk Drug Substance received, reported in the CoA. Details about buffer addition are reported in section 4.2.7.

Table 14 Final buffer composition.

Excipient	Quantity to be added to the tank
WFI	875.0 kg [866.4-883.6] kg
Sodium Chloride (weighted salt)	8840.0 g ± 1 % [8751.6-8928.4] g
Sodium Citrate Dihydrate (weighted salt)	7220.0 g ± 1 % [7147.8-7292.2] g
Polysorbate 80 stock solution	8000.0 g ± 1 % [7920.0-8080.0] g
WFI to rinse PS80 stock solution bottle	2000.0 g ± 1 % [1980.0-2020.0] g

Excipient	Quantity to be added to the tank
Hydrochloric Acid stock solution bottle	pH adjustment approx. 1700 g
Sodium Hydroxide stock solution bottle	pH adjustment (optional)
WFI to reach final weight	q.s.
Total buffer formulation	991.0 kg ± 1 % [981.2-1000.8] kg

1N HCL stock solution

4.0 kg of Hydrochloric Acid will be prepared and stored in a 5 L portable glass container under laminar flow at a concentration of 1 N. The solution will be prepared as pH adjuster and added, in case of need, in order to get the final pH of 6.5. Usually approx. 1.7 kg are needed at the donor site in order to get the final desired pH value. In particular, the dispensing department will dispense 394.2 g of HCl. In the Xtrema solution preparation room of Sterile Area 6 department, approximately 3000 g of WFI will be added to a 5L portable glass container where will be then added the amount of HCl dispensed. Then, after having added additional aliquot of WFI to reach the solution final weight, the system will be mixed with magnetic stirrer under laminar flow at 200 RPM (range 150 – 250 RPM) for at least 15 minutes. At the end of mixing, visual checks will confirm the complete dissolution.

Table 15 Recipe for HCl solution preparation.

Component	Quantity
HCl 37 %	394.2 g (390.3 – 398.1 g)
WFI	Approx. 3000.0 g
WFI to be added to get final weight	q.s.
Total HCl stock solution formulation	4000.0 g ± 1%

1N NaOH stock solution

One (1) kg of Sodium Hydroxide will be prepared and stored in a 2 L portable glass container under laminar flow at a concentration of 1 N. The solution will be prepared as pH adjuster and added, in case of need, in order to get the final pH of 6.5. Usually, no NaOH addition is needed at the donor site Mannheim in order to get the desired pH value.

In particular, the dispensing department will dispense 40.0 g of NaOH. In solution preparation room of Sterile Area 6, approximately 900.0 g of WFI will be added to 2L portable glass container where will be then added the amount of NaOH dispensed. Then, after having added additional aliquot of WFI to reach the solution final weight, the solution will be mixed at 280 RPM (range 220 – 330 RPM) for at least 15 minutes. After mixing, a visual check will confirm the homogeneity of NaOH solution.

Table 16 Recipe for NaOH stock solution preparation.

Component	Quantity
NaOH	40.0 g ± 0.5 %
WFI	Approximately 900.0 g
WFI to be added to get final weight	q.s.
Total NaOH stock solution formulation	1000.0 g ± 1%

Polysorbate 80 (PS80) stock solution

8 kg of PS80 stock solution will be prepared and stored in a 10 L portable glass container under laminar air flow (LAF). The concentration of polysorbate 80 (PS80) in the final buffer tank will be 0.7 mg/mL. The starting amount of PS80 will be added by the dispensing department directly in the autoclaved 10L bottle. It has to be highlighted that the PS80 container of raw material will be used as “single use container”, meaning that, once opened, the leftover raw material will be delivered to the QC Laboratory in order to perform an identification (ID) test and then discarded.

The 10L bottle will be then wrapped with foil in order to protect the PS80 from light and delivered to Sterile Area 6 department. Then, WFI will be added in the solution preparation room in order to get PS80 final concentration. In particular, the dispensing will weight 690.0 g in the glass bottle that will be delivered to Sterile Area 6 where WFI will be added and mixed to obtain the final PS80 solution, mixing using a magnetic stirring bar at 400 RPM (range 350 – 450 RPM) for at least 2 hours. After mixing, a visual check will confirm the homogeneity of PS80 solution.

During manufacturing of validation batches subjected to holding time challenge (see section 5.2.3)

The following holding times will be challenged for PS80:

- from the start of the PS80 dispensing (weighing) to the end of PS80 solution preparation, approximately a **target 10 hours**;
- from the end of the PS80 solution preparation to the end of its addition to the buffer tank, approximately a **target 14 hours**.

Table 17 PS80 stock solution recipe.

Component	Quantity
PS80 weight	690.0 g ± 0.5 %
WFI to be added to get the final weight	q.s.
Total PS80 stock solution formulation	8000.0 g ± 1%

Formulated buffer preparation

991.0 kg of the buffer will be prepared and stored in a 1100 L SS vessel (RTR342), positioned in position RP02 of the Xtrema solution preparation room. At first, WFI from the loop will be added to the buffer tank. Mixing will be activated and kept at minimum speed, identified as 100 RPM during surrogate trial [3] and confirmed during engineering run [5], during excipients addition. Then sodium chloride (weighted salt) and sodium citrate dihydrate (weighted salt) will be added to the tank through the funnel at the level of the open port. Later, PS80 solution will be added into the buffer tank through the funnel and J-tube placed on the open port, in order to minimize foaming. A WFI rinse of the PS80 container will be performed. After the addition of sodium chloride, the system will be mixed for at least 10 minutes. After the addition of sodium citrate dihydrate, the mixing will be carried out for at least 20 minutes, after WFI rinse of PS80, the system will be mixed for at leat 20 minutes. Mixing will be continuous and conducted at a target of 100 RPM (range 100 - 200 RPM). It is specified that the buffer will be mixed for at least 2 hours from mixing activation. A visual check will be performed to confirm complete dissolution after each excipient addition.

Before adding HCl, a pH measurement of the buffer compounding for information only will be executed in production on the floor, within Sterile Area 6 department. HCl will be added[2] starting with

[2] During pH adjustment, it is required to get as much as possible close to the target.

an aliquot of 800 mL, followed by smaller aliquots of 100 mL. pH measured in Sterile Area 6 will be confirmed by QC chemical (blocking IPC). In case of need, NaOH will be added in order to get the final pH value of 6.5. After this point, the mixing will be stopped and WFI will be added to reach final weight.
After having reached the target weight, a final mixing at 200 RPM (range 150 - 250 RPM) for at least 15 minutes will be conducted.
Finally, before proceeding with buffer addition in compounding tank, a sample to be sent to QC laboratory will be taken to check pH and Osmolality.
The order of addition for the above described excipients must be respected.

For PPQs that will be used to manufacture validation batches subjected to Holding time challenge (see section 5.2.3):
Holding time to be challenged from start of buffer preparation to end of buffer transfer into the compounding tank should be approximately **a target of 24 hours**.

Sampling activities foreseen for Buffer preparation step
After pH adjustment in production, a blocking pH check is foreseen (to be executed by QC Chemical department). When compliant result for pH is received, and the final buffer compounding is completed, a second sampling will take place to monitor the following test items:
- pH;
- Osmolality.

In addition, only for one batch of MabThera 100 mg, sample ID **Buf-PS80** will be collected and shipped to Roche SSF (South San Francisco) to analyze polysorbate 80 concentration.

Only for PPQ batches involved in the holding time challenge, samples for Endotoxin and Bioburden will be collected at the end of buffer preparation as time zero (t0).
In addition, only from the first three PPQ batches a sample will be collected for Endotoxin method validation.

Almost at the end of buffer addition into the compounding tank, samples will be collected from the buffer tank RTR342 for Bioburden and Endotoxin. These samples aim to be representative of microbial condition after the overall buffer storage time and will be collected at least after a target of 24 hours from start of buffer preparation for PPQ batches involved in the holding time challenge.

4.2.6 BDS Pooling

The BDS solution will be pooled by means of a peristaltic pump (20 – 50 RPM) into the cleaned and sterilized compounding tank (RTR343) installed in position RP03 of Xtrema solution preparation room. The extremity of the recirculation tubing (SGS04049) connected to the top of the F/T tank – the tubing was previously used to ensure product recirculation during the thawing step - will be disconnected from the F/T tank and connected to the top of the compounding tank (RTR343) through a reducer. Detailed information is provided in section 4.4.1.

The target of RPM of the peristaltic pump will be 40 RPM (range 20 – 50 RPM), identified during the engineering trials.

For the US F/T tank, the extremity of recirculation tubing that will remain connected to the tank will be the one at the F/T tank bottom outlet.

BDS will be transferred into the compounding tank via J-tube and dedicated reducer for MabThera manufacturing. The total amount of BDS needed will be calculated on the basis of the following formulas provided by Roche. The calculation will be reported in the master batch record.

Step 1: Calculate amount of protein needed for batch

$$\text{(a)}\ \ batch\ size\ [L]\ X\ \frac{10g}{L} = amount\ of\ protein\ needed\ [g]$$

where batch size [L] is the input from Attachment 3.

Step 2: Calculate amount of BDS needed

$$\text{(b)}\ \ amount\ of\ BDS\ [Kg] = \frac{amount\ of\ protein\ [g] from\ (a)}{protein\ concentration\ of\ BDS\ [\frac{g}{L}]}\ X\ density\ of\ BDS\ [\frac{Kg}{L}]$$

Where density of BDS: 1.024 kg/L

Protein concentration of BDS [g/L] is the input form CoA for each BDS batch

In case of any BDS leftover (which is to be within the applicable validated range), the F/T will be delivered back to dispensing.

At the end of the holding time challenge, F/T tank will be transferred in the thawing room where samples will be taken, and the recirculation tube will be disposed of. If the F/T tank can be re-frozen,

it will be stored at ≤ -20°C up to 24 months from the BDS manufacturing production date. The delivery of the F/T tank to dispensing must be performed as soon as the BDS pooling is completed.
For every new thawing cycle, new disposable recirculation tubes will be used.
After having transferred the amount of needed BDS in the RTR343 1100L tank, operators will have to weigh the RTR343 tank and calculate the real amount of protein transferred.

Step 3: Calculate amount of BDS transferred

$$\text{(c) } protein\ actually\ transferred\ [g] = \frac{amount\ BDS\ actually\ transferred\ [Kg]\ X\ protein\ concentration\ BDS\ tank\ [\frac{g}{L}]}{density\ of\ BDS\ [\frac{Kg}{L}]}$$

Where Protein concentration of BDS [g/L] is the input form CoA for each BDS batch.

<u>If multiple BDS tanks are used:</u>

Step 1: Calculate the amount of protein transferred from Tank 1
Repeat calculation of (a)
Transfer the BDS from Tank 1 and record the amount transferred in [kg]

Calculate the amount of protein transferred from BDS Tank 1

$$(c)\ protein\ actually\ transferred\ [g] = \frac{amount\ BDS\ actually\ transferred\ [Kg]\ X\ protein\ concentration\ BDS\ tank\ [\frac{g}{L}]}{density\ of\ BDS\ [\frac{Kg}{L}]}$$

Step 2: Calculate the amount of protein [g] still needed from Tank 2

$$(d)\ protein\ still\ needed = protein\ needed\ [g] from\ (a) - protein\ transferred\ [g]\ from\ (c)$$

Step 3: Calculate the amount of BDS still needed from Tank 2

$$(e)\ amount\ of\ BDS\ [Kg] = \frac{protein\ still\ needed\ [g] from\ (d)}{protein\ concentration\ of\ BDS\ [\frac{g}{L}]}\ X\ density\ of\ BDS\ [\frac{Kg}{L}]$$

Step 4: Calculate the amount of protein transferred from Tank 1 and Tank 2

$$protein\ actually\ transferred\ tank\ 1\ [g] = \frac{amount\ BDS\ actually\ transferred\ tank\ 1\ [Kg]\ X\ protein\ concentration\ BDS\ tank\ 1\ [\frac{g}{L}]}{density\ of\ BDS\ [\frac{Kg}{L}]}$$

$$protein\ actually\ transferred\ tank\ 2\ [g] = \frac{amount\ BDS\ actually\ transferred\ tank\ 2\ [Kg]\ X\ protein\ concentration\ BDS\ tank\ 2\ [\frac{g}{L}]}{density\ of\ BDS\ [\frac{Kg}{L}]}$$

$$(f)\ total\ protein\ transferred\ [g] = Tank\ 1\ [g] + Tank\ 2\ [g]$$

Only for PPQs that will use F/T tank n°1 (see also section 4.2.2 and section 5.2.3):

- a target of approximately **16 hours at room temperature** will be challenged, per each use;
- a target of approximately **15 days at 2-8°C** will be challenged, cumulative of the overall F/T tank usage.

Only for PPQs that will be used to manufacture validation batches subjected to Holding time challenge (see section 5.2.3):

Holding time to be challenged from start of BDS addition into the compounding tank to end of Bioburden reduction filtration should be approximately **a target of 24 hours**.

Sampling activities foreseen for BDS pooling step

No sampling is foreseen from the compounding tank after BDS pooling.

4.2.7 Buffer Transfer and Bulk Solution Preparation

For MabThera production, after pooling is completed, the buffer will be added through SGS03744 ("Y" tank connector) and SGS04044 ("extension transfer tubing") assemblies, in order to get the desired final composition. Buffer amount to be transferred will be calculated based on BDS protein content stated in BDS CoA provided by Roche, the data obtained in the **steps** reported in Section 4.2.6, and following the below formula shared by Roche:

Buffer addition

In case of single F/T tank

Based on the real amount of protein transferred (c), the target batch size will be calculated according to the following formula:

$$(d) final\ batch\ size\ [Kg] = \frac{total\ protein\ transferred\ [g]\ from\ \ (c)}{10\,\frac{g}{L}}\ X\ density\ of\ DP\ [\frac{Kg}{L}]$$

Where the density of DP is 1.012 kg/L

After that, the buffer will be added up to the final batch size (d).

In case of multiple F/T tanks

Based on the real amount of protein transferred (f), the target batch size will be calculated according to the following formula:

$$(g)\ final\ batch\ size\ [kg] = \frac{total\ protein\ transferred\ [g]\ from\ (f)}{10\ [\frac{g}{L}]}\ x\ density\ of\ DP\ [\frac{kg}{L}]$$

Where the density of DP is 1.012 kg/L

After that, the buffer will be added up to the final batch size (f).

The calculation for the buffer addition during the manufacturing of the batch will be reported in the master batch record. No buffer filtration is foreseen before the transfer in the compounding tank. The transfer will be performed through nitrogen at a target pressure of 0.5 barg (0.5-1.0 barg).
After buffer addition, a mixing step will be performed, setting the mixing speed at 200 RPM (range 150 – 250 RPM) for NLT 15 minutes and NMT 45 minutes.

Bulk Homogeneity study

When formulated bulk preparation will be completed, samples will be collected and tested for protein concentration to assess bulk homogeneity throughout the compounding tank.
It is specified that bulk solution preparation phase is in common among the two SKUs, 100 mg and 500 mg.
Three samples will be collected from each of the three sampling locations (top, middle and bottom) of the compounding tank (nine samples withdrawn in total) at the end of solution preparation.
Results should be consistent with verified homogeneous formulated bulk from the Engineering batch.

PPQs subjected to bulk homogeneity study will be:

- MabThera 100 mg, maximum batch size;
- MabThera 500 mg, minimum batch size.

Rationale:

Bulk homogeneity will be performed testing the bulk for protein concentration. Analysis will be under Patheon Monza responsibility.
Homogeneity of the validation batches will be assessed by the two-staged approach in accordance with Patheon Corporate Standard guideline “Process Validation-Testing Requirements and Acceptance Criteria” QS09-G03-02 [26], detailed below:

<u>STAGE 1</u>

One sample from each location will be tested for protein concentration.
Solution homogeneity will be demonstrated when:

- One individual value from each location (n=3) is within 98.0 – 102.0%, where 100% is defined as 10.0 mg/mL

Target concentration of:

- **MabThera formulated bulk:** 10.0 mg/mL (9.2 – 10.8 mg/mL)

If this requirement is not met, the other two samples will be tested according to stage 2 below.

STAGE 2

The other two samples from each location will be also tested for protein concentration.

Solution homogeneity will be demonstrated when:

- Each individual value (n=9) from each location is within 95.0 – 105.0%, where 100% is defined as 10.0 mg/mL

Target concentration of:

  - **MabThera formulated bulk:** 10.0 mg/mL (9.2 – 10.8 mg/mL)

- Each location mean is within 98.0 – 102.0%, where 100% is defined as 10.0 mg/mL

Target concentration of:

  - **MabThera formulated bulk:** 10.0 mg/mL (9.2 – 10.8 mg/mL)

- The overall SD is ≤ 3.0%

Products which are considered to be true solutions are expected to have variation in potency related only to sampling and testing variability. The Stage 1 criterion is set based on the maximum variation, which would normally be expected given adequate mixing time. If a product enters Stage 2 the sampling and testing plan will allow for evaluation of differences between the different locations to determine if variation is random or if there is evidence of inadequate mixing.

Sampling activities foreseen for Buffer Transfer and Bulk Solution Preparation step

Samples will be collected according to Sampling and Testing plan, Table A1 on 1 (one) PPQ batch at minimum batch size (either MabThera 100 mg or MabThera 500 mg) and 1 (one) PPQ batch at maximum batch size. Samples will be collected in triplicate from top, middle and bottom position of the compounding tank RTR343.

In addition, samples for the following test items will be collected:

- Leachable, for leachable control (validation purpose only);
- pH, Osmolality and Protein concentration.

When the PPQ batch is subjected to holding time challenge, samples for Bioburden monitoring control and Endotoxins will be collected as time zero (t0).

Bioburden sampling will be conducted from the compounding tank RTR343 almost at the end of Bioburden reduction filtration in order to capture microbial condition representative of the overall bulk drug product actual held. In case of PPQ batches subjected to holding time challenge, the holding should last approximately a target of 24 hours.

4.2.8 Bioburden Reduction Filtration and Storage

The formulated bulk contained in the compounding tank RTR343 will be transferred, by nitrogen pressure, to the storage SS tank RTR344 placed in position RP04 through a Bioburden reduction line (SGS04047) which is equipped with an incorporated filter (FILTER-OPTICAP XL 10 CAPSULE 0.22 µm DURAPORE (KVGLG10HH1)) and through SGS03744 assembly ("Y" tank connector provided with steam thru and Aseptiquick connections).

Filtration pressure applied at the donor site during the bioburden reduction filtration is 0.5 - 1.0 bar. To minimize foam creation during the transfer, as a result of surrogate trial and engineering runs, the pressure applied in the RTR343 tank will be 0.6 bar (range 0.5 - 1.0 bar).

During the bioburden filtration step, there is no need to control the temperature and no flush prior to filtration is requested. After the transfer in the storage tank, the solution does not require any mixing step before the sterilizing filtration, according to the manufacturing process established at the donor site. Only when cold storage at 2-8°C will be needed, mixing at minimum mixing speed (50 RPM) will be performed to guarantee homogeneity in temperature during the cooling phase and turned off during the storage at controlled temperature.

Storage at 2-8 °C before the start of filling will be optional during commercial manufacturing, in case the filling step cannot start within the validated time at room temperature allowed for the formulated bulk.

Only for PPQs that will be used to manufacture validation batches subjected to Holding time challenge (see section 5.2.3):

During the PPQ campaign, approximately a target of 24 hours at room temperature (RT) and 24 hours at 2-8°C will be challenged in order to validated the maximum time at room temperature allowed to the formulated bulk solution before filling and the optional maximum allowed time to the formulated bulk at 2-8°C in case of need for cold storage.

PPQ batches involved in the holding time challenge will be MabThera 100 mg, maximum batch size and MabThera 500 mg, minimum batch size.

At the end of bioburden reduction filtration, a nitrogen overlay (approximately 0.5 barg) in the storage tank will be applied to the tank.

When intermediate storage at 2-8°C is foreseen, there will be no need to re-equilibrate the solution at room temperature before starting the filling considering that the density and viscosity features of the product will not be impacted due to the cool storage period, as per Roche indication (ref TEC-0213431 [14]).

Sampling activities foreseen for Bioburden reduction filtration and storage

After every hold step and temperature exposure condition, Endotoxins and Bioburden samples will be collected to keep monitoring any possible microbial contamination.

4.2.9 Sterile Filtration

After the storage and before starting with the filling operations, the 1100L tank RTR344 will be moved by means of an electrical transpallet from the solution preparation room to the filling room. No mixing step is required before starting with the filling.

Before filling, the bulk solution will be sterilized through two (2) 0.22 µm sterilizing grade membrane filters OPTICAP XL 10 CAPSULE 0.22 µm DURAPORE PVDF (KVGLG10HH1) incorporated in series in the assembly SGS03875. Particularly, the assembly will be connected through a sterile-to-sterile connection to the Y assembly placed at the bottom of the storage tank at one end and to the filling bag (filling bag placed inside isolator) at the other end. The sterile filtration will be performed in grade C through nitrogen, applying a target pressure of 0.6 barg (range 0.5 – 0.7 barg, $\Delta P \leq 1$ bar).

The filtration and the filling temperature will be equal to 2-25°C, considering the possibility to keep the product at 2-8°C and no equilibration before filling.

A filter flush will be performed for all the PPQ batches, prior to start with the sterile filtration and the related amount of solution to be aliquoted will be collected (see Sampling and Testing Plan Table A1) when applicable.

After the sterile filtration, the solution will be conveyed into an 8 L filling bag (minimum and maximum working range 50% - 80% of the nominal volume - set at 5 Kg - for 100 mg, minimum and maximum working range 50% - 80% of the nominal volume (set at 5 Kg) for 500 mg).

Filter flush study

Considering the results obtained during engineering run, the first 500 mL will be discarded downstream the second sterilizing filter, and then a filter flush study will be performed to assess the adsorption and dilution effect is absent. Three aliquots of 500 mL each will be taken and analyzed for protein content. Details are reported in the Sampling and Testing Plan Table A1.

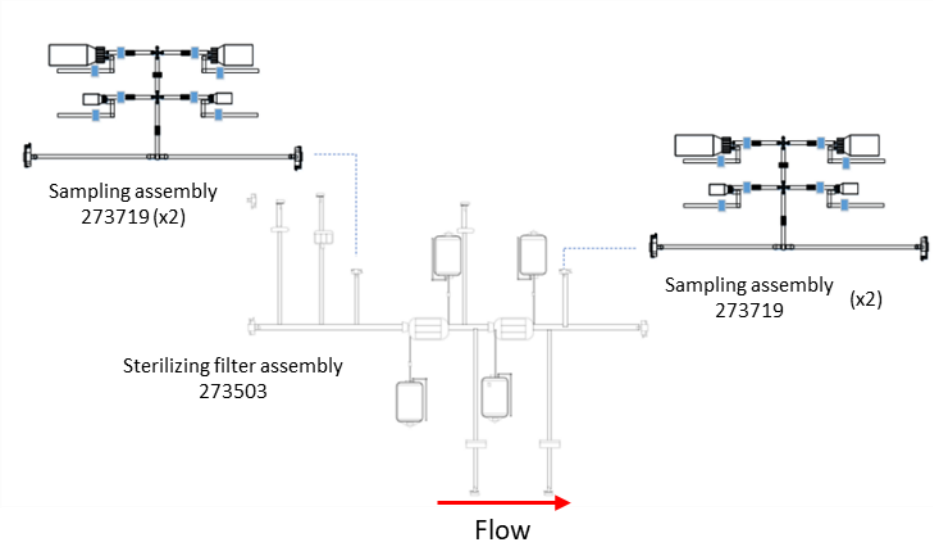
The set-up of the sampling assembly connected to the sterilizing filter assembly is reported in the figure below. The study will be performed on three PPQ batches, and on the fouth PPQ batch 2000 mL will be discarded without aliquoting.

Sampling activities foreseen during sterile filtration

Samples to be analyzed for Endotoxins and Bioburden will be collected at the beginning and at the end of the sterilizing filtration in order to monitor any possible microbiological contamination that may occur during the filling.

As detailed in the section above, aliquots to be tested for protein content will be collected after the second sterilizing filter to perform the filter flush study.

Figure 3 Set-up of sampling assemblies before and after the sterilizing filter assembly.



4.2.9.1 Execution of Pre-use Filter Integrity Test

Before performing all the connections, a pre-use filter integrity test on both sterilizing filters must be executed. The following steps are foreseen:

- The filter will be wetted with about 20L of WFI;
- Pre-use integrity test will be performed using the Bubble point method.

The recipe to be used for the filter integrity test and related parameters will be reported in the master batch record. The bubble point value is ≥ 3450 mbar with WFI at 15-25 °C for KVGLG10HH1 filter type, as per Millipore recommendation.

4.2.9.2 Execution of Post-use Filter Integrity Test

After the filtration, the integrity test (FIT) of filters included in the disposable assembly 273504 will be performed offline.
The following steps are foreseen for each filter:

- Disconnection of the filter from the disposable assembly 273504;
- Flush of the filter with WFI;
- Filter integrity test with bubble point method in accordance to filter's supplier data.

The filters are the following:
- 2 (two) nitrogen filters KEGBG050HH00 (≥ 1170 mbar nitrogen with 100% IPA);
- 1 (one) WFI filter KA3EKVP6G (≥ 3320 mbar nitrogen with WFI);
- 2 (two) barrier filters MSP010012 (≥ 1280 mbar nitrogen with 70/30 % IPA/water);
- 2 (two) sterilizing filters KVGLG10HH1 (≥ 3450 mbar nitrogen with WFI).

For sterile filters, only the filter closer to the filling line will be integrity tested and, in case of failure, the other filter will also be tested.

4.2.10 Vials Filling

The filling operations will be carried on using the Xtrema filling machine, which is installed into an isolator (pharmaceutical grade A), surrounded by grade C. The aseptic filling process in line is an automated system with eight (8) dosing peristaltic pumps and needles for MabThera 100 mg and six (6) dosing peristaltic pumps and needles for MabThera 500 mg. The machine automatically performs the following steps:

- Vial transfer at machine in-feed;
- Weighing of the tare of all the vials (IPC 100%);
- Liquid solution dosing into vials with 8 filling needles for MabThera 100 mg and 6 filling needles for MabThera 500 mg;
- Weighing of the gross weight of all the vials (IPC 100%);
- Rejection of non-conforming vials/transferring conforming vials to the machine outfeed.

In the table below are reported the fill weight parameters for both 100 mg and MabThera 500 mg, together with alert and action limits.
The filling speed operative range identified during the manufacturing of technical batches and media fill are:

- 80 – 180 vials/minute, for MabThera 100 mg;
- 90 – 100 vials/minute, for MabThera 500 mg.

During the filling steps, the process interruption events, and related time will be recorded in the machine record according to SOP-000136665 [15].

Table 18 MabThera filling weight limits.

Dosage	Limits	Fill volume (mL)	Fill weight (g)
100 mg/vial	Upper Action Limit	10.921	11.030
	Upper Alert Limit	10.634	10.740
	Target	**10.525**	**10.630**
	Lower Alert Limit	10.416	10.520
	Lower Action Limit	10.297	10.400
	Theoretical filling speed: 180 vials/minute		
500 mg/vial	Upper Action Limit	52.099	52.620
	Upper Alert Limit	51.366	51.880
	Target	**51.109**	**51.620**

Dosage	Limits	Fill volume (mL)	Fill weight (g)
	Lower Alert Limit	50.851	51.360
	Lower Action Limit	50.396	50.900
	Theoretical filling speed: 100 vials/minute		
	Density of Drug Solution = 1.01 g/mL		

Filling homogeneity study

To ensure the filling homogeneity, samples representative of vials equally distributed during filling phase will be collected. Samples will be analyzed for protein concentration to demonstrate batch uniformity throughout the filling step.

In particular, 3 (three) samples will be taken from 40 (forty) different sampling locations throughout the overall filling process.

PPQ batches involved in the present study will be:

- MabThera 100 mg, minimum batch size;
- MabThera 100 mg, maximum batch size;
- MabThera 500 mg, minimum batch size.

Homogeneity of the above mentioned validation batches (demonstrated using the approach to be applied for products single dose, which have content uniformity requirement as part of release specification) will be assessed by following ASTM E2709, detailed in the Standard Corporate Guideline “Content Uniformity” QS05-G10-01 [27]. In detail:

Table 19 Unit dose test.

Sampling	Testing	Acceptance Criteria
Sample 3 units from 40 locations throughout the batch. Sample 3 units from each significant event	Test 3 samples from 20 locations (including beginning, end and all significant events)	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60
	Test 3 samples from 20 of the remaining locations	PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120

[1] Any result outside 75.0% - 125.0% in PVT Stage 1 will be a failure of the test and will not proceed to PVT Stage 2;
[2] Based on the overall mean being within the range on the look-up table.

The statistical approach to apply for filling phase is the Bargum approach. The homogeneity is demonstrated providing with 90% of assurance that at least 95% of samples taken equally distributed from the batch meet the acceptance criteria for the uniformity of dosage units.

The filling capability will be evaluated (recommended value for Cp and Pp indexes: ≥ 1.33) only to perform an assessment from a statistical point of view over process control.

Actions to be taken in case pump exclusion is needed during the filling

For MabThera 100 mg

No pump can be excluded without exceeding the maximum product volume for fill per filling needle identified during surrogate batches. In case one or more pumps need to be excluded, the portion of the batch must be segregated, and the following additional sampling must be conducted:

- Sub visible particles, taken at beginning, middle and end of the sub-batch
- Sterility, taken at beginning, middle and end of the sub-batch
- Endotoxins, taken at beginning, middle and end of the sub-batch

Chemical analytical tests will be collected as per sampling plan considering the overall filling process (regardless creation of sub-batch) for beginning, middle and end locations.
It is specified that the sub batch would be created, in case of pump exclusion, only to trace segregation of the portion and to tighten the monitoring of the CQA subvisible particles.

For MabThera 500 mg

1 (one) pump can be excluded without exceeding the maximum product volume for fill per filling needle identified during surrogate batches. In case more than one pump need to be excluded, the portion of the batch must be segregated, and the following additional sampling must be conducted:

- Sub visible particles, taken at beginning, middle and end of the sub-batch
- Sterility, taken at beginning, middle and end of the sub-batch
- Endotoxins, taken at beginning, middle and end of the sub-batch

Chemical analytical tests will be collected as per sampling plan considering the overall filling process (regardless creation of sub-batch) for beginning, middle and end locations.
It is specified that the sub batch would be created, in case of pump exclusion, only to trace segregation of the portion and to tighten the monitoring of the CQA subvisible particles.

4.2.11 Stoppering and Crimping

The vials will be stoppered and crimped under restricted access barrier systems (RABS, grade C) equipped with a dedicated HVAC (Heating, Ventilation and Air Conditioning) system and terminal HEPA (high-efficiency particulate absorbing filter) filters for particle protection, using crimping machine ALU400 – SA3122 (CPL012). The machine is particularly suitable for crimping of aseptic products since it can operate in a classified environment under laminar flow in a conventional sterile chamber or an isolator.

The IMA ALU400 rotary crimping machine with a continuous motion will be used to apply and flange stoppered vials. The machine is equipped with a Sea Vision system in order to check the stopper position and presence. The check is performed at 100% and not compliant vials are automatically discarded.

Crimping parameters were challenged during surrogate batches [3], where suitability of the proposed operative ranges for crimping pressure and capping height was tested [3]. During the engineering trial, crimping parameters for MabThera 500 mg and MabThera 100 mg were run at the target values, confirming suitability of the selected target [5].
Crimping parameters for MabThera 500mg and MabThera 100 mg (target values and height/pressure ranges) are reported in the table below.

Table 20 Crimping parameters - MabThera 500 mg.

Conditions	Crimping height	Crimping Pressure
Minimum	67.5 mm	Minimum pressure - 90 KPa
Target	**68.0 mm**	**Target pressure - 100 KPa**
Maximum	68.5 mm	Maximum pressure - 120 KPa
Crimping speed: ≤ 100 vials/minute		

Table 21 Crimping parameters - MabThera 100 mg.

Conditions	Process Parameter	Crimping Pressure
Minimum	46.0 mm	Minimum pressure - 80 KPa
Target	**46.5 mm**	**Target pressure - 90 KPa**
Maximum	47.0 mm	Maximum pressure - 100 KPa
Crimping speed: ≤ 180 vials/minute		

The maximum crimping speed allowed will be 100 vials/minute for MabThera 500 mg and 180 vials/minute for MabThera 100 mg[3]. The suitable target value identified during engineering runs for crimping speed is 100 vials/minute for MabThera 500 mg and 175 vials/minute for MabThera 100 mg. According to SOP-000110739 [28], an IPC check for correct crimping operations is performed every 30 ± 5 minutes on 8 vials in case of MabThera 100 mg or 6 vials in case of MabThera 500 mg (one per each crimping head).
Process parameters to be monitored are detailed in section 5.2.2.

During the unloading, crimped vials will be collected in black propylene trays. The trays will be placed on pallets and then sent to warehouse at 2-8°C for intermediate cold storage.

Sample collection during MabThera 100 mg and MabThera 500 mg unloading from Xtrema filling machine

The following analytical tests will be performed on the samples collected at the unloading of Xtrema filling line, according to Sampling and Testing Plan Table A1:

- Leachable, only from the PPQ batches involved in the holding time challenge;
- Visible and Subvisible Particles, only from the PPQ batch manufactured at maximum batch size
- Protein content, in order to assess filling homogeneity throughout the batch, only for 1 (one) PPQ of MabThera 100 mg at minimum batch size, the PPQ batch of MabThera 100 mg at maximum batch size and the PPQ batch of MabThera 500 mg;
- Container Closure Integrity, the sample size will be identified on the basis of ISO 2859-1, applying a general inspection level III (single sampling plan for normal inspection);
- Chemical and Microbiological release tests;

Only from the first three PPQ batches, samples will be collected for Endotoxins method validation.
Only from the batch of MabThera 500 mg, samples will be collected for Sterility method validation.

[3] Crimping speed depends on filling speed.

4.2.12 Visual Inspection

After being removed from cold storage, the vials will be transported to the inspection room.

During PPQ batches, the first time point to check equilibration of vials will be set after approximately 15 hours for MabThera 500 mg and approximately 14 hours for MabThera 100 mg, based on data collected during engineering runs [5]. Following checks, if needed, will be every approximately 30 minutes.

To perform the equilibration check, operators will take one box from the middle of the pallet and from that box, 10 vials from the middle position will be checked for the absence of condensate and temperature check (T ≥ 15 °C).

A check for absence of bubble, prior to perform the visual inspection, must be performed. The relevant instructions will be reported in the Master Batch Record.

For MabThera 500 mg:

Visual inspection will be 100% manual. Defect list (refer to TEC-0218416 “Defect Classification Gap Assessment for Avastin and Mabthera) is reported in **Table 22**.

For MabThera 100 mg:

PPQ batches will be 100% automatically visually inspected on Seidenader machine CS-30 (SPE025). Ejects from the AVI process will be inspected manually. Defect list is reported in **Table 23** (refer to TEC-0218416 “Defect Classification Gap Assessment for Avastin and Mabthera).

Table 22 Defect list for Manual Visual Inspection.

Defect	Description	Classification
VIAL	Vial with defected glass (chipped – body, bottom)	M
	Cracked vial (body, bottom)	C
	Dirty external glass	m
	Surface scratch on vial body (length > 1 cm, width > 2 mm)	m
PRODUCT	Empty vial	C
	Vial with glass fragment, particles, foreign bodies in the solution	C
CLOSURE	Vial without stopper	C
	Vial with wrong stopper (mix up – lyo vs liquid)	C
	Vial without seal / flip-off	C
	Foreign seal (mix up)	C
	Vial with defected flip-off/seal (scratched, dented, dirty, damaged)	m
	Seal with wrongly positioned/non-sealing seal – not crimped	C
	Seal with wrongly positioned/non-sealing seal – partially crimped	M
	Partially detached flip-off (evident)	m

Table 23 Defect list for automatic visual inspection.

Defect	Description	Classification
VIAL	Vial with defected glass (chipped – body, bottom)	M
	Cracked vial (body, bottom)	C
	Dirty external glass	m
	Surface scratch on vial body (length > 1 cm, width > 2 mm)	m
PRODUCT	Empty vial	C
	Glass particle 400-600 micron	C
	Glass particle 600-800 micron	C
	Glass particle 800-1000 micron	C
	Stainless steel 400-600 micron	C
	Stainless steel 600-800 micron	C
	Stainless steel 800-1000 micron	C
	Rubber stopper 200-400 micron	C
	Rubber stopper 400-600 micron	C
	Rubber stopper 600-800 micron	C
	Rubber stopper 800-1000 micron	C
	Fiber 600 - 800 micron (white and dark)	C
	Fiber 800 - 1000 micron (white and dark)	C
CLOSURE	Vial without stopper	C
	Vial with wrong stopper (mix up – lyo vs liquid)	C
	Vial without seal / flip-off	C
	Foreign seal (mix up)	C
	Vial with defected flip-off/seal (scratched, dented, dirty, damaged)	m
	Seal with wrongly positioned/non-sealing seal – not crimped	C
	Seal with wrongly positioned/non-sealing seal – partially crimped	M
	Partially detached flip-off (evident)	m

Vials from the inspected batch will be randomly sampled as per ISO 2859-1, applying a general inspection level III (plan for normal inspection), as per SOP-000118671 [16], to perform a statistical control (AQL); during the visual inspection activities as per Patheon Monza SOP-000028049 [17] QC Packaging operators will perform the statistical check (AQL). The sampling plan is defined according to the batch size and the critical defects acceptance criteria (zero defects), as per SOP-000028049 [17].

Table 24 Defect list for automatic visual inspection.

Defect category	Description
m	Minor defects do not impact product performance or compliance; they are often cosmetic in nature, affecting only product appearance or pharmaceutical elegance.
M	Major defects carry the risk of a temporary impairment or medically reversible reaction or involve a remote probability of a serious adverse reaction. This classification is also assigned to any defect which causes impairment to the use of the product. These may result in a malfunction that makes the product unusable
C	Critical defects are those that may cause serious adverse reaction or death of the patient if the product is used. This classification includes any nonconformity that compromises the integrity of the container and thereby risks microbiological contamination of the sterile product.

Table below shows the AQL that will be applied during the statistical control.

Table 25 AQL Table.

AQL for Critical defects	AQL for Major defects	AQL for minor defects
None Allowed	0.65	2.5

Visible particles test will be executed according to USP <790> and Ph.Eur.2.9.20 using an AQL of 0.65. Table 2 A (Single sampling plans for normal inspection) of ISO2859-1 defines the acceptance criteria for each classification of defects (Critical, Major or minor) as per SOP-000028049 [17].
The attachment #4 and attachment #5 of this protocol will be used by QC Packaging analysts to record the statistical check (AQL) activities, foreseen by this protocol, respectively for MabThera 500 mg and MabThera 100 mg. Furthermore, these attachments present the defect list that will be applied during the statistical control and the related acceptance criteria.

Sample collection after visual inspection

Samples will be collected for Comparability test and Visual Inspection certification process, and shipped to the client Roche to be analyzed, according to Sampling and Testing plan, Table A1.
Retain sampled will also be collected.

4.2.13 Storage and Shipment of finished drug product (DP)

Upon Visual Inspection completion, the finished product will be stored into the Warehouse cold stored at 2-8°C. The samples will be shipped under Roche responsibility.

Rejected units identified during the visual inspection step will be stored by Patheon Monza until all analytical results are available. Later, Roche will communicate if they have to be shipped or if they can be disposed of.

For the sample's shipment set up, the Akylux black boxes coming from production will be used. Vials will be secured by placing the appropriate alveolar and space filler in case of the 50mL dosage.

4.3 MANUFACTURING PROCESS FLOW

In the following figure it is reported a scheme of the manufacturing steps for MabThera 100 mg and MabThera 500 mg PPQ batches.

Figure 4 MabThera 100 mg and MabThera 500 mg - Process steps.

Materials	Process	Controls	Process conditions
BDS in F/T tank	**BDS STORAGE**		Cell T ≤ – 20°C
	BDS THAWING		Thawing room T =17-23 °C Heat transfer fluid temperature set point: 23°C
	BDS RECIRCULATION DURING THAWING		Thawing room T= 17-23°C Heat transfer fluid temperature set point: 23°C .
	BDS ROOM TEMPERATURE STORAGE	ID, Endotoxin, Bioburden, Leachables	Thawing room T = 15-25 °C
	BDS COLD STORAGE (OPTIONAL)	Bioburden, endotoxin	Cell T = 2- 8 °C
Excipients for Buffer Solution: sodium chloride, sodium citrate dihyrdate, PS80 stock solution. NaOH and HCl stock solutions for pH adjustment	**BUFFER PREPARATION**	Bioburden, Endotoxin, pH, Osmolality	Solution preparation room T=18-23 °C
	BUFFER OPTIONAL STORAGE AT ROOM TEMPERATURE	Bioburden, Endotoxin	Solution preparation room T=18-23 °C
	BDS TRANSFER INTO THCOMPOUNDING TANK. RE-FREEZING OF RESIDUAL BDS IN F/T TANK		Solution preparation room T=18-23 °C
	BUFFER TRANSFER IN COMPOUNDING TANK		Solution preparation room T=18-23 °C
	BDS MIXING	Bioburden, Endotoxin Leachables, pH, Osmolality, Protein content	Solution preparation room T=18-23 °C Mixing speed (150-250 rpm) Mixing time (15-45 min)
	BIOBURDEN REDUCTION FILTRATION	Post use Filter Integrity test Bioburden	Solution preparation room T=18-23 °C P = [0,5 -1] barg
	BULK STORAGE AT ROOM TEMPERATURE	Bioburden Endotoxin	Solution preparation room T=18-23 °C
	BULK COLD STORAGE (OPTIONAL)	Bioburden, Endotoxin	Solution preparation room T =18-23°C. Storage tank thermoregulated at T = 2-8°C

Materials		Process	Controls	Process conditions
		STERILE FILTRATION	Pre use and post use Filter Integrity test Flush study $\Delta P \leq 1$ barg	Filling room T =18-23°C.
10 mL washed and depyrogenated vials for MabThera 100 mg 50 mL washed and depyrogenated vials for MabThera 500 mg Stoppers sterilized in autoclave Red seals (MabThera 100 mg) Grey seals (MabThera 500 mg)		**ASEPTIC FILLING, STOPPERING AND CRIMPING**	Leachable, Visible and Subvisible particles, Filling Weight, Filling Homogeneity, CCIT, QC DP Release Chem Test QC DP Release Micro Test	Filling room T=18-23°C
		DP STORAGE PRIOR TO INSPECTION		Cell T=2-8 °C
		MABTHERA 500 100% MVI MABTHERA 100 (100% AVI + MVI FOR EJECTS)	IPC: AQL inspection	T=15-25 °C after equilibration
		DP STORAGE AND SHIPMENT		T=2-8 °C

4.4 MANUFACTURING EQUIPMENT TRAIN

Here is the list of the main equipment to be used for the manufacturing steps of MabThera 100 mg and MabThera 500 mg batches.

Table 26 MabThera 100mg and MabThera 500mg manufacturing equipment train.

Process Step	Equipment / Room
MabThera BDS storage (upon receipt)	F/T tanks will be stored in the cell (PTH cell ID: FRC422, room 2116). This cell is at -25 °C.
Thawing / re-freezing of MabThera BDS	F/T tank placed in two thawing stations (TWU001 SN S452788 and TWU002 SN S453427) placed in Roche thawing room (PTH ID 2204)
MabThera DS temporary storage, after thawing and after BDS pooling at 2-8°C (if necessary)	F/T tank stored in a 2-8°C cell (room 2207)
Buffer preparation	1x 1100L stainless steel tank (equipment ID: RTR342)
	J tube
	Funnel
	3 glass bottles
Pooling of MabThera BDS and buffer transfer in compounding tank for bulk solution preparation	F/T tank and 1 x 1100 L stainless steel tank (equipment ID: RTR343)
	32-14MP eccentric reducer
	J tube
BB filtration: solution transfer from compounding tank to storage tank through BB filter	Stainless steel trolley for the support of the disposable assembly that incorporates 1 (one) bioburden reduction filter
BDP storage in the storage tank	1 x 1100L stainless steel tank (equipment ID: RTR344)
Transport of storage tank in the filling room	Transpallet for tank transportation
Sterilizing filtration by two (2) 0.22µm sterilizing filters by nitrogen pressure	Stainless steel trolley for the support of the disposable assembly that incorporates 2 (two) in series sterilizing filters for sterile filtration
Vials Washing	Machine Vega8 (LFL013)
Vials Depyrogenation	Depyrogenation tunnel 1250FL DH (TST010)
Equipment sterilization	De Lama autoclave (ATC025) Or De Lama autoclave (ATC026)
Vials Filling	Machine Xtrema (INF021)

Process Step	Equipment / Room
Vials Capping	ALU400 SA3122 (CPL012)
DP storage at 2-8°C before visual inspection	Vials in 2-8°C (cells FRC048, FRC044, FRC068, FRC091, FRC114)
Manual Visual Inspection	Optical benches rooms 7, 7C, 232, 409, 1117, 1128
Automatic Visual Inspection	CS30 (SPE025)
Storage of vials after visual inspection	Cell 2-8°C (PTH ID: FRC044, room 1212)

The disposable assemblies to be used for MabThera validation batches activities are detailed in the **Table 27**.

All assemblies are provided by the supplier, Saint Gobain, already sterilized by gamma irradiation and ready to use.

All the assemblies are introduced in the solution preparation room (room 823) and Xtrema filling room (room 843) of Sterile Area 6 through a dedicated airlock (room 824) and their packaging is removed just before performing their connections.

Table 27 Disposable assemblies to be used for MabThera validation batches.

Process step	Material description	Patheon Monza code	Patheon Monza Specification number	Supplier code
BDS recirculation during thawing	Two (2) disposable assemblies (connected in series) to connect F/T tanks inlet and outlet of the product through Lynx ST	273492	SMV-1040	SGS04049
BDS pooling in compounding tank	Two (2) disposable assemblies to connect F/T tanks product outlet to the product inlet of the compounding 1100 L tank through tri-clamp connections	273492	SMV-1040	SGS04049
Buffer transfer from the buffer tank to the compounding tank	Two (2) Y disposable tubes provided with steam-thru port to be connected to the tank and 2 (two) Aseptiquik ports for the connection to the extension tube disposable assembly	273498	SMV-1041	SGS03744
	One (1) disposable extension tube with Aseptiquik ports for the connection of the SS buffer tank to the SS compounding tank through the Y assembly	273501	SMV-1136	SGS04044
Bioburden reduction filtration and BDP transfer from compounding tank to storage tank	One (1) disposable system to transfer the solution from the compounding tank to the storage tank and for BB filtration. It is provided with one (1) Opticap XL10 capsule filter with 0,22 µm Durapore membrane for bioburden reduction filtration, provided with two Aseptiquik ports for the connection of the compounding tank to the storage tank through the Y assembly	273496	SMV-1049	SGS04047

Process step	Material description	Patheon Monza code	Patheon Monza Specification number	Supplier code
Transfer of BDP from SS tank to the filling line and sterilizing filtration for MabThera 100 mg	One (1) Assembly for sterilizing filtration, provided with 2 (two) sterilizing filters (KVGLG10HH1 0.22 µm Opticap ® XL 10 capsule filters) already integrated for redundant filtration.	273503	SMV-1039	SGS03875
	One (1) 8L filling bag provided with 10x SPT-60L surge tube 4.8mm x 8.0mm, 10x Accusil pump tube 6.8mm x3.2 mm, 10x SPT-60L dose tube 3.2mm x 6.8mm, 10x SS needles 3.0mm x 3.5mm	274138	SMV-1295	SGS03665
	One (1) disposable extension tube for the connection of the SS tank to the assembly for sterile filtration	273501	SMV-1136	SGS04044
Transfer of solution from SS tank to the filling line and sterilizing filtration for MabThera 500 mg	One (1) Assembly for sterilizing filtration, provided with two (2) sterilizing filters (KVGLG10HH1 0.22 µm Opticap ® XL 10 capsule filters) already integrated for redundant filtration.	273503	SMV-1039	SGS03875
	One (1) 8L filling bag provided with 10x SPT-60L surge tube 8 mm x 11.2mm, 10x Accusil pump tube 6.8mmv x 10.2 mm , 10x SPT-60L dose tube 6 mm x 10.2 mm, 10x SS needles 6.0mm x 5.0 mm	274130	SMV-1050	SGS03667
Sampling assembly	Sampling assembly provided with 2 PETG Nalgene bottles of 500 mL and 2 PETG Nalgene bottles of 30 mL.	273719	SMV-1045	SGS04719

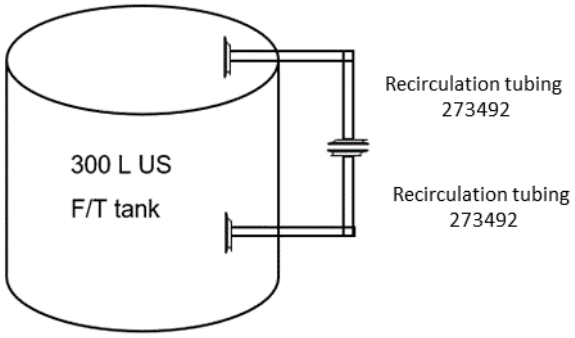
4.4.1 SET UP INSTRUCTIONS

4.4.1.1 MabThera 100mg and MabThera 500mg set up in the thawing room

In the thawing room 2204, the recirculation of the BDS will be performed from the bottom output valve of the F/T tank to the top valve of the F/T tank through two disposable assemblies “recirculation tubing” (Patheon Monza code 273492) connected in series. The assemblies are provided with 1.5” Lynx ST connections. The recirculation will be performed by peristaltic pump 620w NR. After the thawing, the peristaltic pump will be inverted to let the emptying of the tube during the challenging of the holding time.

Figure 5 shows the set up in the thawing room.

Figure 5 Set up in thawing room (both for MabThera 100 mg and MabThera 500 mg).



4.4.1.2 MabThera 500mg and MabThera 100mg set up in solution preparation room

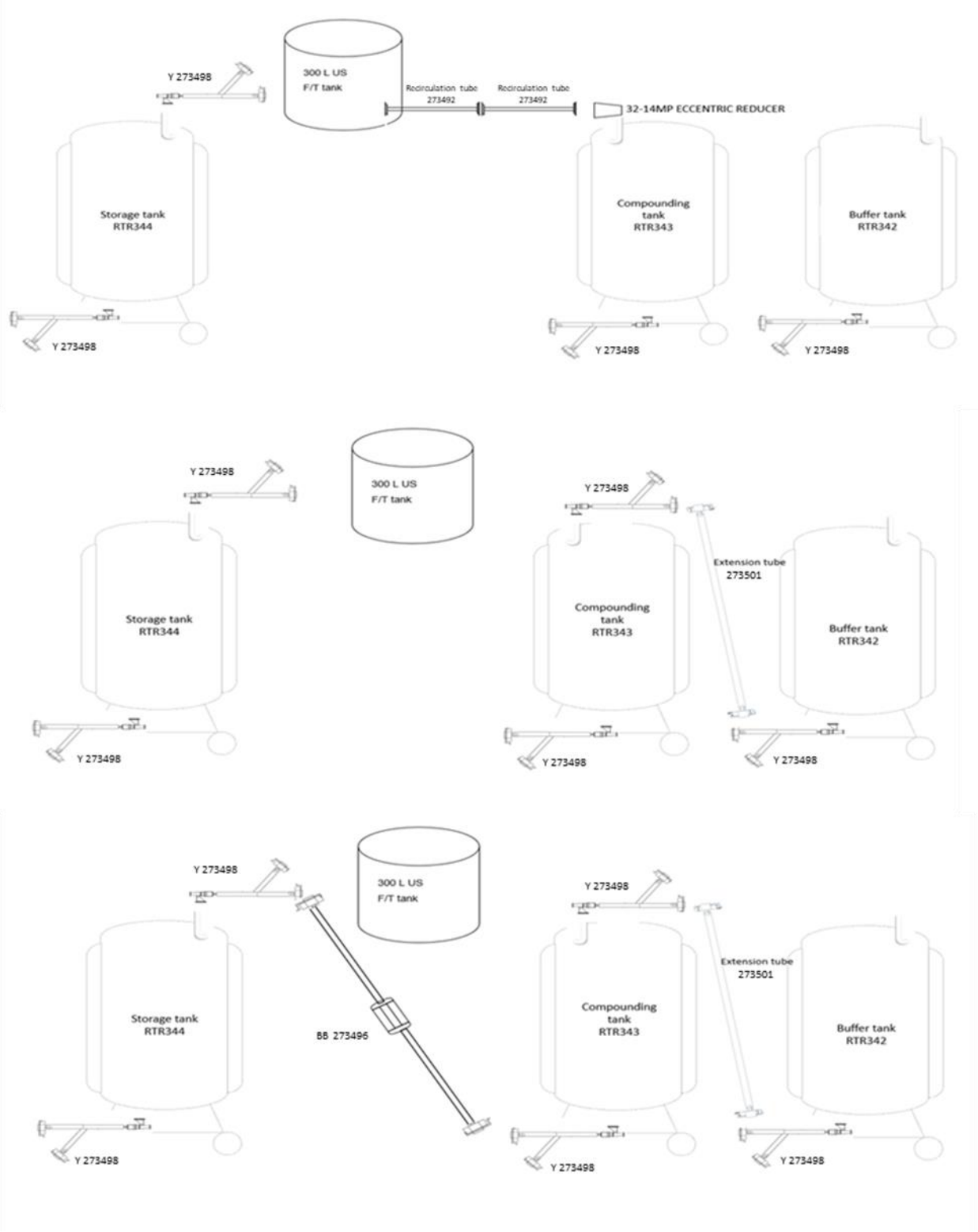
The F/T tank will be then moved in the Xtrema solution preparation room 823 of the Sterile Area 6 department. In the solution preparation room the following 1100 L tanks are needed:

- Buffer tank (RTR342) in position RP02;
- Compounding tank (RTR343) in position RP03;
- Storage tank (RTR344) in position RP04.

First, the BDS will be transferred (through peristaltic pump code PMP584) from the F/T tank to the compounding tank through two recirculation tubing in series and the eccentric adaptor. Then the compounding tank will be connected to the buffer tank to allow the transfer (through nitrogen) of the buffer from the buffer tank to the compounding tank. Finally, the compounding tank will be connected to the storage tank through the bioburden reduction filtration assembly (transfer of product by nitrogen).

Figure 6 shows the set up in the solution preparation room.

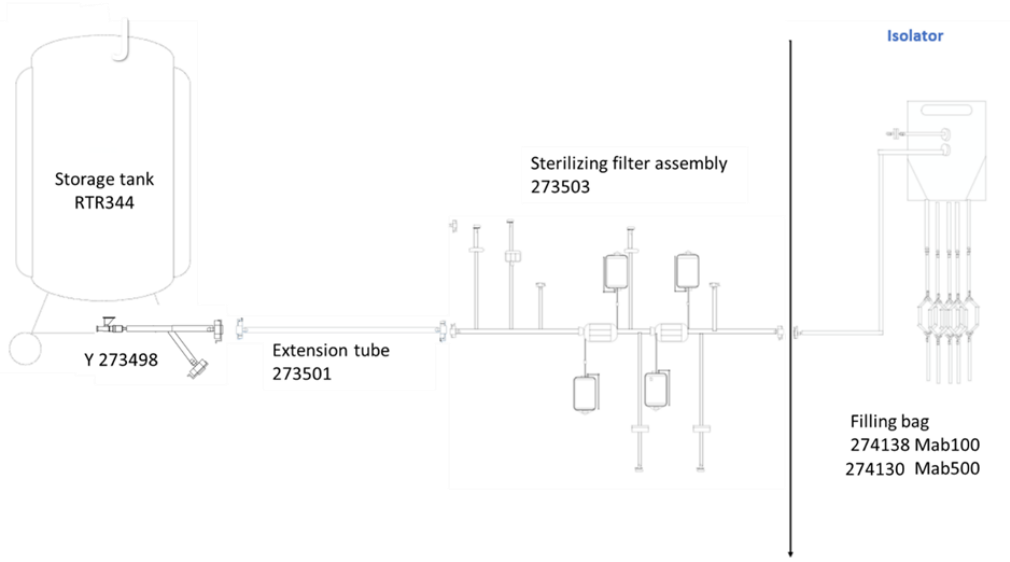
Figure 6 Set up in solution preparation room (both MabThera 100mg and MabThera 500mg).



4.4.1.3 MabThera 500mg and MabThera 100mg set up in filling room

In the following picture it is reported the set up in the solution preparation room for the filling of MabThera 500 mg in 50 mL vials and MabThera 100mg in 10mL vials:

Figure 7 Set up in filling room.



5 VALIDATION PROGRAM

5.1 OVERVIEW

This process validation is aimed at establishing documented evidence providing a high degree of assurance that the manufacturing process of MabThera 100 mg and MabThera 500 mg consistently produces products which meets their pre-determined specifications and quality attributes.

For each validation batch the following aspects will be documented:

- all process parameters and operating conditions which can influence the quality attributes of the product;
- the results of the controls and tests carried out during or at the end of the various phases of manufacturing.

This data will come partly from routine in-process control and monitoring activities included in the relevant QC methods and SOPs for all commercial batches, and also from additional controls and tests performed for validation purposes. Detailed instructions for validation execution regarding the different manufacturing phases are given in the following sections.

Process validation will be completed once all the actions described in this protocol are successfully completed. At the end of validation activities Patheon will prepare a final Process Validation Report, which summarizes and discusses the main results. Roche and Patheon share the responsibility for the approval of the Process Validation Protocol and the Process Validation Report.

5.2 DESCRIPTION OF ACTIVITIES

5.2.1 GENERAL

For each manufacturing step the process parameters and operational conditions will be documented, according to Section 5.2.2.
For potential Critical parameters an acceptance range is given. Process parameters that are not considered critical do not have defined acceptance limits but will be monitored to establish a baseline for manufacturing process performance in view of future production batches.
In the same Section 5.2.2 the in-process controls to be performed by Production personnel are indicated.
The actual process parameters and the results of in-process controls performed by production are recorded in detail on the Batch Manufacturing Records and will be documented in the final Process Validation Report.

The Sampling and Testing Summary (Table A1 - Attachment 1) illustrates the testing to be performed on product samples to be collected in the various manufacturing steps, addressing responsibilities for execution and acceptance criteria.
Controls and tests written in plain typefaces refer to test activities that will have to be performed by Patheon QC/Prod. dept.'s as routine activities for future commercial batches. **Bold** type indicates additional or modified testing/sampling activities for validation purposes only.

Validation batch samples to be forwarded to QC Laboratories for testing should be appropriately identified with:
• Product name ('MabThera 100mg', 'MabThera 500mg');
• Lot number;
• Manufacturing step;
• ID number of the sample;
• Date (time, if necessary).

Patheon Monza QC department and Roche will provide Patheon Monza Validation department with the results of all the tests performed by its laboratories, making reference to laboratory notebook for raw data traceability.
Patheon Monza Validation department will prepare the final Process Validation Report, which summarizes the results of the validation activities and formalizes the conclusions.

5.2.2 PROCESS PARAMETERS

5.2.2.1 Dispensing: BDS thawing / refreezing step

The following parameters will be documented during the thawing step.

Table 28 Parameters to be documented during the thawing step.

Parameter	Specification	pCPP (Y/N)
Bulk Drug substance weight in Freeze/Thaw tanks	Weight ≥ 51.5 kg / Record	Y
Number of freeze/thaw cycle	N° of cycles ≤ 3 / Record	Y
Heat transfer fluid temperature set point	Target = 23 °C (Temperature ≤ 26°C) / Record	Y
Recirculation Mixing peristaltic pump rpm	21 RPM (19RPM-23RPM)	Y
Recirculation mixing duration	Time ≥ 10 hours / Record	Y
Thaw operation duration	Time ≥ 17 hours Record	Y

The following parameters will be documented during the refreezing step.

Table 29 Parameters to be documented during refreezing step.

Parameter	Specification	pCPP (Y/N)
Bulk Drug substance weight in Freeze/Thaw tanks	Weight ≥ 51.5 kg / Record	Y
Number of freeze[4]/thaw cycle	N° of cycles ≤ 3 / Record	Y
Heat transfer fluid temperature set point	Target: -50°C (Temperature ≤ 26°C) / Record	Y
Freeze operation duration	Target: at least 19 hours / Record	Y

[4] It is specified that the first freezing cycle is used by the BDS manufacturer. Therefore, 2 freezing cycles remain available at Patheon Monza, Thermo Fisher Scientific.

5.2.2.2 Buffer preparation

The following parameters will be documented during the HCl solution preparation step.

Table 30 Parameters to be documented during HCl solution preparation.

Parameter	Specification	pCPP (Y/N)
Start of HCl solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N
HCl solution start of mixing (date dd.mm.yyyy, time hh:mm)	Record	N
HCl solution mixing speed (date dd.mm.yyyy, time hh:mm)	200 RPM (150 - 250 RPM)	N
HCl solution mixing time	≥ 15 minutes	N
End of HCl solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N

The following parameters will be documented during the NaOH solution preparation step.

Table 31 Parameters to be documented during NaOH solution preparation.

Parameter	Specification	pCPP (Y/N)
Start of NaOH solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N
NaOH solution start of mixing (date dd.mm.yyyy, time hh:mm)	Record	N
NaOH solution mixing speed (date dd.mm.yyyy, time hh:mm)	280 RPM (220 – 330 RPM)	N
NaOH solution mixing time	≥ 15 minutes	N
End of NaOH solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N

The following parameters will be documented during the PS80 solution preparation step.

Table 32 Parameters to be documented during PS80 solution preparation.

Parameter	Specification	pCPP (Y/N)
Start of PS80 solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N
PS80 solution start of mixing (date dd.mm.yyyy, time hh:mm)	Record	N
PS80 solution mixing speed (date dd.mm.yyyy, time hh:mm)	400 RPM (350 – 450 RPM)	N
PS80 solution mixing time	≥ 2 hours	N
End of PS80 solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N

The following parameters will be documented during the formulated buffer solution preparation step.

Table 33 Parameters to be recorded during formulated buffer solution preparation.

Parameter	Specification	pCPP (Y/N)
Initial weight of the buffer tank	Record	N
Start of buffer solution preparation (date dd.mm.yyyy, time hh:mm)	Record	N
WFI addition	875.0 kg (866.4 – 883.6 kg)	N
Start of mixing in the buffer tank (date dd.mm.yyyy, time hh:mm)	Record	N
Mixing speed (RPM) during excipients addition	100 RPM (100 - 200 RPM)	N
Quantity of sodium chloride to be compounded	8840.0 g (8751.6 – 8928.4 g)	N
Mixing time after addition of sodium chloride	≥ 10 minutes	N
Quantity of sodium citrate dihydrate to be compounded	7220.0 g (7147.8 – 7292.2 g)	N
Mixing time after addition of sodium citrate dihydrate	≥ 20 minutes	N
Quantity of PS80 solution to be compounded	8000.0 g (7920.0 - 8080.0 g)	N
Mixing time after WFI rinse of PS80 container	≥ 20 minutes	N
Quantity of HCl to be compounded (for pH adjustment)	Q.s. to 6.5 (6.2 – 6.8)	N

Parameter	Specification	pCPP (Y/N)
Excipients order addition	Respected	N
End of mixing in the buffer tank before reaching the final weight (date dd.mm.yyyy, time hh:mm)	Record	N
Buffer mixing time (starting from mixing activation)	≥ 2 hours	N
Final weight of the tank	991.0 kg [981.2 - 1000.8 kg]	Y
Start of mixing in the tank after reaching the final weight of the tank (date dd.mm.yyyy, time hh:mm)	Record	N
Mixing rate (RPM) after having reached the final weight of the tank	200 RPM (150 – 250 RPM)	Y
Mixing time after having reached the final weight of the tank	≥ 15 minutes	Y
Mixing temperature	15-25 °C / Record	Y
End of mixing in the buffer tank (date dd.mm.yyyy, time hh:mm)	Record	N

5.2.2.3 BDS Pooling

The following parameters will be documented during the BDS pooling step.

Table 34 Parameters to be recorded during BDS pooling.

Parameter	Specification	pCPP (Y/N)
Initial weight of the compounding tank	Record	N
Start of transfer (date dd.mm.yyyy, time hh:mm)	Record	N
Peristaltic pump mixing rate (RPM)	40 RPM (20 - 50 RPM)	N
End of transfer (date dd.mm.yyyy, time hh:mm)	Record	N
Final weight of the compounding tank	(*) Q ± 0.4 kg	Y

(*) Calculation of Q is to be performed in the executed batch record.

5.2.2.4 Buffer transfer and bulk solution preparation

The following parameters will be documented during the formulated bulk solution preparation step.

Table 35 Parameters to be recorded during compounding.

Parameter	Specification	pCPP (Y/N)
Initial weight of compounding tank	Record	N
Transfer pressure	Record Target 0.5 barg (0.5-1.0 barg)	N
Start of buffer transfer (date dd.mm.yyyy, time hh:mm)	Record	N
End of buffer transfer (date dd.mm.yyyy, time hh:mm)	Record	N
Start of mixing in compounding tank (date dd.mm.yyyy, time hh:mm)	Record	N
Mixing rate (RPM)	200 RPM (150 – 250 RPM)	Y
Final weight of compounding tank	A ± 0.4 kg[5]	Y
Mixing temperature	[2-25] °C /Record	Y
Mixing time	NLT 15 minutes NMT 45 minutes	Y

[5] The final weight of the compounding tank is calculated based on the reference batch size and the actual amount of BDS pooled. Calculations will be reported in the MBR.

Parameter	Specification	pCPP (Y/N)
End of mixing in compounding tank (date dd.mm.yyyy, time hh:mm)	Record	N

5.2.2.5 Bioburden reduction filtration and storage

The following parameters will be documented during the bioburden reduction filtration step.

Table 36 Parameters to be recorded during bioburden reduction filtration and storage steps.

Parameter	Specification	pCPP (Y/N)
Filtration pressure	Target = 0.6 barg Range = 0.5 - 1 barg /Record	Y
Volume to surface area ratio (batch size / filter area)	Record[6]	Y
Filter integrity test post use	≥ 3450 mbar	Y
Filtration time	Record	N
Initial weight of storage tank	Record	N
Start of formulated bulk transfer (date dd.mm.yyyy, time hh:mm)	Record	N
End of formulated bulk transfer (date dd.mm.yyyy, time hh:mm)	Record	N
Final weight of storage tank	Record	N
Temperature in the compounding tank before Bioburden reduction filtration	Record [2-25 °C]	N
Temperature in the storage tank at the end of Bioburden reduction filtration	Record [2-25 °C]	N
Mixing rpm during cooling down (*)	Target = 50 RPM /Record	N
Mixing time during cooling down (*)	Record	N

(*) These parameters will be evaluated during manufacturing of batches involved in the HT challenge because storage at 2-8°C will be performed. During commercial, considering that this step is optional, monitoring will be required and evaluated only in case optional storage at 2-8°C will be performed.

[6] After the execution of PPQ batches, a minimum and maximum values for volume to surface area ratio will be validated.

5.2.2.6 Sterile filtration

The following parameters will be documented during the sterile filtration step.

Table 37 Parameters to be recorded during sterile filtration step.

Parameter	Specification	pCPP (Y/N)
Filter flush with product at the beginning of the sterilizing filtration	2000 mL	Y
Filtration ΔP on filters	Record ΔP ≤ 1 bar (target 0.6 barg, range 0.5-0-7 barg)	Y
Volume to surface area ratio (*)	Record	Y
Filtration time	≤ 72 hours[7]	Y
Temperature during filtration	[2-25 °C]	Y

(*) For this point, rely on the calculation already performed at bioburden reduction filtration step and storage, considering that:
- no weight load is present in filling room, the weight will be considered (as worst case) the weight in the storage tank at the end of the bioburden reduction step;
- bioburden filter and sterilizing filters are identical.

Table 38 Parameters to be recorded during integrity tests.

Parameter	Criteria	Bubble point -value	pCPP (Y/N)
Pre-Use Sterilizing Filter Integrity test	Conform	≥ 3450 mbar	Y
Post-use Sterilizing Filters Integrity test	Conform	≥ 3450 mbar	Y
Barrier Filters Integrity test	Conform	≥ 1280 mbar	N
WFI filter Integrity test	Conform	≥ 3320 mbar	N
Nitrogen filters Integrity test	Conform	≥ 1170 mbar	N

[7] As per VAL-0127392 [29].

5.2.2.7 Vials filling and crimping

The following parameters will be documented during the filling step.

Table 39 Parameters to be recorded during filling.

Parameter	Specification	pCPP
Filling machine speed	Target =100 vials/min [90 vials/min – 100 vials/min] for MabThera 500 mg Target =180 vials/min [80 vials/min – 180 vials/min] for MabThera 100 mg Record	Y
Temperature of the storage tank at beginning of filling	2 – 25 °C	Y
Start of filling (date dd.mm.yyyy, hh:mm)	Record	N
End of filling (date dd.mm.yyyy, hh:mm)	Record	N
Filling duration[8]	≤ 48 hours	Y
Filling interruption	30 minutes[9]	Y
Flush volume at filling needle after prime	At least 520 mL per each fill needle for MabThera 500 mg At least 168 mL per each fill needle for MabThera 100 mg[10]	Y
Product volume for fill per filling needle (only for MabThera 100 mg, maximum Batch size)	Calculate: Batch size [g] / filling weight [g]	Y
Pressure value in storage tank during filling	Target =0.6 barg, range 0.5-0.7 barg for MabThera 100 mg Target = 0.6 barg, range 0.5-0.7 barg for MabThera 500 mg Record	N

[8] Maximum filling time allowed by Media Fill.
[9] Maximum filling interruption allowed by Media Fill. Suitability for the product is confirmed by peroxide uptake study conducted during engineering run [5].
[10] Set according to outcomes of engineering run [5].

Parameter	Specification	pCPP
IPC vials weight	MabThera 100 mg: USL = 11.030 g UAL = 10.740 g Target = 10.630 g LAL = 10.520 g LSL = 10.400 g MabThera 500 mg USL = 52.620 g UAL = 51.880 g Target = 51.620 g LAL = 51.3600 g LSL = 50.900 g	Y
Yield after filling	80.0 % – 100.0 %	N

Note: USL = Upper Specification Limit; UAL = Upper Alert Limit; LAL = Lower Alert Limit; LSL = Lower Specification Limit

Table 40 Parameters to be recorded for VPHP.

Parameter	Specification	pCPP
End of aeration (*)	Record	N
start of bag/tubing installation	Record	N
end of bag/tubing installation	Record	N
Start of sterile filtration	Record	N
Starting of the filling	Record	N
End of pump calibration/beginning of production	Record	N

(*) This information is reported in the machine report therefore information can be retrieved.

The following parameters will be documented during the crimping step.

Table 41 Parameters to be recorded during crimping step.

Parameter	Specification	pCPP
Crimping machine speed	MabThera 100mg ≤ 180 vials/minute MabThera 500mg ≤ 100 vials/minute Record	N
Crimping Pressure	Target = 100 KPa [90-120] KPa for MabThera 500mg Target = 90 KPa [80-100] KPa for MabThera 100mg Record	Y
Crimping Height	Target 46.5 mm, range 46.0 – 47.0 mm for MabThera 100 mg Target 68 mm, range 67.5 - 68.5mm for MabThera 500 mg Record	Y
Start of crimping (date dd.mm.yyyy, hh:mm)	Record	N
End of crimping (date dd.mm.yyyy, hh:mm)	Record	N

5.2.2.8 Visual Inspection

The following parameters will be documented:

Table 42 Parameters to be recorded during visual inspection.

Parameter	Specification	pCPP
End time of storage at 2-8°C before visual inspection (date dd.mm.yyyy, time hh:mm)	Record	N
Start of Visual Inspection (date dd.mm.yyyy, time hh:mm)	Record	N
End of Visual Inspection (date dd.mm.yyyy, time hh:mm)	Record	N
Number of vials discarded for each defect category	Record	N
Yield after visual inspection	80.0 % - 100.0 %	N
Start time of storage at 2-8°C after visual inspection (date dd.mm.yyyy, time hh:mm)	Record	N

5.2.3 HOLDING TIMES

The holding times will be established with documented evidence that the intermediates and bulk products remain of appropriate quality before the next step of processing and will support meeting the acceptance criteria and release specifications of the drug product.

Based on the PPQ strategy in place (see section 1.1), Holding Times to be challenged will be simulated during the manufacturing of the following batches:

- MabThera 100 mg, maximum batch size;
- MabThera 500 mg, minimum batch size.

The table below summarizes the hold times that will be considered.

Table 43 Holding times to be considered in MabThera 100mg and MabThera 500mg manufacturing.

Hold time		Description	Duration	Type
Product HTs	**HT1**	From the start of the PS-80 dispensing (weighing) to the end of PS-80 stock solution preparation	Target 10 hours	To be challenged
	HT2	From the end of the PS-80 solution preparation to the end of its addition to the buffer preparation tank (RTR342)	Target 14 hours	To be challenged
	HT3	F/T tank n°1: From start of exposure at room temperature to end of exposure at room temperature	Target 16 hours[11]	To be challenged
	HT4	F/T tank n°1: From start of exposure at 2-8°C to end of exposure at 2-8°C	Target 15 days	To be challenged
	HT5	From start of buffer preparation to end of buffer transfer into the compounding tank	Target 24 hours	To be challenged
	HT6	From start of BDS addition into the compounding tank to end of Bioburden reduction filtration	Target 24 hours	To be challenged
	HT7	From start of Bioburden reduction filtration to end of filling (operations at room temperature)	Target 24 hours (before start of filling) Actual time needed to fill the batch	To be challenged
	HT8	From start of storage at 2-8°C to end of storage at 2-8°C	Target 24 hours	To be challenged
	HT9	From start of BDS pooling to end of visual inspection at room temperature	≤ 147 hours	To be respected
Media Fill HT	**HT-MF**	From start of sterile filtration to end of filling	≤ 48 hours	To be respected

[11] Cumulative TOR (involving the overall "life cycle" of the tank in Thermo Fisher) ≤ 48 hours should be in any case respected.

5.2.4 MEDIA FILL

The aseptic simulation study ("Media fill"), covering the production equipment and operators used for MabThera 100mg and MabThera 500mg is outside the scope of this Protocol.
Operational procedure and acceptance criteria are contained in Patheon Monza internal SOP 000026985 [18] and in specific protocols.

5.2.5 DEVIATIONS

Any deviation from protocol or manufacturing procedure, acceptance criteria or applicable SOPs shall be for instance documented on the Validation Discrepancy Form of Attachment 6. The Discrepancy form has to be filled in by Patheon Monza Validation as soon as they are notified of the occurred event.

The following information shall be reported in the form:

- Event description (short description of the event, which shall cover the minimum requirements of SOP-000027262 "Gestione delle Deviazioni" [19]), including the indication if the event is repeated within the same validation exercise or related ones;
- Possible root cause (preliminary evaluation, based on the data and information available at the time of event notification);
- Impact assessment;
- Corrective action – Description of the activities necessary to solve the event (and to avoid recurrence, if applicable). Corrective actions may be related for example to Master Batch Record update, validation documentation for subsequent batches update, SOP update, etc. These actions can be tracked with a Stand Alone CAPA according to SOP-000041158 "Gestione delle CAPA" [20].

If a Deviation is opened for non-compliant results, Production, Quality Assurance, Quality Control and Validation jointly conduct an investigation to identify the cause, the possible corrective actions and preventative actions and the impact on the validation study, as required by SOP000027262 "Gestione delle Deviazioni" [19].
Batch release can not be done until all deviations have been approved according to SOP-000027262 [19].
Deviations from this Process Validation Protocol will be managed according to Patheon Monza Process Validation Master Plan Q001AA10 [6].

5.2.6 QC LABORATORY METHODS

The Chemical methods followed by Patheon Monza QC Chemical department to perform the testing activity on the validation batches, according to Table A1, are documented in the Analytical Methods P4-0319 and P6-0319. The methods followed by Patheon QC Micro department to perform the testing activity on the validation batches, according to Table A1, are documented in the Test Methods ASN1491 ed.001 for Bioburden and Sterility and ASB1491 ed. 001 for Endotoxin.

5.3 ACCEPTANCE CRITERIA

Process validation will be considered successfully accomplished (the manufacturing process of MabThera 100 mg and MabThera 500 mg will be considered validated) if the following requirements are satisfied:

- ✓ all activities described in section 5 and in Table A1, have been completed as indicated;
- ✓ Patheon Monza QC and Roche have provided all the results to Patheon Validation;
- ✓ the results of all controls and tests correspond to the requirements defined in Table A1;
- ✓ all deviations and non-conformities encountered during manufacturing have been documented and their resolution formally executed and approved;
- ✓ the final Process Validation Report, which summarizes and assesses the main results of the process validation, has been issued by Patheon Monza Validation department and approved by Roche and Patheon Monza management.

5.4 CHANGE CONTROL

Departures from what is established in this Process Validation Protocol will be managed according to Patheon Monza Site Process Validation Master Plan [6].

Once validation is completed, any change to the MabThera 100 mg and MabThera 500 mg manufacturing procedures must be evaluated and authorized according to Patheon Monza internal SOP-000027399 (“Creation and update of Production Master documents”) [21] and SOP-000027336 (“Change control”) [22]. According to the latter SOP any substantial modification to the process must be analyzed to evaluate the need for revalidation of the process itself or of part of it, and for approval by the Client Roche.

6 GLOSSARY

AVI: Automatic Visual Inspection

BDS: Bulk Drug Substance

BDP: Bulk Drug Product

BOM: Bill of Materials

CCIT: Container Closure Integrity Test

DP: Drug Product

F/T: Freeze/Thaw

GMP: Good Manufacturing Practices

GPA: Granulomatosis with Polyangiitis

HT: Holding Time

ID: Identification/Identity

LAF: laminar Air Flow

MBR: Master Batch Record

MPA: Microscopic Polyangiitis

NLT: No Less Than

NMT: No More Than

PE: Polyethylene

PS80: Polysorbate 80

PTH: Patheon

RT: Room Temperature

RTP: Rapid Transfer Port

SS: Stainless Steel

STC: Steam Through Connectors

SKU: Stock Keeping Unit

TIR: Time In Refrigeration

TOR: Time Out of Refrigeration

VPHP: Vapor Phase Hydrogen Peroxide

7 DOCUMENT INFORMATION

Table 44 Revision History.

Version	Reason for change	Author	Date
00	Issue for comments	J. Di Babbo	19/10/2022
01	Issue for approval	J. Di Babbo	27/03/2023

Table 45 Reference Documents.

Ref. #	Document Title	Document #
[1]	Introduction of MabThera 100mg and 500 mg in Sterile Area 6	QR#191938
[2]	Surrogate trial protocol	TT237A011
[3]	Surrogate trial report	TT237D011
[4]	Engineering trial protocol	TT237B011 and Addendum 1
[5]	Engineering trial report	TT237C011
[6]	Validation Master Plan	Q001AA10
[7]	Technology Transfer Plan of Avastin and MabThera	TTP237/01
[8]	Continued Process Verification - CPV	SOP-000031006
[9]	Product Validation Master Plan - MabThera 100mg and MabThera 500mg	Q486AA01
[10]	MabThera 100mg DA SPERLARE	Code 352518 Ver.1 Var 01
[11]	MabThera 100mg	Code 363303 Ver.1 Var 01
[12]	MabThera 500mg DA SPERLARE	Code 352519 Ver.1 Var 01
[13]	MabThera 500mg	Code 363303 Ver.1 Var 01
[14]	Process Gap Assessment in frame of the transfer of Mabthera IV and Avastin from Roche Mannheim Operations 1 to Thermo Fischer / Patheon Monza Sterile Area 6	TEC-0213431
[15]	Usage of Xtrema Filling line ST6	SOP-000136665
[16]	New projects – QC analysts qualification flow to MVI	SOP-000118671

Ref. #	Document Title	Document #
[17]	QC statistical control of vials containing liquid/lyophilized product	SOP-000028049
[18]	Simulation of Aseptic Process: Media Fill	SOP-000026985
[19]	Handling of deviations	SOP-000027262
[20]	Handling of CAPA	SOP-000041158
[21]	Creation and update of Production Master documents	SOP-000027399
[22]	Change control	SOP-000027336
[23]	Flow of APIs Bevacizumab and Rituximab	SOP-000233649
[24]	F/T validation package	RPT-0305064
[25]	Use, cleaning and logistic security of Sterile Area 6 autoclaves	SOP-000111043
[26]	Corporate Standard guideline “Process Validation-Testing Requirements and Acceptance Criteria”	QS09-G03-02
[27]	Content Uniformity	QS05-G10-01
[28]	Usage and cleaning of crimping machine for liquids - Xtrema	SOP-000110739
[29]	Bacterial Retention Study	VAL-0127392
[30]	PQ Freeze and Thaw processes that have been performed on US 300L and EU 300L Cryo Vessels	E1295AN01
[31]	PQ Freeze and Thaw processes that have been performed on US 120L Cryo Vessels	E1295BN01
[32]	Defect Classification Gap Assessment for Avastin and Mabthera	TEC-0218416

Instructions for samples handling

All the **liquid formulated bulk** samples have to be moved in the cold room **+2 to +8 °C** until testing, except for blocking test pH that will be moved at room temperature and immediately sent to QC Chemical department to be analyzed.
The samples must be analyzed as soon as possible.
All MabThera **drug product** should be stored at **2-8 °C**.
The samples to be sent to the client must be stored in the Warehouse.

ID Legend
The letter "-T; -M; -B" indicate respectively bottom, middle and top (Tank location)
The letter "/B; /M; /E" indicate respectively beginning, middle and end (Timing of the sampling during the activity)

Istruzioni per la gestione dei campioni

*Tutti i campioni **liquidi del bulk** devono essere mantenuti alla temperatura +**2 to +8 °C** fino all'analisi, ad eccezione del test bloccante di pH che sarà mantenuto a temperatura ambiente e consegnati immediatamente al reparto QC Chimico per l'analisi.*
I campioni devono essere analizzati il prima possibile.
*Tutti i **prodotti finiti** possono essere conservati alla temperatura +**2 to +8 °C**.*

Legenda ID
Le lettere "-T; -M; -B" indicano rispettivamente posizione alta, media e bassa (posizione del Tank).
Le lettere "/B; /M; /E" indicano rispettivamente inizio, metà e fine (istante di campionamento durante le attività).

Tank 1 – Batch Number 3132583

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
LEACH-F/T	Leachable	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 100mL	Recirculation tubing code 273492 (500 mL bottle) 2-8 °C	Report Result (refer to Roche Study Report)	Dispensing / QC Chemical and then Warehouse (Client: Roche Basel)	……	……	……

Nota: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
ENDO-F/T	Endotoxins	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Recirculation tubing code 273492 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Dispensing / QC Micro	……	……	……

Nota: Il risultato dell'analisi deve essere disponibile prima del successivo utilizzo del Tank 1 nell'ambito della campagna. / Note: the result of the analysis must be available before the next usage of the Tank 1 within the production campaign.

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
BB-F/T	Bioburden	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Recirculation tubing code 273492 2-8 °C	≤ 10 CFU/10 mL	Dispensing / QC Micro	……	……	……

Nota: Il risultato dell'analisi deve essere disponibile prima del successivo utilizzo del Tank 1 nell'ambito della campagna. / Note: the result of the analysis must be available before the next usage of the Tank 1 within the production campaign.

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Endotoxins Validation / *Validazione delle Endotossine*									
ENDO-F/T-VAL	Endotoxins	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL	Recirculation tubing code 273492 2-8 °C	N.A.	Dispensing / QC Micro	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: sample to be collected only from the first three batches manufactured.

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Bioburden Validation / *Validazione del Bioburden*									
BB-F/T-VAL	Bioburden	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 1250 mL	Recirculation tubing code 273492 (3 x 500 mL bottles) 2-8 °C	N.A.	Dispensing / QC Micro	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: sample to be collected only from the first three batches manufactured.

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After 1st time at 2-8°C / *Dopo il primo stoccaggio a 2-8 °C*									
ENDO-F/T (1st 2-8°C)	Endotoxins	When/ ***Quando***: At the completion of the first storage at 2-8 °C. / ***Al termine del primo staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Dispensing / QC Micro	……	……	……

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After 1st time at 2-8°C / *Dopo il primo stoccaggio a 2-8 °C*									
BB-F/T (1st 2-8°C)	Bioburden	When/ ***Quando***: At the completion of the first storage at 2-8 °C. / ***Al termine del primo staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Dispensing / QC Micro	……	……	……

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After 1st TOR challenge / *Dopo la prima sfida del TOR*									
ENDO-F/T (1st RT)	Endotoxins	When/ ***Quando***: At the completion of the 1st TOR challenge. / ***Al termine della prima sfida del TOR.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Production Sterile Area 6/ QC Micro	……	……	……

Nota per Sterile 6: Durante la sfida del TOR, avvicinarsi il più possibile alle 16 (sedici) ore previste da protocollo (senza superarle). Per la data e l'orario di inizio esposizione a temperature ambiente, fare riferimento al FORM-000225917. *Note for Sterile Area 6: During the TOR challenge, get as much as possible close to the 16 (sixteen) hours foreseen by the protocol (that do not have to be overcome). For the start date and time of exposure at room temperature, refer to FORM-000225917.*

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After 1st TOR challenge / *Dopo la prima sfida del TOR*									
BB-F/T (1st RT)	Bioburden	When/ ***Quando***: At the completion of the 1st TOR challenge. / ***Al termine della prima sfida del TOR.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota per Sterile 6: Durante la sfida del TOR, avvicinarsi il più possibile alle 16 (sedici) ore previste da protocollo (senza superarle). Per la data e l'orario di inizio esposizione a temperature ambiente, fare riferimento al FORM-000225917. *Note for Sterile Area 6: During the TOR challenge, get as much as possible close to the 16 (sixteen) hours foreseen by the protocol (that do not have to be overcome). For the start date and time of exposure at room temperature, refer to FORM-000225917.*

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After 2nd time at 2-8°C / *Dopo il secondo stoccaggio a 2-8 °C*									
ENDO-F/T (2nd 2-8°C)	Endotoxins	When/ ***Quando***: At the completion of the second storage at 2-8 °C. / ***Al termine del secondo staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Dispensing / QC Micro	……	……	……

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After 2nd time at 2-8°C / *Dopo il secondo stoccaggio a 2-8 °C*									
BB-F/T (2nd 2-8°C)	Bioburden	When/ ***Quando***: At the completion of the second storage at 2-8 °C. / ***Al termine del secondo staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Dispensing / QC Micro	……	……	……

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After 2nd TOR challenge / *Dopo la seconda sfida del TOR*									
ENDO-F/T (2nd RT)	Endotoxins	When/ ***Quando***: At the completion of the 2nd TOR challenge. / ***Al termine della seconda sfida del TOR.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Production Sterile Area 6/ QC Micro	……	……	……

Nota per Sterile 6: Durante la sfida del TOR, avvicinarsi il più possibile alle 16 (sedici) ore previste da protocollo (senza superarle). Per la data e l'orario di inizio esposizione a temperature ambiente, fare riferimento al FORM-000225917. *Note for Sterile Area 6: During the TOR challenge, get as much as possible close to the 16 (sixteen) hours foreseen by the protocol (that do not have to be overcome). For the start date and time of exposure at room temperature, refer to FORM-000225917.*

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After 2nd TOR challenge / *Dopo la seconda sfida del TOR*									
BB-F/T (2nd RT)	Bioburden	When/ ***Quando***: At the completion of the 2nd TOR challenge. / ***Al termine della seconda sfida del TOR.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota per Sterile 6: Durante la sfida del TOR, avvicinarsi il più possibile alle 16 (sedici) ore previste da protocollo (senza superarle). Per la data e l'orario di inizio esposizione a temperature ambiente, fare riferimento al FORM-000225917. *Note for Sterile Area 6: During the TOR challenge, get as much as possible close to the 16 (sixteen) hours foreseen by the protocol (that do not have to be overcome). For the start date and time of exposure at room temperature, refer to FORM-000225917.*

Tank 2 – Batch Number 3132585

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
ID-F/T	ID-CZE	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 20 mL + 1 x 20 mL for contingency	Recirculation tubing code 273492 2-8 °C	Positive identity (corresponds)	Dispensing/ QC Chemical	……	……	……

Nota: Il QC Chimico deve aliquotare 5 mL e consegnare il campione al QC Packaging per la conservazione del contro campione (T ≤ 20°C) / Note: QC Chemical must aliquot 5 mL and deliver the sample to QC Packaging which will store ita s retain sample (T ≤ 20°C)

Tank 2 – Batch Number 3132585

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
LEACH-F/T	Leachable	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ ***Dove***: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 100mL	Recirculation tubing code 273492 (500 mL bottle) 2-8 °C	Report Result (refer to Roche Study Report)	Dispensing / QC Chemical and then Warehouse (Client: Roche Basel)	……	……	……

Nota: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

Tank 2 – Batch Number 3132585

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End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
ENDO-F/T	Endotoxins	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Recirculation tubing code 273492 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Dispensing/ QC Micro	……	……	……

Tank 2 – Batch Number 3132585

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Table A1: Sampling and Testing Summary Note**: *Bold** typefaces indicate tests performed for validation purpose only*

Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
End of Thawing of F/T tank / *Fine scongelo del F/T tank*									
BB-F/T	Bioburden	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Recirculation tubing code 273492 2-8 °C	≤ 10 CFU/10 mL	Dispensing / QC Micro	……	……	……

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Endotoxins Validation / *Validazione delle Endotossine*									
ENDO-F/T-VAL	Endotoxins	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL	Recirculation tubing code 273492 2-8 °C	N.A.	Dispensing/ QC Micro	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: sample to be collected only from the first three batches manufactured.

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Bioburden Validation / *Validazione del Bioburden*									
BB-F/T-VAL	Bioburden	When/ ***Quando***: At the completion of the thawing. / ***Al termine dello scongelo.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 1250 mL	Recirculation tubing code 273492 (3 x 500 mL bottles) if taken after thawing Sampling assembly code 273719 (3 x 500 mL bottles) if taken after 2-8 °C storage 2-8 °C	N.A.	Dispensing/ QC Micro	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: sample to be collected only from the first three batches manufactured.

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After storage of F/T tank at 2-8°C / *Dopo stoccaggio del F/T tank a 2-8 °C*									
ENDO-F/T (2-8°C)	Endotoxins	When/ ***Quando***: At the completion of the storage at 2-8 °C. / ***Al termine dello staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Dispensing/ QC Micro	……	……	……

Nota 1: nel caso di stoccaggi multipli a 2-8 °C nel corso della campagna, prelevare il campione al termine di ogni stoccaggio a 2-8 °C. / Note 1: in case cold storage at 2-8°C is needed multiple times during the validation campaign, collect the sample at the end of every hold.

Nota 2: campione prelevato a scopo di convalida. Tuttavia, per la futura produzione commerciale il prelievo del campione Bioburden dovrà essere mantenuto alla fine dell' hold step della DS (quindi prelevato prima del ricongelo oppure prima del pooling – in caso di ultimo utilizzo). / Note 2: sample collected for validation purposes. However, for future commercial manufacturing collection of Bioburden sample will need to take place at the end of the DS hold step (therefore, sampled before refreezing or before pooling – in case of last usage).

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After storage of F/T tank at 2-8°C / *Dopo stoccaggio del F/T tank a 2-8 °C*									
BB-F/T (2-8°C)	Bioburden	When/ ***Quando***: At the completion of the storage at 2-8 °C. / ***Al termine dello staccaggio a 2-8 °C.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Dispensing / QC Micro	……	……	……

Nota 1: nel caso di stoccaggi multipli a 2-8 °C nel corso della campagna, prelevare il campione al termine di ogni stoccaggio a 2-8 °C. / Note 1: in case cold storage at 2-8°C is needed multiple times during the validation campaign, collect the sample at the end of every hold.

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After time of F/T tank at room temperature / *Dopo il tempo trascorso dal F/T tank a temperature ambiente*									
ENDO-F/T (RT)	Endotoxins	When/ ***Quando***: At the completion of time at room temperature. / ***Al termine del tempo a temperatura ambiente.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 10 mL + 1 x 10 mL for contingency	Sampling Assembly code 273719 2-8 °C	≤ 1.0 EU/mg (≤ 55.0 EU/mL)	Production Sterile Area 6/ QC Micro	……	……	……

Nota 1: nel caso di utilizzi multipli nel corso della campagna, prelevare il campione al termine di ogni permanenza a temperatura ambiente. / Note 1: in case F/T tank is used multiple times during the validation campaign, collect the sample at the end of every hold step at room temperature.

Nota 2: campione prelevato a scopo di convalida. Tuttavia, per la futura produzione commerciale il prelievo del campione Bioburden dovrà essere mantenuto alla fine dell' hold step della DS (quindi prelevato prima del ricongelo oppure prima del pooling – in caso di ultimo utilizzo). / Note 2: sample collected for validation purposes. However, for future commercial manufacturing collection of Bioburden sample will need to take place at the end of the DS hold step (therefore, sampled before refreezing or before pooling – in case of last usage).

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After time of F/T tank at room temperature / *Dopo il tempo trascorso dal F/T tank a temperature ambiente*									
BB-F/T (RT)	Bioburden	When/ ***Quando***: At the completion of time at room temperature. / ***Al termine del tempo a temperatura ambiente.*** Where/ **Dove**: From the sampling assembly of the recirculation tubing. / ***Dal sistema di campionamento del tubo di ricircolo.***	1 x 25 mL	Sampling Assembly code 273719 2-8 °C	≤ 10 CFU/10 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota 1: nel caso di utilizzi multipli nel corso della campagna, prelevare il campione al termine di ogni permanenza a temperatura ambiente. / Note 1: in case F/T tank is used multiple times during the validation campaign, collect the sample at the end of every hold step at room temperature.

Nota 2: campione prelevato a scopo di convalida. Tuttavia, per la futura produzione commerciale il prelievo del campione Bioburden dovrà essere mantenuto alla fine dell' hold step della DS (quindi prelevato prima del ricongelo oppure prima del pooling – in caso di ultimo utilizzo). / Note 2: sample collected for validation purposes. However, for future commercial manufacturing collection of Bioburden sample will need to take place at the end of the DS hold step (therefore, sampled before refreezing or before pooling – in case of last usage).

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During Buffer Preparation / *Durante la preparazione del Buffer*									
pH-Buf-IPC	pH (*)	When/ ***Quando***: After end of buffer pH adjustment ./ ***Alla fine dell'aggiustamento del pH del buffer.*** Where/ **Dove**: From the top of buffer tank RTR342. / ***Dal boccaporto del serbatoio di preparazione del buffer RTR342.***	1 x 20 mL	Pipette and Falcon 2-8 °C	6.2 – 6.8	Production Sterile Area 6/ QC Chemical	……	……	……

(*) IPC bloccante. Fermarsi e attendere i risultati dal QC Chimico. / Blocking IPC. Interrupt the operations and wait for result from QC Chemical department.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
HT-Buf-ENDO (t0)	Endoxotin	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 0.25 EU/mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-ENDO-VAL	Endoxotin	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 10mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	N.A.	Production Sterile Area 6 / QC Micro	……..	……..	……..

Nota: campione da prelevare solo dai primi 3 (tre) lotti di convalida prodotti. / Note: sample to be collected only from the first (3) three validation batches produced.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
HT-Buf-BB (t0)	Bioburden	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 100 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-Chem	pH	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 30 mL	Nalgene bottle 2 – 8 °C	6.2 – 6.8	Production Sterile Area 6/ QC Chemical	……	……	……
	Osmolality				324 – 396 mOsm/kg				

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-PS80	Polysorbate 80 content	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 100 mL	Nalgene bottle 2 – 8 °C	0.55 - 0.85 mg/mL	Production Sterile Area 6/ Warehouse (Client: Roche - SSF)	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-ENDO	Endoxotin	When/ ***Quando***: Almost at the end of buffer transfer into the compounding tank / ***Quasi al termine del trasferimento della soluzione buffer all'interno del tank di preparazione.*** Where/ **Dove**: From the buffer tank RTR342, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione del buffer RTR342, usando il sistema di campionamento Novaseptum sul fondo***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 0.25 EU/mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del buffer nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected after a target of 24 hours from the start of buffer preparation when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-BB	Bioburden	When/ ***Quando***: Almost at the end of buffer transfer into the compounding tank / ***Quasi al termine del trasferimento della soluzione buffer all'interno del tank di preparazione.*** Where/ **Dove**: From the buffer tank RTR342, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione del buffer RTR342, usando il sistema di campionamento Novaseptum sul fondo***	1 x 250 mL	Novaseptum bag 250 mL (273746) 2 – 8 °C	≤ 100 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del buffer nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected after a target of 24 hours from the start of buffer preparation when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
HT-Bulk-ENDO (t0)	Endoxotin	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank RTR343 (before BB filter). / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione RTR343 (prima del filtro BB)***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL	Production / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
HT-Bulk-BB (t0)	Bioburden	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank RTR343 (before BB filter). / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione RTR343 (prima del filtro BB)***	1 x 25 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 10 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
End of compounding step - after mixing / A fine preparazione – dopo il mixing									
LEACH-BULK	Leachable	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ ***Dove***: From the compounding tank RTR343, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione RTR343, usando il sistema di campionamento Novaseptum sul fondo***	1 x 100mL	Novaseptum bag 250 mL (code 271723) 2-8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 1: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

Nota 2: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note 2: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
End of compounding step - after mixing / A fine preparazione – dopo il mixing									
Bulk-Chem	pH	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the compounding tank RTR343, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione RTR343, usando il sistema di campionamento Novaseptum sul fondo***	1 x 40 mL	Nalgene bottle 2 – 8 °C	6.2 – 6.8	Production Sterile Area 6 / QC Chemical	……	……	……
	Osmolality				324 – 396 mOsm/kg				
	Protein content				9.2 – 10.8 mg/mL				

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During bulk solution transfer into the storage tank / Durante il trasferimento della soluzione nel tank di stoccaggio									
BH-B	Protein content	When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the beginning of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, all'inizio del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL	Nalgene bottle / Falcon 2 – 8 °C	Stage 1 Test 1 sample per location Individual Values: 98.0 – 102.0% Target: 10.0 mg/mL Stage 2 Test the other 2 sample per location Individual Values: 95.0 – 105.0% Each Location Mean (n=3) 98.0 – 102.0% Overall SD ≤ 3.0% Target: 10.0 mg/mL	Production Sterile Area 6/ QC Chemical	……	……	……
BH-M		When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the middle of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, a metà del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL						
BH-T		When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the end of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, alla fine del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL						

Nota: Campione da prelevare soltanto da 1 lotto PPQ a minimo batch size e 1 lotto PPQ a massimo batch size. / Note: Sample to be collected only on 1 PPQ batch at minimum batch size and 1 PPQ batch at maximum batch size.

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During Bioburden reduction filtration / Durante la filtrazione di riduzione Bioburden									
Bulk-BB	Bioburden	When/ ***Quando***: Almost at the end of Bioburden filtration. / ***Quasi alla fine della filtrazione Bioburden*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank RTR343 (before BB filter) / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione RTR343 (prima del filtro BB)***	1 x 25 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 10 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del bulk nel caso in cui il lotto sia coinvolto in sfida holding time. /
Note: Sample to be collected after a target of 24 hours from the start of bulk preparation when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Room temperature / Sfida tempo di stoccaggio – Temperatura ambiente									
HT-Sto-ENDO (t24 RT)	Endotoxin	When/ ***Quando***: After a target of 24 hours from the beginning of bioburden reduction filtration. / ***Dopo un target di 24 ore dall'inizio della filtrazione Bioburden*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Room temperature / Sfida tempo di stoccaggio – Temperatura ambiente									
HT-Sto-BB (t24 RT)	Bioburden	When/ ***Quando***: After a target of 24 hours from the beginning of bioburden reduction filtration. / ***Dopo un target di 24 ore dall'inizio della filtrazione Bioburden*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Cold Storage at 2-8 °C / Sfida tempo di stoccaggio – Temperatura controllata 2-8 °C									
HT-Sto-ENDO (t24, 2-8 °C)	Endotoxin	When/ ***Quando***: After a target of 24 hours from the beginning of Cold Storage. / ***Dopo un target di 24 ore dall'inizio dello stoccaggio a temperatura controllata*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL	Production / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Cold Storage at 2-8 °C / Sfida tempo di stoccaggio – Temperatura controllata 2-8 °C									
HT-Sto-BB (t24, 2-8 °C)	Bioburden	When/ ***Quando***: After a target of 24 hours from the beginning of Cold Storage. / ***Dopo un target di 24 ore dall'inizio dello stoccaggio a temperatura controllata*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 100 mL	Production / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Start of filling / Inizio riempimento									
Flush-Z1	Protein concentration	When/ ***Quando***: Beginning of Sterile filtration, after discard of 500 mL solution. / ***All'inizio della filtrazione sterilizzante, dopo aver scartato 500mL di soluzione*** Where/ **Dove**: From the sampling assembly AFTER sterile filters. / ***Dal sistema di campionamento DOPO i filtri sterilizzanti.***	1 x 500 mL	Sampling Assembly (273719) 2 – 8 °C	For information only	Production Sterile Area 6/ QC Chemical	.....	.....	.....
Flush-Z2			1 x 500 mL		For information only				
Flush-Z3			1 x 500 mL		9.2 – 10.8 mg/mL				

Nota: Campione da prelevare solo su 3 lotti PPQ. / Note: Sample to be collected only for 3 PPQ batches.

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Start of filling / Inizio riempimento									
Beg-Fill-ENDO	Endotoxin	When***/ Quando***: Beginning of Sterile filtration. / ***All'inizio della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 10 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 1.0 EU/mL	Production Sterile Area 6/ QC Micro	……	……	……

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Start of filling / Inizio riempimento									
Beg-Fill-BB	Bioburden	When***/ Quando***: Beginning of Sterile filtration. / ***All'inizio della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 250 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

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Start of filling / Inizio riempimento									
Bulk-Content	Polysorate 80 content Protein content	When***/ Quando***: Beginning of Sterile filtration. / ***All'inizio della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 100 mL	Sampling Assembly (273719) - 70 °C	Protein Content - 9.2-10.8 mg/mL (Target 10.0 mg/mL); PS80: FIO	Production Sterile Area 6/ Warehouse (Client: Roche - SSF)	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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End of filling / Fine riempimento									
End-Fill-ENDO	Endotoxin	When***/ Quando***: End of Sterile filtration. / ***Alla fine della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 10 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 1.0 EU/mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: La fine della filtrazione sterilizzante corrisponde a circa 19'000 vials prodotti per MabThera 100 mg minimo batch size e a circa 57'000 flaconi per MabThera 100 mg massimo batch size (numero di vials calcolati sulla base del range minimo di resa).

Note: The end of sterilizing filtration corresponds to about 19’000 vials produced for MabThera 100 mg minimum batch size and to about 57’000 vials for MabThera 100 mg maximum batch size (number of vials calculated on the bases of the minimum yield value).

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End of filling / Fine riempimento									
End-Fill-BB	Bioburden	When***/ Quando***: End of Sterile filtration. / ***Alla fine della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 250 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: La fine della filtrazione sterilizzante corrisponde a circa 19'000 vials prodotti per MabThera 100 mg minimo batch size e a circa 57'000 flaconi per MabThera 100 mg massimo batch size (numero di vials calcolati sulla base del range minimo di resa).

Note: The end of sterilizing filtration corresponds to about 19’000 vials produced for MabThera 100 mg minimum batch size and to about 57’000 vials for MabThera 100 mg maximum batch size (number of vials calculated on the bases of the minimum yield value).

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During the filling / Durante il riempimento									
FILL-1	Polysorbate 80 content Protein content	When/ ***Quando***: Beginning of filling, very first vials filled / ***All'inizio del riempimento, le primissime vials riempite*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Vials 2, 4, 6, 8, 10, 12, 14, 16, 18, 20	- 70 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6/ Warehouse (Client: Roche - SSF)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time, a partire dalle dalle vial conformi della fase di calibrazione. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge, starting from good vials of calibration.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

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During the filling / Durante il riempimento									
LEACH-FILL-2	Leachable	When/ ***Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Vials 1, 3, 5, 7, 9, 11, 13, 15, 17, 19	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (After 1st hold up volume) / Durante il riempimento (dopo il primo hold up volume)									
LEACH-FILL-3	Leachable	When/ ***Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	From vial 41 to vial 50	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 2L filled) / Durante il riempimento (dopo circa 2L riempiti)									
LEACH-FILL-4	Leachable	When/ ***Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	From vial 201 to vial 210	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling (approx. after 5L filled) / Durante il riempimento (dopo circa 5L riempiti)									
LEACH-FILL-5	Leachable	When/ ***Quando***: During the filling of the second box / ***Durante il riempimento della seconda scatola*** Where/ **Dove**: Xtrema. Unloading, from the second box / ***Dallo scarico buoni linea Xtrema, dalla seconda scatola.***	10 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 10L filled) / Durante il riempimento (dopo circa 10L riempiti)									
LEACH-FILL-6	Leachable	When/ ***Quando***: During the filling of the fourth box / ***Durante il riempimento della quarta scatola*** Where/ **Dove**: Xtrema. Unloading, from the fourth box / ***Dallo scarico buoni linea Xtrema, dalla quarta scatola.***	10 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 15L filled) / Durante il riempimento (dopo circa 15L riempiti)									
LEACH-FILL-7	Leachable	When/ ***Quando***: During the filling of the seventh box/ ***Durante il riempimento della settima scatola*** Where/ **Dove**: Xtrema. Unloading, from the seventh box / ***Dallo scarico buoni linea Xtrema, dalla settima scatola.***	10 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 20L filled) / Durante il riempimento (dopo circa 20L riempiti)									
LEACH-FILL-8	Leachable	When***/ Quando***: During the filling of the tenth box/ ***Durante il riempimento della decima scatola*** Where/ **Dove**: Xtrema. Unloading, from the tenth box / ***Dallo scarico buoni linea Xtrema, dalla decima scatola.***	10 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling / Durante il riempimento									
LEACH-FILL-SEGREGATE (0 -3 L)	N.A.	When***/ Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Group 1: From vial 21 to vial 40 Group 2: From vial 51 to vial 200 Group 3: From vial 211 to vial 299	2 – 8 °C	N.A.	Production Sterile Area 6/ Warehouse (Client: Roche)	……	……	……

Nota 1: Si specifica che campioni da prelevare per filling homogeneity potrebbero ricadere all'interno della porzione da segregare. / Note 1: It is specified that samples to be collected for filling homogeneity may be fall within the present portion to be segregated.
Nota 2: Identificare i vials in gruppi. Il numero effettivo di vials presenti nel gruppo potrebbe non corrispondere al valore numerico atteso se la porzione è stata oggetto di altri campionamenti previsti dal presente piano. / Note 2: Only the group of vials need to be identified. The actual number of vials that are part of the group may not correspond to the expected if the portion is subjected to other sampling activities foreseen by the present sampling plan.
Nota 3: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 3: Sample to be collected only from the PPQ batches involved in the holding time challenge.

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During the filling / Durante il riempimento									
VP-B	Visible particles	When/ ***Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	10 vials + 20 vials of contingency	2 – 8 °C	Practically free from particles	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……
SVP-B	Subvisible particles		4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300		……	……	……

Nota 1: Campioni da prelevare solo PPQ prodotto a batch size Massimo, dopo il campione LEACH-FILL-8 rappresentativo del litro 20. / Note 1: Samples must be collected only from the PPQ at maximum batch size, after sample ID LEACH-FILL-8 representative of liter 20.
Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine riempimento. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of filling.

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During the filling / Durante il riempimento									
VP-M	Visible particles	When/ ***Quando:*** to be identified at the middle of filling/ **da identificare *a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	10 vials + 20 vials of contingency	2 – 8 °C	Practically free from particles	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……
SVP-M	Subvisible particles		4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300		……	……	……

Nota 1: Campioni da prelevare solo PPQ prodotto a batch size Massimo, dopo il campione LEACH-FILL-8 rappresentativo del litro 20. / Note 1: Samples must be collected only from the PPQ at maximum batch size, after sample ID LEACH-FILL-8 representative of liter 20.
Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine riempimento. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of filling.

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During the filling / Durante il riempimento									
VP-E	Visible particles	When/ ***Quando***: to be identified at the end of filling / **da identificare a *fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	10 vials + 20 vials of contingency	2 – 8 °C	Practically free from particles	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……
SVP-E	Subvisible particles		4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300		……	……	……

Nota 1: Campioni da prelevare solo PPQ prodotto a batch size Massimo, dopo il campione LEACH-FILL-8 rappresentativo del litro 20. / Note 1: Samples must be collected only from the PPQ at maximum batch size, after sample ID LEACH-FILL-8 representative of liter 20.
Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine riempimento. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of filling.

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-1	Protein content	When/ ***Quando***:Beginning of filling / ***Inizio riempimento***[12] Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-2	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-3	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

[12] Campione da prelevare dopo **FILL-1**, quando applicabile. / Sample to be collected after **FILL-1,** when applicable.

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-4	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-5	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-6	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-7	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-8	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-9	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-10	Protein content	When/ ***Quando:*** Approximately When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-11	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-12	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-13	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-14	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-15	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-16	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-17	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-18	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-19	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-20	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-21	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-22	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-23	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-24	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-25	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-26	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-27	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-28	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-29	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-30	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-31	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-32	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-33	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-34	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-35	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-36	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-37	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……
FH-38	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			
FH-39	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6 / QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-40	Protein content	When/ ***Quando:*** Approximately after 594 vials from the previous sampling point / ***dopo circa 594 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-1	Protein content	When/ ***Quando***:Beginning of filling / ***Inizio riempimento***[13] Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-2	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-3	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

[13] Campione da prelevare dopo **FILL-1**, quando applicabile. / Sample to be collected after **FILL-1,** when applicable.

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-4	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-5	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-6	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-7	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-8	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-9	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-10	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-11	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-12	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-13	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-14	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-15	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-16	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-17	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-18	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-19	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-20	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-21	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-22	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-23	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-24	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-25	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-26	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-27	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-28	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-29	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-30	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-31	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-32	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-33	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-34	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-35	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-36	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-37	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	.....	.....	.....
FH-38	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-39	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at maximum batch size / Durante il riempimento – PPQ a batch size massimo									
FH-40	Protein content	When/ ***Quando:*** Approximately after 1775 vials from the previous sampling point / ***dopo circa 1775 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6 / QC Chemical	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-B	Vacuum decay	When/ ***Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	167 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-M	Vacuum decay	When/ ***Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	166 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-E	Vacuum decay	When/ ***Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	167 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at maximum batch size / Durante il riempimento – PPQs a batch size massimo									
CCI-B	Vacuum decay	When/ ***Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	267 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at maximum batch size / Durante il riempimento – PPQs a batch size massimo									
CCI-M	Vacuum decay	When/ ***Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	266 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at maximum batch size / Durante il riempimento – PPQs a batch size massimo									
CCI-E	Vacuum decay	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	267 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
REL-B	Container / Appearance	When/ ***Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap red Seal silver Appearance: liquid	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 10.0 mL				
	Uniformity of dosage unit				Compliant according to Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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During the filling / Durante il riempimento									
STE-B	Sterility	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
ENDO-B	Endotoxin	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/ Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling / Durante il riempimento									
REL-M	Container / Appearance	When/ ***Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap red Seal silver Appearance: liquid	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 10.0 mL				
	Uniformity of dosage unit				Compliant according to Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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Table A1: Sampling and Testing Summary Note**: *Bold*** *typefaces indicate tests performed for validation purpose only*

Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
STE-M	Sterility	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	6 vial + 6 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
ENDO-M	Endotoxin	When/ ***Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
REL-E	Container / Appearance	When/ ***Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap red Seal silver Appearance: liquid	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 10.0 mL				
	Uniformity of dosage unit				Compliant according to Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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Table A1: Sampling and Testing Summary Note**: *Bold*** *typefaces indicate tests performed for validation purpose only*

Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
STE-E	Sterility	When**/ *Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/ Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling / Durante il riempimento									
ENDO-E	Endotoxin	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
FP-ENDO-VAL	Endotoxin – Method Validation	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	5 vial + 5 vial of contingency	2 – 8 °C	N.A.	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: Sample to be collected only from the first three batches produced.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-B	Subvisible particles	When***/ Quando:*** to be identified at the beginning of the filling of the sub-batch/ **da identificare *all'inizio del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine sub lotto. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of sub batch.

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/ Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-B	Sterility	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-B	Endotoxin	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-M	Subvisible particles	When***/ Quando:*** to be identified at the middle of the filling of the sub-batch/ ***da identificare a metà del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine sub lotto. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of sub batch.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-M	Sterility	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	6 vial + 6 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/ Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-M	Endotoxin	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-E	Subvisible particles	When***/ Quando:*** to be identified at the end of the filling of the sub-batch/ ***da identificare alla fine del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine sub lotto. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of sub batch.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-E	Sterility	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-E	Endotoxin	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the visual inspection / Durante l'ispezione visiva									
COMP-100	Comparability	When***/ Quando:*** *random during* visual inspection/ random durante l'***ispezione visiva.*** Where/ **Dove**: After visual inspection is performed / ***dopo aver effettuato l'ispezione visiva.***	130 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Visual Inspection / Warehouse (Client: Roche - Basel)	……	……	……

Nota: Campione da prelevare solo su due lotti PPQ di MabThera 100 mg. / Note: Sample to be collected only from two PPQ batches of MabThera 100 mg.

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During the visual inspection / Durante l'ispezione visiva									
VI-CERT	Visual Inspection Certification process	When***/ Quando:*** *during* visual inspection/ durante l'***ispezione visiva.*** Where/ **Dove**: After visual inspection is performed, in part from good units directly after AVI and in part from good units after MVI / ***dopo aver effettuato l'ispezione visiva, in parte dalle unità buone direttamente dopo l' AVI e in parte dalle unità buone dopo la MVI***	1300 vials	2 – 8 °C	N.A.	Production Visual Inspection / Warehouse (Client: Roche)	……	……	……

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During Buffer Preparation / *Durante la preparazione del Buffer*									
pH-Buf-IPC	pH (*)	When/ ***Quando***: After end of buffer pH adjustment ./ ***Alla fine dell'aggiustamento del pH del buffer.*** Where/ **Dove**: From the top of buffer tank RTR342. / ***Dal boccaporto del serbatoio di preparazione del buffer RTR342.***	1 x 20 mL	Pipette and Falcon 2-8 °C	6.2 – 6.8	Production Sterile Area 6/ QC Chemical	……	……	……

(*) IPC bloccante. Fermarsi e attendere i risultati dal QC Chimico. / Blocking IPC. Interrupt the operations and wait for result from QC Chemical department.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
After Buffer Preparation / *Dopo la preparazione del Buffer*									
HT-Buf-ENDO (t0)	Endoxotin	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 0.25 EU/mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Table A1: Sampling and Testing Summary Note**: *Bold** typefaces indicate tests performed for validation purpose only*

Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-ENDO-VAL	Endoxotin	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 10mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	N.A.	Production Sterile Area 6 / QC Micro	……..	……..	……..

Nota: campione da prelevare solo dai primi 3 (tre) lotti di convalida prodotti. / Note: sample to be collected only from the first (3) three validation batches produced.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
HT-Buf-BB (t0)	Bioburden	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 100 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-Chem	pH	When/ ***Quando***: At the end of buffer preparation, after mixing. / ***Al termine della preparazione della soluzione buffer, dopo miscelazione.*** Where/ **Dove**: From the sampling system Novaseptum at the middle of the buffer tank RTR342. / ***Dal sistema di campionamento Novaseptum a metà del tank di buffer RTR342***	1 x 30 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	6.2 – 6.8	Production Sterile Area 6/ QC Chemical	……	……	……
	Osmolality				324 – 396 mOsm/kg				

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-ENDO	Endoxotin	When/ ***Quando***: Almost at the end of buffer transfer into the compounding tank / ***Quasi al termine del trasferimento della soluzione buffer all'interno del tank di preparazione.*** Where/ **Dove**: From the buffer tank RTR342, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione del buffer RTR342, usando il sistema di campionamento Novaseptum sul fondo***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 0.25 EU/mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del buffer nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected after a target of 24 hours from the start of buffer preparation when the validation batch is involved in the holding time challenge.

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After Buffer Preparation / *Dopo la preparazione del Buffer*									
Buf-BB	Bioburden	When/ ***Quando***: Almost at the end of buffer transfer into the compounding tank / ***Quasi al termine del trasferimento della soluzione buffer all'interno del tank di preparazione.*** Where/ **Dove**: From the buffer tank RTR342, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione del buffer RTR342, usando il sistema di campionamento Novaseptum sul fondo***	1 x 250 mL	Novaseptum bag 250 mL (273746) 2 – 8 °C	≤ 100 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del buffer nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected after a target of 24 hours from the start of buffer preparation when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
HT-Bulk-ENDO (t0)	Endoxotin	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank RTR343 (before BB filter). / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione RTR343 (prima del filtro BB)***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL		……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
HT-Bulk-BB (t0)	Bioburden	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank (before BB filter). / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione (prima del filtro BB)***	1 x 25 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 10 mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
LEACH-BULK	Leachable	When***/ Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ ***Dove***: From the compounding tank RTR343, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione RTR343, usando il sistema di campionamento Novaseptum sul fondo***	1 x 100mL	Novaseptum bag 250 mL (code 271723) 2-8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 1: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

Nota 2: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note 2: Sample to be collected only when the validation batch is involved in the holding time challenge.

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End of compounding step - after mixing / A fine preparazione – dopo il mixing									
Bulk-Chem	pH	When/ ***Quando***: At the end of compounding step, after mixing / ***Al termine della preparazione, dopo l'agitazione finale*** Where/ **Dove**: From the compounding tank RTR343, using the sampling system Novaseptum at the bottom. / ***Dal tank di preparazione RTR343, usando il sistema di campionamento Novaseptum sul fondo***	1 x 40 mL	Nalgene bottle 2 – 8 °C	6.2 – 6.8	Production Sterile Area 6/ QC Chemical	……	……	……
	Osmolality				324 – 396 mOsm/kg				
	Protein content				9.2 – 10.8 mg/mL				

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During bulk solution transfer into the storage tank / Durante il trasferimento della soluzione nel tank di stoccaggio									
BH-B	Protein content	When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the beginning of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, all'inizio del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL	Nalgene bottle / Falcon 2 – 8 °C	Stage 1 Test 1 sample per location Individual Values: 98.0 – 102.0% Target: 10.0 mg/mL Stage 2 Test the other 2 sample per location Individual Values: 95.0 – 105.0% Each Location Mean (n=3) 98.0 – 102.0% Overall SD ≤ 3.0% Target: 10.0 mg/mL	Production Sterile Area 6/ QC Chemical	……	……	……
BH-M		When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the middle of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, a metà del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL						
BH-T		When/ ***Quando***: During formulated bulk transfer in the storage tank. / ***Durante il trasferimento del bulk formulato nel tank di stoccaggio*** Where/ **Dove:** From the bottom of the compounding tank RTR343, at the end of solution transfer into the storage tank. / ***Dal fondo del tank di preparazione RTR343, alla fine del trasferimento della soluzione nel tank di stoccaggio***	3 x 5mL						

Nota: Campione da prelevare soltanto da 1 lotto PPQ a minimo batch size e 1 lotto PPQ a massimo batch size. / Note: Sample to be collected only on 1 PPQ batch at minimum batch size and 1 PPQ batch at maximum batch size.

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
During Bioburden reduction filtration / Durante la filtrazione di riduzione Bioburden									
Bulk-BB	Bioburden	When/ ***Quando***: Almost at the end of Bioburden filtration. / ***Quasi alla fine della filtrazione Bioburden.*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the compounding tank RTR343 (before BB filter) / ***Dal sistema di campionamento Novaseptum sul fondo del tank di preparazione RTR343 (prima del filtro BB)***	1 x 25 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 10 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: Campione da prelevare dopo un target di 24 ore dall'inizio della preparazione del bulk nel caso in cui il lotto sia coinvolto in sfida holding time. /
Note: Sample to be collected after a target of 24 hours from the start of bulk preparation when the validation batch is involved in the holding time challenge.

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
Storage Holding Time – Room temperature / Sfida tempo di stoccaggio – Temperatura ambiente									
HT-Sto-ENDO (t24 RT)	Endotoxin	When/ ***Quando***: After a target of 24 hours from the beginning of bioburden reduction filtration. / ***Dopo un target di 24 ore dall'inizio della filtrazione Bioburden*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Room temperature / Sfida tempo di stoccaggio – Temperatura ambiente									
HT-Sto-BB (t24 RT)	Bioburden	When/ ***Quando***: After a target of 24 hours from the beginning of bioburden reduction filtration. / ***Dopo un target di 24 ore dall'inizio della filtrazione Bioburden*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6/ QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Cold Storage at 2-8 °C / Sfida tempo di stoccaggio – Temperatura controllata 2-8 °C									
HT-Sto-ENDO (t24, 2-8 °C)	Endotoxin	When/ ***Quando***: After a target of 24 hours from the beginning of Cold Storage. / ***Dopo un target di 24 ore dall'inizio dello stoccaggio a temperatura controllata*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 10 mL	Novaseptum syringe 20 mL (273746) 2 – 8 °C	≤ 1.0 EU/mL	Production / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Storage Holding Time – Cold Storage at 2-8 °C / Sfida tempo di stoccaggio – Temperatura controllata 2-8 °C									
HT-Sto-BB (t24, 2-8 °C)	Bioburden	When/ ***Quando***: After a target of 24 hours from the beginning of Cold Storage. / ***Dopo un target di 24 ore dall'inizio dello stoccaggio a temperatura controllata*** Where/ **Dove**: From the sampling system Novaseptum at the bottom of the storage tank. / ***Dal sistema di campionamento Novaseptum sul fondo del tank di stoccaggio***	1 x 250 mL	Novaseptum bag 250 mL (271723) 2 – 8 °C	≤ 10 CFU / 100 mL	Production / QC Micro	……	……	……

Nota: Campione da prelevare solo nel caso in cui il lotto sia coinvolto in sfida holding time. / Note: Sample to be collected only when the validation batch is involved in the holding time challenge.

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Start of filling / Inizio riempimento									
Flush-Z1	Protein concentration	When/ ***Quando***: Beginning of Sterile filtration, after discard of 500 mL solution. / ***All'inizio della filtrazione sterilizzante, dopo aver scartato 500mL di soluzione*** Where/ **Dove**: From the sampling assembly AFTER sterile filters. / ***Dal sistema di campionamento DOPO i filtri sterilizzanti.***	1 x 500 mL	Sampling Assembly (273719) 2 – 8 °C	For information only	Production Sterile Area 6/ QC Chemical	……	……	……
Flush-Z2			1 x 500 mL		For information only				
Flush-Z3			1 x 500 mL		9.2 – 10.8 mg/mL				

Nota: Campione da prelevare solo su 3 lotti PPQ. / Note: Sample to be collected only for 3 PPQ batches.

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Start of filling / Inizio riempimento									
Beg-Fill-ENDO	Endotoxin	When***/ Quando***: Beginning of Sterile filtration. / ***All'inizio della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 10 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 1.0 EU/mL	Production / QC Micro	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
Start of filling / Inizio riempimento									
Beg-Fill-BB	Bioburden	When***/ Quando***: Beginning of Sterile filtration. / ***All'inizio della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 250 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6/ QC Micro	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
End of filling / Fine riempimento									
End-Fill-ENDO	Endotoxin	When***/ Quando***: End of Sterile filtration. / ***Alla fine della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 10 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 1.0 EU/mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: La fine della filtrazione sterilizzante corrisponde a circa 3'900 vials prodotti per MabThera 500 mg minimo batch size (numero di vials calcolati sulla base del range minimo di resa).

Note: The end of sterilizing filtration corresponds to about 3'900 vials produced for MabThera 500 mg minimum batch size (number of vials calculated on the bases of the minimum yield value).

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
End of filling / Fine riempimento									
End-Fill-BB	Bioburden	When***/ Quando***: End of Sterile filtration. / ***Alla fine della filtrazione sterilizzante*** Where/ **Dove**: From the sampling assembly BEFORE sterile filters. / ***Dal sistema di campionamento PRIMA dei filtri sterilizzanti.***	1 x 250 mL	Sampling Assembly (273719) 2 – 8 °C	≤ 10 CFU / 100 mL	Production Sterile Area 6 / QC Micro	……	……	……

Nota: La fine della filtrazione sterilizzante corrisponde a circa 3'900 vials prodotti per MabThera 500 mg minimo batch size (numero di vials calcolati sulla base del range minimo di resa).
Note: The end of sterilizing filtration corresponds to about 3'900 vials produced for MabThera 500 mg minimum batch size (number of vials calculated on the bases of the minimum yield value).

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During the filling / Durante il riempimento									
LEACH-FILL-1	Leachable	When***/ Quando***: Beginning of filling, very first vials filled / ***All'inizio del riempimento, le primissime vials riempite*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Vials 1 and 2	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6/ QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time, a partire dalle dalle vial conformi della fase di calibrazione. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge, starting from good vials of calibration.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling (after 1st hold up volume) / Durante il riempimento (dopo il primo hold up volume)									
LEACH-FILL-2	Leachable	When/ ***Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Vials 19 and 20	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 2L filled)/ Durante il riempimento (dopo circa 2L riempiti)									
LEACH-FILL-3	Leachable	When/ ***Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Vials 41 and 42	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: ATTENZIONE, le vials devono essere numerate progressivamente in ordine di uscita. / Note 2: ATTENTION, vials should be numbered progressively in exit order.

Nota 3: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 3: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (approx. after 5L filled) / Durante il riempimento (dopo circa 5L riempiti)									
LEACH-FILL-4	Leachable	When***/ Quando***: During the filling, at the end of loading of the first box / ***Durante il riempimento, a fine riempimento prima scatola*** Where/ **Dove**: Xtrema. Unloading, from the first box / ***Dallo scarico buoni linea Xtrema, dalla prima scatola.***	2 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (appro. after 10L filled) / Durante il riempimento (dopo circa 10L riempiti)									
LEACH-FILL-5	Leachable	When/ ***Quando***: During the filling of the fourth box / ***Durante il riempimento della quarta scatola*** Where/ **Dove**: Xtrema. Unloading, from the fourth box / ***Dallo scarico buoni linea Xtrema, dalla quarta scatola.***	2 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling (appro. after 15L filled) / Durante il riempimento (dopo circa 15L riempiti)									
LEACH-FILL-6	Leachable	When/ ***Quando***: During the filling of the sixth box/ ***Durante il riempimento della sesta scatola*** Where/ **Dove**: Xtrema. Unloading, from the sixth box / ***Dallo scarico buoni linea Xtrema, dalla sesta scatola.***	2 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling (appro. after 20L filled) / Durante il riempimento (dopo circa 20L riempiti)									
LEACH-FILL-7	Leachable	When/ ***Quando***: During the filling of the eighth box / ***Durante il riempimento dell'ottava scatola*** Where/ **Dove**: Xtrema. Unloading, from the eighth box / ***Dallo scarico buoni linea Xtrema, dall'ottava scatola.***	2 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Sterile Area 6 / QC Chemical and then Warehouse (Client: Roche - Basel)	……	……	……

Nota 1: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 1: Sample to be collected only from the PPQ batches involved in the holding time challenge.

Nota 2: Il campione dovrà essere aliquotato dal reparto QC Chimico come segue: 2 x 35 mL (contenitore in vetro), 2 x 15 mL (contenitore in PP). Le aliquote dovranno essere ripartite il prima possibile. / Note 2: QC Chemical must aliquot the sample as follows: 2 x 35 mL (glass container), 2 x 15 mL (PP container). Aliquoting must take place as soon as possible.

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During the filling / Durante il riempimento									
LEACH-FILL-SEGREGATE (0 -3 L)	N.A.	When***/ Quando***: During the filling / ***Durante il riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	Group 1: From vial 3 to vial 18 Group 2: From vial 21 to vial 40 Group 3: From vial 43 to vial 60	2 – 8 °C	N.A.	Production Sterile Area 6/ Warehouse (Client: Roche)	……	……	……

Nota 1: Si specifica che campioni da prelevare per filling homogeneity potrebbero ricadere all'interno della porzione da segregare. / Note 1: It is specified that samples to be collected for filling homogeneity may be fall within the present portion to be segregated.
Nota 2: Identificare i vials in gruppi. Il numero effettivo di vials presenti nel gruppo potrebbe non corrispondere al valore numerico atteso se la porzione è stata oggetto di altri campionamenti previsti dal presente piano. / Note 2: Only the group of vials need to be identified. The actual number of vials that are part of the group may not correspond to the expected if the portion is subjected to other sampling activities foreseen by the present sampling plan.
Nota 3: Campione da prelevare solo dai lotti PPQ soggetti a sfida holding time. / Note 3: Sample to be collected only from the PPQ batches involved in the holding time challenge.

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-1	Protein content	When/ ***Quando***:Beginning of filling / ***Inizio riempimento***[14] Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-2	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-3	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

[14] Campione da prelevare dopo **LEACH-FILL-1**, quando applicabile. / Sample to be collected after **LEACH-FILL-1, when applicable.**

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-4	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-5	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-6	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-7	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-8	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-9	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-10	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-11	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-12	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-13	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-14	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-15	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-16	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-17	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-18	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-19	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-20	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-21	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-22	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-23	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-24	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-25	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-26	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-27	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-28	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-29	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-30	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-31	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-32	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-33	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-34	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-35	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-36	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-37	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production Sterile Area 6/ QC Chemical	……	……	……
FH-38	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			
FH-39	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C		Production Sterile Area 6/ QC Chemical			

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During the filling – PPQ at minimum batch size / Durante il riempimento – PPQ a batch size minimo									
FH-40	Protein content	When/ ***Quando:*** Approximately after 122 vials from the previous sampling point / ***dopo circa 122 vials dal precedente campionamento.*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vials + 3 vials of contingency	2 – 8 °C	PVT Stage 1 Individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=60 PVT Stage 2 All individual values 75.0% - 125.0% Meets 90% confidence 95% coverage for n=120	Production / QC Chemical	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-B	Vacuum decay	When/ ***Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	105 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-M	Vacuum decay	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	105 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

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During the filling – PPQs at minimum batch size / Durante il riempimento – PPQs a batch size minimo									
CCI-E	Vacuum decay	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	105 vials + 20 vials of contingency	2 – 8 °C	No leakage detected (all vials compliant)	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
REL-B	Container / Appearance	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap grey Seal silver Appearance: liquid	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 50.0 mL				
	Uniformity of dosage unit				Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02>				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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During the filling / Durante il riempimento									
STE-B	Sterility	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling / Durante il riempimento									
ENDO-B	Endotoxin	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/ Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling / Durante il riempimento									
REL-M	Container / Appearance	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap grey Seal silver Appearance: liquid	Production / Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 50.0 mL				
	Uniformity of dosage unit				Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02>				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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Table A1: Sampling and Testing Summary Note**: *Bold*** *typefaces indicate tests performed for validation purpose only*

Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
STE-M	Sterility	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	6 vial + 6 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection	……	……	……

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During the filling / Durante il riempimento									
ENDO-M	Endotoxin	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID *ID Campione*	Parameter *Parametro*	Sampling Point *Punto di campionamento*	Quantity *Quantità*	Sampling/Storage Conditions *Condizioni di Campionamento/ Stoccaggio*	Acceptance Criteria *Criterio di accettazione*	Sampling / Testing *Responsibility Responsabilità campionamento/test*	Delivered by (sign/date) *Consegnato da (sigla / data)*	Received by (sign/date) *Ricevuto da (sigla / data)*	QA (sign/date) *QA (sigla / data)*
During the filling / Durante il riempimento									
REL-E	Container / Appearance	When/ ***Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	27 vials + 55 vials of contingency	2 – 8 °C	Container:Flip-Off Cap grey Seal silver Appearance: liquid	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……
	Clarity				Description: clear to opalescent Ph. Eur. Opalescent Value: max. Ref. III				
	Color				Description: colorless to pale yellow Ph. Eur. Color Scale: not more colored than Y6				
	pH				6.2 – 6.8				
	Osmolality				324 – 396 mOsmol/kg				
	Extractable volume (min)				Ph. Eur./USP/JP: corresponds Min : ≥ 50.0 mL				
	Uniformity of dosage unit				Ph.Eur. 2.9.5, Ph.Eur. 2.9.6 / USP <905> / JP <6.02>				
	Content of protein (by UV)				9.2 – 10.8 mg/mL				
	Identity of Rituximab (CZE)				Positive identity (corresponds)				
	Purity by SE-HPLC				Monomer ≥ 97.5 area%				
	Purity by IE-HPLC				Fc Peak 25.0 – 31.0 area% Fab Peak 60.0 – 65.0 area%				
	Potency by Bioassay				0.8 – 1.3 E5 U/mL				
	Visible particles				Practically free from visible particles				
	Subvisible particles				Particles ≥ 2µm per Container : report Particles ≥ 5 µm per Container : report Particles ≥ 10 µm per Container : ≤ 3000 Particles ≥ 25 µm per Container : ≤ 300				

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During the filling / Durante il riempimento									
STE-E	Sterility	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
ENDO-E	Endotoxin	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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Sample ID *ID Campione*	**Parameter** *Parametro*	**Sampling Point** *Punto di campionamento*	**Quantity** *Quantità*	**Sampling/Storage Conditions** *Condizioni di Campionamento/ Stoccaggio*	**Acceptance Criteria** *Criterio di accettazione*	**Sampling / Testing** *Responsibility Responsabilità campionamento/test*	**Delivered by (sign/date)** *Consegnato da (sigla / data)*	**Received by (sign/date)** *Ricevuto da (sigla / data)*	**QA (sign/date)** *QA (sigla / data)*
During the filling / Durante il riempimento									
FP-ENDO-VAL	Endotoxin – Method Validation	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	5 vial + 5 vial of contingency	2 – 8 °C	N.A.	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota: Campione da prelevare solo dai primi 3 lotti prodotti. / Note: Sample to be collected only from the first three batches produced.

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Table A1: Sampling and Testing Summary Note**: *Bold*** *typefaces indicate tests performed for validation purpose only*

Sample ID ***ID Campione***	**Parameter** ***Parametro***	**Sampling Point** ***Punto di campionamento***	**Quantity** ***Quantità***	**Sampling/Storage Conditions** ***Condizioni di Campionamento/ Stoccaggio***	**Acceptance Criteria** ***Criterio di accettazione***	**Sampling / Testing** ***Responsibility Responsabilità campionamento/test***	**Delivered by (sign/date)** ***Consegnato da (sigla / data)***	**Received by (sign/date)** ***Ricevuto da (sigla / data)***	**QA (sign/date)** ***QA (sigla / data)***
During the filling / Durante il riempimento									
FP-STE-VAL	Sterility – Method Validation	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	70 vials + 70 vials of contingency	2 – 8 °C	N.A.	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-B	eble particles	When***/ Quando:*** to be identified at the beginning of the filling of the sub-batch/ **da identificare *all'inizio del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine sub lotto. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of sub batch.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-B	Sterility	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-B	Endotoxin	When***/ Quando:*** to be identified at the beginning of filling/ **da identificare *all'inizio del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-M	Subvisible particles	When***/ Quando:*** to be identified at the middle of the filling of the sub-batch/ ***da identificare a metà del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

Nota 2: L'analisi dovrà essere effettuata facendo un pooling dei campioni prelevati a inizio/metà/fine sub lotto. / Note 2: The analysis must be performed pooling samples collected at beginning/middle/end of sub batch.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-M	Sterility	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	6 vial + 6 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-M	Endotoxin	When***/ Quando:*** to be identified at the middle of filling/ ***da identificare a metà del riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
SVP-SUB-E	Subvisible particles	When***/ Quando:*** to be identified at the end of the filling of the sub-batch/ ***da identificare alla fine del riempimento del sublotto*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	4 vials + 12 vials of contingency	2 – 8 °C	Particles ≥ 2µm per Container: report Particles ≥ 5 µm per Container: report Particles ≥ 10 µm per Container: ≤ 3000 Particles ≥ 25 µm per Container: ≤ 300	Production Sterile Area 6/ Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
STE-SUB-E	Sterility	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	7 vial + 7 vial of contingency	2 – 8 °C	No growth (corresponds)	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the filling of the sub-batch/ Durante il riempimento del sublotto									
ENDO-SUB-E	Endotoxin	When***/ Quando:*** to be identified at the end of filling/ ***da identificare a fine riempimento*** Where/ **Dove**: Xtrema. Unloading / ***Dallo scarico buoni linea Xtrema.***	3 vial + 3 vial of contingency	2 – 8 °C	≤1.0 EU/mL	Production Sterile Area 6 / Warehouse (waiting for visual inspection)	……	……	……

Nota 1: Campioni da prelevare solo in caso di creazione lotto barrato per esclusione pompe. / Note 1: Samples must be collected only in case of barred batch following pumps exclusions.

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During the visual inspection / Durante l'ispezione visiva									
COMP-500	Comparability	When***/ Quando:*** *random during* visual inspection/ random durante l'***ispezione visiva.*** Where/ **Dove**: After visual inspection is performed / ***dopo aver effettuato l'ispezione visiva.***	130 vials	2 – 8 °C	Report Result (refer to Roche Study Report)	Production Visual Inspection / Warehouse (Client: Roche - Basel)	……	……	……

List of CQAs for the product MabThera

Container

Appearance

Clarity

Color

Ph

Osmolality

Extractable volume (min)

Uniformity of dosage unit

Content of protein

Identity of Rituximab

Purity by SE-HPLC

Purity by IE-HPLC

Potency

Visible Particles

Subvisible particles

Container Closure Integrity

Sterility

Bacterial endotoxins

WEIGHT ALLOCATION FORM FOR PPQ BATCHES

MabThera 100 mg (code 352518 - 363303) – Batch #B0001 – Maximum batch size

Batch size [L] to be considered for the calculation: 747 L

Rituximab Drug Substance, Intravenous (IV)

Allocated BDS: Supplier Batch number 3132583, Patheon code 102706

MabThera 100 mg (code 352518 - 363303) – Batch #B0002 - Minimum batch size

Batch size [L] to be considered for the calculation: 250 L

Rituximab Drug Substance, Intravenous (IV)

Allocated BDS: Supplier Batch number 3132585, Patheon code 102706

MabThera 100 mg (code 352518 - 363303) – Batch #B0003 - Minimum batch size

Batch size [L] to be considered for the calculation: 250 L

Rituximab Drug Substance, Intravenous (IV)

Allocated BDS: Supplier Batch number 3132585, Patheon code 102706

MabThera 500 mg (code 352519 - 363304) – Batch #B0001 - Minimum batch size

Batch size [L] to be considered for the calculation: 250 L

Rituximab Drug Substance, Intravenous (IV)

Allocated BDS: Supplier Batch number: 3132583 + 3132585, Patheon code 102706

ATTACHMENT 4: AQL – STATISTICAL CONTROL (AQL) FORM FOR VISUAL INSPECTION – MABTHERA 500 MG

Duplicate this attachment if necessary / Duplicare questo allegato se necessario

PRODUCT/PRODOTTO: MabThera 500mg CODE/CODICE:
BATCH NUMBER/N°LOTTO: SAMPLE SIZE (number of vial to be controlled)/ N°campioni da controllare

			Giorno 1 / Day 1			Giorno 2 / Day 2			Giorno 3 / Day 3		
Defect Difetto	**Type of defect Tipo di difetto**	**Category Categoria**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**
Chiusura / *Closure*	Flacone senza tappo / *Vial without stopper*	C									
	Flacone con tappo sbaglito (scambio-lyo vs liquido) / *Vial with wrong stopper (mixup – lyo vs liquid)*	C									
	Flacone senza ghiera / flip-off / *Vial without seal / flip-off*	C									
	Ghiera errata (mixup) / *Foreign seal (mixup)*	C									
	Flacone con flip-off/ghiera difettosi (tagliati, ammaccati, sporchi, danneggiati) / *Vial with defected flip-off/seal (scratched, dented, dirty, damaged)*	m									
	Ghiera posizionata male / ghiera non sigillante – non sigillata / *Seal with wrongly positioned/non-sealing seal – not crimped*	C									
	Ghiera posizionata male / ghiera non sigillante – parzialmente sigillata / *Seal with wrongly positioned/non-sealing seal – Partially crimped*	M									

			Giorno 1 / Day 1			**Giorno 2 / Day 2**			**Giorno 3 / Day 3**		
Defect **Difetto**	**Type of defect** **Tipo di difetto**	**Category** **Categoria**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**
Chiusura/closure	Flip-off parzialmente staccato (evidente) /*Partially detached flip-off (evident)*	m									
Contenitore / *Container*	Flacone con difetto di vetro (scheggiato – corpo, fondo) / *Vial with defected glass (chipped – body, bottom)*	M									
	Vial crepato (corpo, fondo) / *Cracked vial (body, bottom)*	C									
	Vetro sporco esternamente / *Dirty external glass*	m									
	Superficie del flacone graffiata (lunghezza > 1 cm, larghezza > 2mm) / *Surface scratch on vial body (length > 1 cm, width > 2 mm)*	m									
Prodotto / *Product*	Flacone vuoto / *Empty vial*	C									
	Flacone con vetro, particelle e corpi estranei in soluzione / *Vial with glass fragment, particles, foreign bodies in the solution*	C									
Data e sigla analista											

C: Critico/Critical M: Maggiore/Major m: Minore/Minor

Totale difetti Critici / Total quantity of critical defects (C): n° ……

Totale difetti Maggiori / Total quantity of major defects (M): n° ……..…

Totale difetti Minori / Total quantity of minor defects (m): n° ……

AQL acceptance criteria				
Single sampling plans for normal inspection – level III	**B.size: 1201-3200 S.size 200 ☐ (Equivalency with ISO Critical AQL 0.065)**		**B.size: 3201-10000 S.size 315 ☐ (Equivalency with ISO Critical AQL 0.040)**	
Difetti: AQL	**AC**	**AC**	**AC**	**RE**
C = 0	**0**	**0**	**0**	**1**
M 0.65	**3**	**4**	**5**	**6**
m 2.5	**10**	**11**	**14**	**15**
"Visible particulates in injection" testing as per USP <790> / ph.Eur 2.9.20				
Single sampling plans for normal inspection – level III	**B.size: 1201-3200 200 flaconi ☐**		**B.size: 3201-10000 315 flaconi ☐**	
Difetti: AQL	**AC**	**RE**	**AC**	**RE**
0.65	**3**	**4**	**5**	**6**

Result: **Conform [ ] / Not conform [ ]** **Result:** **Conform [ ] / Not conform [ ]**

QC Packaging Team Leader: ……..Date/Data: ……

QC Packaging Supervisor: ……..….. Date/Data:…….

ATTACHMENT 5: STATISTICAL CONTROL (AQL) FORM FOR VISUAL INSPECTION – MABTHERA 100 MG

Duplicate this attachment if necessary / Duplicare questo allegato se necessario

PRODUCT/PRODOTTO: MabThera 100mg CODE/CODICE:
BATCH NUMBER/N°LOTTO: SAMPLE SIZE (number of vial to be controlled)/ N°campioni da controllare

			Giorno 1 / Day 1			Giorno 2 / Day 2			Giorno 3 / Day 3		
Defect Difetto	**Type of defect Tipo di difetto**	**Category Categoria**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**	**1° shift 1° turno**	**2° shift 2° turno**	**3° shift 3° turno**
Chiusura / *Closure*	Flacone senza tappo / *Vial without stopper*	C									
	Flacone con tappo sbaglito (scambio-lyo vs liquido) / *Vial with wrong stopper (mixup – lyo vs liquid)*	C									
	Flacone senza ghiera / flip-off / *Vial without seal / flip-off*	C									
	Ghiera errata (mixup) / *Foreign seal (mixup)*	C									
	Flacone con flip-off/ghiera difettosi (tagliati, ammaccati, sporchi, danneggiati) / *Vial with defected flip-off/seal (scratched, dented, dirty, damaged)*	m									
	Ghiera posizionata male / ghiera non sigillante – non sigillata / *Seal with wrongly positioned/non-sealing seal – not crimped*	C									
	Ghiera posizionata male / ghiera non sigillante – parzialmente sigillata / *Seal with wrongly positioned/non-sealing seal – Partially crimped*	M									
	Flip-off parzialmente staccato (evidente) /*Partially detached flip-off (evident)*	m									
Contenitore / *Container*	Flacone con difetto di vetro (scheggiato – corpo, fondo) / *Vial with defected glass (chipped – body, bottom)*	M									

			Giorno 1 / Day 1			Giorno 2 / Day 2			Giorno 3 / Day 3		
Defect **Difetto**	**Type of defect** **Tipo di difetto**	**Category** **Categoria**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**	**1° shift** **1° turno**	**2° shift** **2° turno**	**3° shift** **3° turno**
	Vial crepato (corpo, fondo) / *Cracked vial (body, bottom)*	C									
Contenitore / *Container*	Vetro sporco esternamente / *Dirty external glass*	m									
	Superficie del flacone graffiata (lunghezza > 1 cm, larghezza > 2mm) / *Surface scratch on vial body (length > 1 cm, width > 2 mm)*	m									
Prodotto / *Product*	Flacone vuoto / *Empty vial*	C									
	Flacone con vetro, particelle e corpi estranei in soluzione / *Vial with glass fragment, particles, foreign bodies in the solution*	C									
Data e sigla analista											

C: Critico/Critical M: Maggiore/Major m: Minore/Minor

Totale difetti Critici / Total quantity of critical defects (C): n° ……

Totale difetti Maggiori / Total quantity of major defects (M): n° ……..…

Totale difetti Minori / Total quantity of minor defects (m): n° ……

AQL acceptance criteria						
Single sampling plans for normal inspection – level III	B.size: 3201-10000 S.size 315 ☐ (Equivalency with ISO Critical AQL 0.040)		B.size: 10001-35000 S.size 500 ☐ (Equivalency with ISO Critical AQL 0.025)		B.size: 35001150.000 S.size 800 ☐ (Equivalency with ISO Critical AQL0.015)	
Difetti: AQL	AC	RE	AC	RE	AC	RE
C = 0	0	1	0	1	0	1
M 0.65	5	6	7	8	10	11
m 2.5	14	15	21	22	21	22

"Visible particulates in injection" testing as per USP <790> / ph.Eur 2.9.20						
Single sampling plans for normal inspection – level II	B.size: 3201-10000 315 flaconi ☐		B.size: 10001-35000 500 flaconi ☐		B.size: 35001-150.000 S.size 800 ☐	
Difetti: AQL	AC	RE	AC	RE	AC	RE
0.65	5	6	7	8	10	11

Result: Conform [ ] / Not conform [ ] **Result: Conform [ ] / Not conform [ ]**

QC Packaging Team Leader: ……..Date/Data: ……

QC Packaging Supervisor:…….…. Date/Data:……

MODULO PER DISCREPANZE DI CONVALIDA
VALIDATION DISCREPANCY FORM

- Duplicare la presente pagina secondo necessità / Copy this page as necessary

Prodotto *Product*	**Step di produzione** *Manufacturing step*	**Prova n°** *Run n°*

Event Description:

Possible root cause:

Impact evaluation:

Corrective/Preventative action:

	Nome *Name*	Firma *Signature*	Data *Date*
SCRITTO DA *FILLED BY* (P&CV)			
RIVISTO DA *REVIEWED BY* (P&CV)			
APPROVATO DA *APPROVED BY* (MSAT Supervisor)			
APPROVATO DA *APPROVED BY* (Quality Systems and Compliance Sr Manager)			

ATTACHMENT 7

Roche's MEMO - Validation strategy for homogeneity mixing unit

Memo

Roche

To:	Laura Palmaroli (Patheon Monza, part of Thermo Fisher Scientific)	Copies:	Vanessa Cervi (Roche), Operations Manager Shrinivas Tata (Roche) Quality Manager
From:	Costanza Ciaponi Global MSAT	Roche	
Date:	27 October 2022		

Validation strategy for homogeneity in mixing unit: Compliance to Roche and Health Authorities Guidelines

Scope

This memo serves as integration to Process Validation Protocol P800AB01 "MabThera 100mg/10mL and MabThera 500mg/50mL, Sterile Area 6" to support and justify the validation approach adopted for the homogeneity assessment of the bulk at the end of the compounding operations, for the manufacturing process to be transferred in Patheon Monza, part of Thermo Fisher Scientific.

To demonstrate the homogeneity at the end the compounding operation the following bulk homogeneity studies are considered suitable:

- One Surrogate study performed at maximum batch size (TT237D011);
- One Mabthera and one Avastin Engineering run performed at minimum batch size (for MabThera TT237C011, for Avastin TBD);
- One Mabthera and one Avastin PPQ batch performed at maximum batch size (for MabThera P800AB01, for Avastin TBD) ;
- One Mabthera and one Avastin PPQ batch performed at minimum batch size (for MabThera P800AB01, for Avastin TBD).

Note: Two MabThera and Avstin drug product configurations (MabThera 100mg/10mL vial and MabThera 500mg/50mL vial, Avastin 100mg/4ml and Avastin 400mg/16ml) are being transferred to Patheon Monza, part of Thermo Fisher Scientific. The compounding and mixing steps are the same for both configurations of the two products (TTP23701). Following Avastin engineering run and PPQ batches manufacturing, in case of any significant modification to the mixing processing parameters, the present Memo will be revisited.

1/3

Validation strategy for homogeneity in mixing unit: Compliance to Roche and Health Authorities Guidelines

Roche

Justification of the validation approach for bulk homogeneity of Mabthera and Avastin at Patheon Monza, part of Thermo Fisher Scientific.

The validation strategy adopted and described in Process Validation Protocol P800AB01 is compliant to Roche and Health Authorities guidelines as per what reported below.

Roche References

- According to Roche TEC-0132616 (Risk Ranking Report for Mixing Unit Operation) mixing homogeneity is volume dependent. For a given mixing time and speed, the average applied mixing energy per volume is lower for a high product volume in the vessel. For homogeneity study, shortest mixing time should be done at lowest mixing speed and maximum product volume in vessel. The conditions detailed in Roche TEC-0132616 are satisfied by the validation approach described in the Scope paragraph of the present memo.

- According to Roche TEC-0132616 (Risk Ranking Report for Mixing Unit Operation) a surrogate with representative formulation characteristics can be used. In case mixing of two solutions (e.g. dilution of concentrated drug substance with formulation buffer) the impact of density ratio needs to be assessed. If surrogate solutions are used, the density ratio should match or exceed the density ratio of the drug substance and the formulation buffer in case the density ratio is higher than 1.08. This conditions from Roche TEC-0132616 is fulfilled by the surrogate study as explained in the Roche memo "Avastin and Mabthera: Usage of surrogate for mixing trial" provided on 10 December 2021.

- According to Roche MSC-0101933 (Guidance for Process Performance Qualification (PPQ) Batch Bracketing for Roche Drug Product Network) to study the impact of batch size, small-scale studies and/or at-scale studies are performed. Successful completion of these studies demonstrate that operating within the defined batch size ranges has no impact on the product or the process and is therefore acceptable. Therefore, bracketing using one batch at the minimum batch size and one batch at the maximum batch size during PPQ is used for verification. This condition from Roche MSC-0101933 is confirmed with the bracketed approach described in the Scope paragraph of the present memo.

- According to Roche MSC-0104684 "Best Practice for the Justification and Documentation of Expected Number of Batch/Study Replicates Supporting Process Validation for Biologics DS and DP Mixing, Freeze/Thaw and Refiltration Unit Operations" performing a single replicate of process design studies may be justified as test conditions are worst case relative to the target used during routine manufacturing. PPQ batches produced at target may be used to further confirm that there is indeed no impact on CQAs. This condition from Roche MSC-0104684 is fully supported by the bracketed approach described in the Scope paragraph of the present memo.

Roche

2/3

Health Authorities Guidelines

- According to EMA Guidelines for process validation of finished products, EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1, Effective Nov. 2016: "The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. A bracketing approach may be acceptable for different strengths, batch sizes and pack sizes" A bracketing approach is defined as "A validation scheme / protocol designed such that only batches on the extremes of certain predetermined and justified design factors, e.g., strength, batch size, pack size are tested during process validation. The design assumes that validation of any intermediate levels is represented by the validation of the extremes". The bracketed approach described in the Scope paragraph of the present memo is compliant to the EMA Guidelines for process validation of finished products.

- According to FDA guidance for Industry "Process Validation: General Principles and Practices", 2011: "it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data. Previous credible experience with sufficiently similar products and processes can also be helpful". Specific studies may be executed to define the acceptable parameter ranges for the process and to justify worst case conditions for PPQ batch bracketing. The bracketed approach described in the Scope paragraph of the present memo is compliant to the FDA guideline "Process Validation: General Principles and Practices".

Sincerely,

DocuSigned by:
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Signing Reason: I am the author of this document
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ATTACHMENT 8

Roche's MEMO – PPQ bracketing approach

Memo

Roche

To:	Karin Russo Giovanni Di Lemma Silvia Redaelli (**Patheon Monza**)	Copies: Laura Palmaroli, Paola Marzorati, Mattia Pegoraro (**Patheon Monza**)
From:	Hossam Farouk Vanessa Cervi Edith Vernier	**F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel**
Date:	05 March 2021	

Avastin and Mabthera PPQ/Engineering bracketing approach

In light of the current preparations to transfer the manufacturing processes of Avastin and Mabthera from Roche Mannheim to Patheon Monza, we would like to confirm that the below PPQ bracketing approach and the proposed engineering runs are fully in line with Roche's product specific knowledge, Roche regulatory guidelines and similar transfers performed for the same products.

The proposed approach was prepared by Roche SMEs and reviewed by Roche's Quality and Technical regulatory experts. The bracketing approach considers two variables: the multiple configurations using packaging materials of the same type (glass vials) and the batch size range.

Regarding the packaging material configuration, the bracketing is primarily governed by the fill volume: lowest fill volume is considered worst case regarding potential leachables from the rubber stopper and glass (volume to surface ratio).
Regarding the Batch size, please note that according to previous validation studies performed at Roche Mannheim for the same products, the batch size had no negative influence on the product quality (VAL-0126370 and VAL-0123449). The batch size impact should be evaluated as part of process design, consequently both of the variables should be seen as independent variables.

PPQ Approach

PPQ	Avastin		Mabthera	
	Presentation	**Batch Size**	**Presentation**	**Batch Size**
PPQ1	100mg/4mL 6mL vial	Min	100mg/10mL 10mL vial	Min
PPQ2	100mg/4mL 6mL vial	Min	100mg/10mL 10mL vial	Min
PPQ3 (Maximum vial amount)	100mg/4mL 6mL vial	Max	100mg/10mL 10mL vial	Max
PPQ4	400mg/16mL 20mL vial	Min	500mg/50mL 50mL vial	Min

1/2

Supporting Characterization studies

Run type	Material	Number of runs	Size	Fill duration	Study/Challenges	Rational
PQ FT skid	Surrogate	tbd	max	NA	Completion of thaw/freeze	-Max vessel volume is worst-case for obtaining fully frozen/thawed and homogenous solution -Placebo shows similar F/T behaviors like active
PQ mixing tank	Surrogate	1 per mixing equipment and mixing process type	Covering batch size range	NA	Definition of acceptable mixing conditions (e.g., agitation speed, mixing durations, and product volumes)	Study should cover the batch size range to show visible movement of the fluid surface without splashing and foaming
			max	NA	Mixing homogeneity	-Worst-case process parameter conditions for homogeneity: lowest mixing speed, shortest mixing time at maximum vessel volume -Suitable surrogate taking into account mixing type (e.g., mixing of DS of similar product concentration and viscosity, mixing of bulk drug substance and formulation buffer, mixing of solid into liquid)
PQ filling line	Water/ Surrogate	per Patheon's qualification concept	max	max	Manufacturability Fill accuracy Tubing fatigue	-Vial type/size specific -Max fill is worst-case for tubing fatigue -Not product specific
ER	Product	1 (split fill with format part change)	min	NA	-Fill accuracy / Fill interruption -Maximum filtration pressure -Filter/Line flush -H2O2 uptake -Mixing stress	-Batch size is independent of the list of parameters listed to be challenged at the filling step -Minimum volume is worst-case for potential sheared product per volume due to mixing

The above approach may also be adapted according to the outcome of the ongoing process gap assessment and the related characterization studies.

Sincerely,

Hossam Farouk
Operations Site Manager
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Vanessa Cervi
Quality Site Manager
05MAR21

Edith Vernier
Global Process Scientist
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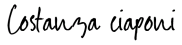
Costanza ciaponi costanza.ciaponi@roche.com Global Project Manager (Global MSAT, PTT) F. Hoffmann-La Roche Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: DA4D026D-7C6A-474B-99B3-E4D0679C5B4D Using IP Address: 151.50.122.116 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/29/2023 3:21:23 AM Viewed: 3/29/2023 3:21:46 AM Signed: 3/29/2023 3:22:30 AM
Electronic Record and Signature Disclosure: Accepted: 8/17/2021 12:51:56 AM ID: 32be3e1a-7a3d-4e5d-b7f4-669d378c772a Company Name: F.Hoffmann-La Roche Ltd. - CFR Part 11 - Sub 2		
shrinivas tata shrinivas.tata@roche.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: BA4B6485-229D-4B89-A4AB-5FAD68D525C5 Using IP Address: 196.3.50.248 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/29/2023 3:22:51 AM Viewed: 3/29/2023 3:32:47 AM Signed: 3/29/2023 3:42:03 AM
Electronic Record and Signature Disclosure: Accepted: 2/5/2021 9:05:56 AM ID: 473a9f2a-a765-4aab-9683-9a9f7f987c0b Company Name: F.Hoffmann-La Roche Ltd. - CFR Part 11 - Sub 2		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/29/2023 3:21:23 AM
Certified Delivered	Security Checked	3/29/2023 3:32:47 AM
Signing Complete	Security Checked	3/29/2023 3:42:03 AM
Completed	Security Checked	3/29/2023 3:42:03 AM

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