PROJECT: MAB-X CLINIC

IOM REPORT - OUTPUT-INPUT RISK ANALYSIS

Project Information

Product Type : Drug **TRL :** 3 **Sprint :** 1

Abstract :

mAb-X is a humanized IgG1 monoclonal antibody targeting the interleukin-2 receptor ?-chain (CD25) to inhibit T-cell activation and prevent allograft rejection. Early clinical evaluation in renal transplant recipients shows good tolerability and a dose-dependent reduction in activated lymphocytes. The antibody is administered intravenously every two weeks and demonstrates a favorable pharmacokinetic profile with sustained receptor occupancy. Ongoing studies aim to confirm its efficacy and safety in broader transplant populations.

No questions recorded for this sprint.

Start Date : 2025-11-03 **End Date :** 2026-07-24

Manager

Pr. Thierry Bastogne
julie D

Contributors

François RAGOT
Yasmine Massali
TBgmail

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Unit 1: UPSTREAM

Steps:

Step 1.1: Cryovials in Liquid Nitrogen

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Cell viability after thawing	>90%
Identity test	STR profiling or antibody expression marker
Mycoplasma testing	*No specification*
Sterility test	*No specification*
Record of freezing/thawing cycle	traceability

Step 1.2: Cell Revival

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification

Cell count and viability	Trypan Blue or automated cell counter
pH and osmolality of the medium	*No specification*
Glucose and lactate levels	*No specification*
Microscopic observation	morphology, contamination check

Step 1.3: Inoculum Preparation

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Viable cell density	target range before transfer
Metabolite monitoring	glucose, glutamine, lactate, ammonia
Osmolality	*No specification*
Cell morphology	microscopy
Absence of contamination	visual or rapid tests

Step 1.4: Bioreactor Production

Material Attributes:

- Feed composition
- Basal medium quality
- Bioreactor type

Performance Parameters:

- pH
- Aeration rate & Oxygen flowrate
- Feeding mode
- Feed rate and schedule
- Culture duration
- Headspace pressure of the bioreactor
- Agitation speed
- Temperature
- Flowrate of surface air

In-Process Controls (Step)

IPC Name	Specification
pH, temperature, DO	real-time probes
Viable cell density and viability	Daily sampling - From Output
Glucose, lactate, glutamine, ammonia concentration	*No specification*
Product titer	ELISA or HPLC for monitoring yield
Agitation speed and aeration rate	Mesures des vraies grandeurs physiques dans le bioréacteur - From Output
CO? and O? gas flow rates	*No specification*

Step 1.5: Centrifugation

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Supernatant turbidity or optical density (clarity check)	clarity check
Temperature monitoring	*No specification*
Volume recovery yield	*No specification*

Step 1.6: Depth Filtration

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Differential pressure across the filter	*No specification*
Filtration flow rate	*No specification*
Conductivity and pH of filtrate	*No specification*

In-Process Controls (IPCs)

IPC Name	Specification	Step
Cell viability after thawing	>90%	Cryovials in Liquid Nitrogen

IPC Name	Specification	Step
Identity test	STR profiling or antibody expression marker	Cryovials in Liquid Nitrogen
Mycoplasma testing	*No specification*	Cryovials in Liquid Nitrogen
Sterility test	*No specification*	Cryovials in Liquid Nitrogen
Record of freezing/thawing cycle	traceability	Cryovials in Liquid Nitrogen
Cell count and viability	Trypan Blue or automated cell counter	Cell Revival
pH and osmolality of the medium	*No specification*	Cell Revival
Glucose and lactate levels	*No specification*	Cell Revival
Microscopic observation	morphology, contamination check	Cell Revival
Viable cell density	target range before transfer	Inoculum Preparation
Metabolite monitoring	glucose, glutamine, lactate, ammonia	Inoculum Preparation
Osmolality	*No specification*	Inoculum Preparation
Cell morphology	microscopy	Inoculum Preparation
Absence of contamination	visual or rapid tests	Inoculum Preparation
pH, temperature, DO	real-time probes	Bioreactor Production
Viable cell density and viability	Daily sampling - From Output	Bioreactor Production
Glucose, lactate, glutamine, ammonia concentration	*No specification*	Bioreactor Production
Product titer	ELISA or HPLC for monitoring yield	Bioreactor Production
Agitation speed and aeration rate	Mesures des vraies grandeurs physiques dans le bioréacteur - From Output	Bioreactor Production

IPC Name	Specification	Step
CO? and O? gas flow rates	*No specification*	Bioreactor Production
Supernatant turbidity or optical density (clarity check)	clarity check	Centrifugation
Temperature monitoring	*No specification*	Centrifugation
Volume recovery yield	*No specification*	Centrifugation
Differential pressure across the filter	*No specification*	Depth Filtration
Filtration flow rate	*No specification*	Depth Filtration
Conductivity and pH of filtrate	*No specification*	Depth Filtration
DO	Dissolved oxygen measured in real time - From Output	*No step*

Unit 2: DOWNSTREAM

Steps:

Step 2.1: Capture Chromatography

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
UV absorbance (280 nm) to monitor elution peak	*No specification*
Protein concentration in load and eluate	*No specification*

IPC Name	Specification
Pressure drop across the column	*No specification*

Step 2.2: Viral Inactivation

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
pH measurement and control during inactivation	*No specification*
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*

Step 2.3: Intermediate Chromatography

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
UV absorbance during elution	*No specification*
Conductivity and pH monitoring	*No specification*
Pressure drop across the column	*No specification*

Step 2.4: Polishing Chromatography

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
UV absorbance (protein peak separation)	*No specification*
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*
Conductivity and pressure	*No specification*
Yield and concentration	*No specification*

Step 2.5: Viral Filtration

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Differential pressure (?P) across filter	*No specification*
Filtrate turbidity and clarity	*No specification*
Filtrate flow rate	*No specification*
Filter integrity test (before/after run)	*No specification*

Step 2.6: Concentration / Diafiltration (TFF)

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Permeate and retentate flow rates	*No specification*
TMP monitoring	*No specification*
Protein concentration (UV, BCA)	*No specification*
Conductivity and pH (to confirm buffer exchange)	*No specification*

Step 2.7: Sterile Filtration (0.22 µm)

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Filter integrity test	*No specification*
Filtration pressure and time	*No specification*
Protein concentration and yield	*No specification*

In-Process Controls (IPCs)

IPC Name	Specification	Step
UV absorbance (280 nm) to monitor elution peak	*No specification*	Capture Chromatography

IPC Name	Specification	Step
Protein concentration in load and eluate	*No specification*	Capture Chromatography
Pressure drop across the column	*No specification*	Capture Chromatography
pH measurement and control during inactivation	*No specification*	Viral Inactivation
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*	Viral Inactivation
UV absorbance during elution	*No specification*	Intermediate Chromatography
Conductivity and pH monitoring	*No specification*	Intermediate Chromatography
Pressure drop across the column	*No specification*	Intermediate Chromatography
UV absorbance (protein peak separation)	*No specification*	Polishing Chromatography
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*	Polishing Chromatography
Conductivity and pressure	*No specification*	Polishing Chromatography
Yield and concentration	*No specification*	Polishing Chromatography
Differential pressure (?P) across filter	*No specification*	Viral Filtration
Filtrate turbidity and clarity	*No specification*	Viral Filtration
Filtrate flow rate	*No specification*	Viral Filtration
Filter integrity test (before/after run)	*No specification*	Viral Filtration
Permeate and retentate flow rates	*No specification*	Concentration / Diafiltration (TFF)

IPC Name	Specification	Step
TMP monitoring	*No specification*	Concentration / Diafiltration (TFF)
Protein concentration (UV, BCA)	*No specification*	Concentration / Diafiltration (TFF)
Conductivity and pH (to confirm buffer exchange)	*No specification*	Concentration / Diafiltration (TFF)
Filter integrity test	*No specification*	Sterile Filtration (0.22 µm)
Filtration pressure and time	*No specification*	Sterile Filtration (0.22 µm)
Protein concentration and yield	*No specification*	Sterile Filtration (0.22 µm)

Unit 3: Fill & Finish

Steps:

Step 3.1: Formulation & Sterile Filtration

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Filter integrity test	pre- and post-use
Protein concentration (UV or HPLC)	*No specification*
Sterility testing (aseptic assurance)	*No specification*

Step 3.2: Filling

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Sterility and cleanliness of components	*No specification*
In-line weight check or volume control	fill weight verification
Container closure integrity testing (CCIT)	*No specification*
Sterility and aseptic process simulation (media fill)	*No specification*

Step 3.3: Quality Control & Packaging

Material Attributes:

No Material Attributes available

Performance Parameters:

No Performance Parameters available

In-Process Controls (Step)

IPC Name	Specification
Visual inspection of all units	*No specification*
Label verification (OCR/barcode scan)	*No specification*
Stability sampling	*No specification*

In-Process Controls (IPCs)

IPC Name	Specification	Step

Filter integrity test	pre- and post-use	Formulation & Sterile Filtration
Protein concentration (UV or HPLC)	*No specification*	Formulation & Sterile Filtration
Sterility testing (aseptic assurance)	*No specification*	Formulation & Sterile Filtration
Sterility and cleanliness of components	*No specification*	Filling
In-line weight check or volume control	fill weight verification	Filling
Container closure integrity testing (CCIT)	*No specification*	Filling
Sterility and aseptic process simulation (media fill)	*No specification*	Filling
Visual inspection of all units	*No specification*	Quality Control & Packaging
Label verification (OCR/barcode scan)	*No specification*	Quality Control & Packaging
Stability sampling	*No specification*	Quality Control & Packaging

In-Process Controls (IPCs)

Unit 1 : UPSTREAM

IPC Name	Specification	Step
Cell viability after thawing	>90%	Cryovials in Liquid Nitrogen
Identity test	STR profiling or antibody expression marker	Cryovials in Liquid Nitrogen

IPC Name	Specification	Step
Mycoplasma testing	*No specification*	Cryovials in Liquid Nitrogen
Sterility test	*No specification*	Cryovials in Liquid Nitrogen
Record of freezing/thawing cycle	traceability	Cryovials in Liquid Nitrogen
Cell count and viability	Trypan Blue or automated cell counter	Cell Revival
pH and osmolality of the medium	*No specification*	Cell Revival
Glucose and lactate levels	*No specification*	Cell Revival
Microscopic observation	morphology, contamination check	Cell Revival
Viable cell density	target range before transfer	Inoculum Preparation
Metabolite monitoring	glucose, glutamine, lactate, ammonia	Inoculum Preparation
Osmolality	*No specification*	Inoculum Preparation
Cell morphology	microscopy	Inoculum Preparation
Absence of contamination	visual or rapid tests	Inoculum Preparation
pH, temperature, DO	real-time probes	Bioreactor Production
Viable cell density and viability	Daily sampling - From Output	Bioreactor Production
Glucose, lactate, glutamine, ammonia concentration	*No specification*	Bioreactor Production
Product titer	ELISA or HPLC for monitoring yield	Bioreactor Production
Agitation speed and aeration rate	Mesures des vraies grandeurs physiques dans le bioréacteur - From Output	Bioreactor Production
CO? and O? gas flow rates	*No specification*	Bioreactor Production

IPC Name	Specification	Step
Supernatant turbidity or optical density (clarity check)	clarity check	Centrifugation
Temperature monitoring	*No specification*	Centrifugation
Volume recovery yield	*No specification*	Centrifugation
Differential pressure across the filter	*No specification*	Depth Filtration
Filtration flow rate	*No specification*	Depth Filtration
Conductivity and pH of filtrate	*No specification*	Depth Filtration
DO	Dissolved oxygen measured in real time - From Output	*No step*

Unit 2 : DOWNSTREAM

IPC Name	Specification	Step
UV absorbance (280 nm) to monitor elution peak	*No specification*	Capture Chromatography
Protein concentration in load and eluate	*No specification*	Capture Chromatography
Pressure drop across the column	*No specification*	Capture Chromatography
pH measurement and control during inactivation	*No specification*	Viral Inactivation
Product integrity (via HPLC or UV absorbance) after neutralization	*No specification*	Viral Inactivation
UV absorbance during elution	*No specification*	Intermediate Chromatography

IPC Name	Specification	Step
Conductivity and pH monitoring	*No specification*	Intermediate Chromatography
Pressure drop across the column	*No specification*	Intermediate Chromatography
UV absorbance (protein peak separation)	*No specification*	Polishing Chromatography
Product purity (SDS-PAGE, SEC-HPLC)	*No specification*	Polishing Chromatography
Conductivity and pressure	*No specification*	Polishing Chromatography
Yield and concentration	*No specification*	Polishing Chromatography
Differential pressure (?P) across filter	*No specification*	Viral Filtration
Filtrate turbidity and clarity	*No specification*	Viral Filtration
Filtrate flow rate	*No specification*	Viral Filtration
Filter integrity test (before/after run)	*No specification*	Viral Filtration
Permeate and retentate flow rates	*No specification*	Concentration / Diafiltration (TFF)
TMP monitoring	*No specification*	Concentration / Diafiltration (TFF)
Protein concentration (UV, BCA)	*No specification*	Concentration / Diafiltration (TFF)
Conductivity and pH (to confirm buffer exchange)	*No specification*	Concentration / Diafiltration (TFF)
Filter integrity test	*No specification*	Sterile Filtration (0.22 µm)
Filtration pressure and time	*No specification*	Sterile Filtration (0.22 µm)

IPC Name	Specification	Step
Protein concentration and yield	*No specification*	Sterile Filtration (0.22 µm)

Unit 3 : Fill & Finish

IPC Name	Specification	Step
Filter integrity test	pre- and post-use	Formulation & Sterile Filtration
Protein concentration (UV or HPLC)	*No specification*	Formulation & Sterile Filtration
Sterility testing (aseptic assurance)	*No specification*	Formulation & Sterile Filtration
Sterility and cleanliness of components	*No specification*	Filling
In-line weight check or volume control	fill weight verification	Filling
Container closure integrity testing (CCIT)	*No specification*	Filling
Sterility and aseptic process simulation (media fill)	*No specification*	Filling
Visual inspection of all units	*No specification*	Quality Control & Packaging
Label verification (OCR/barcode scan)	*No specification*	Quality Control & Packaging
Stability sampling	*No specification*	Quality Control & Packaging

FMECA Analysis :

Scoring Matrix

The scoring matrix is based on the combination of **Uncertainty** and **Severity**.
Higher values indicate a higher impact and risk.
Threshold Low (9) is highlighted in **green**, and Threshold High (25) is highlighted in **red**.

UNCERTAINTY	SEVERITY			
	1	3	10	25
1	1	3	10	25
2	2	6	20	50
3	3	9	30	75
4	4	12	40	100
5	5	15	50	125

Interpretation of the Scoring Matrix

The scoring matrix helps assess the risk associated with different combinations of **Severity** and **Uncertainty**. Below is an explanation of what each combination means:

Severity	Uncertainty	Interpretation
Direct Impact (25)	Limited Data (4)	This combination indicates a **critical risk**. The severity is high, meaning the issue has a major impact on product quality. Since there is limited data, further investigations are needed to mitigate the risk.
Moderate Impact (10)	Clinical Data Available (2)	A **moderate risk** level. The impact exists, but available clinical data provides confidence in product performance. Regular monitoring is still recommended.
Low Impact (3)	Regulatory Data (1)	A **low-risk scenario**. The process is well-controlled and backed by regulatory data. No immediate concerns, but ongoing verification is advised.

FMECA Analysis for mAb-X clinic

OUTPUT NAME	UNIT	STEP	RISK DEFINITION	IMPACTED CATEGORY	SEVERITY	JUSTIFICATIONS	UNCERTAINTY	JUSTIFICATIONS	RPN
Viable cell density and viability	UPSTREAM	Bioreactor Production	*N/A*	Quality	**Direct impact**	*N/A*	**supportive data from clinical studies with this product or similar ones**	*N/A*	50
Glucose, lactate, glutamine, ammonia concentration	UPSTREAM	Bioreactor Production	*N/A*	Quality	**Moderate or indirect impact**	*N/A*	**supportive data from clinical studies with this product or similar ones**	*N/A*	20
Product titer	UPSTREAM	Bioreactor Production	*N/A*	Efficacy	**Direct impact**	*N/A*	**supportive data from clinical studies with this product or similar ones**	*N/A*	50

OUTPUT NAME	UNIT	STEP	RISK DEFINITION	IMPACTED CATEGORY	SEVERITY	JUSTIFICATIONS	UNCERTAINTY	JUSTIFICATIONS	RPN
DO	UPSTREAM	Bioreactor Production	Event causing hypoxia and hyperoxia	Quality	**Moderate or indirect impact**	Hypoxia (Low DO): Reduced cell growth and viability due to insufficient oxygen for cellular respiration. Hyperoxia (High DO): Oxidative stress: Excess oxygen can generate reactive oxygen species (ROS), damaging cells and reducing viability. DO fluctuations can alter the glycosylation pattern of mAbs, affecting effector functions	**supportive data from clinical studies with this product or similar ones**	*N/A*	20

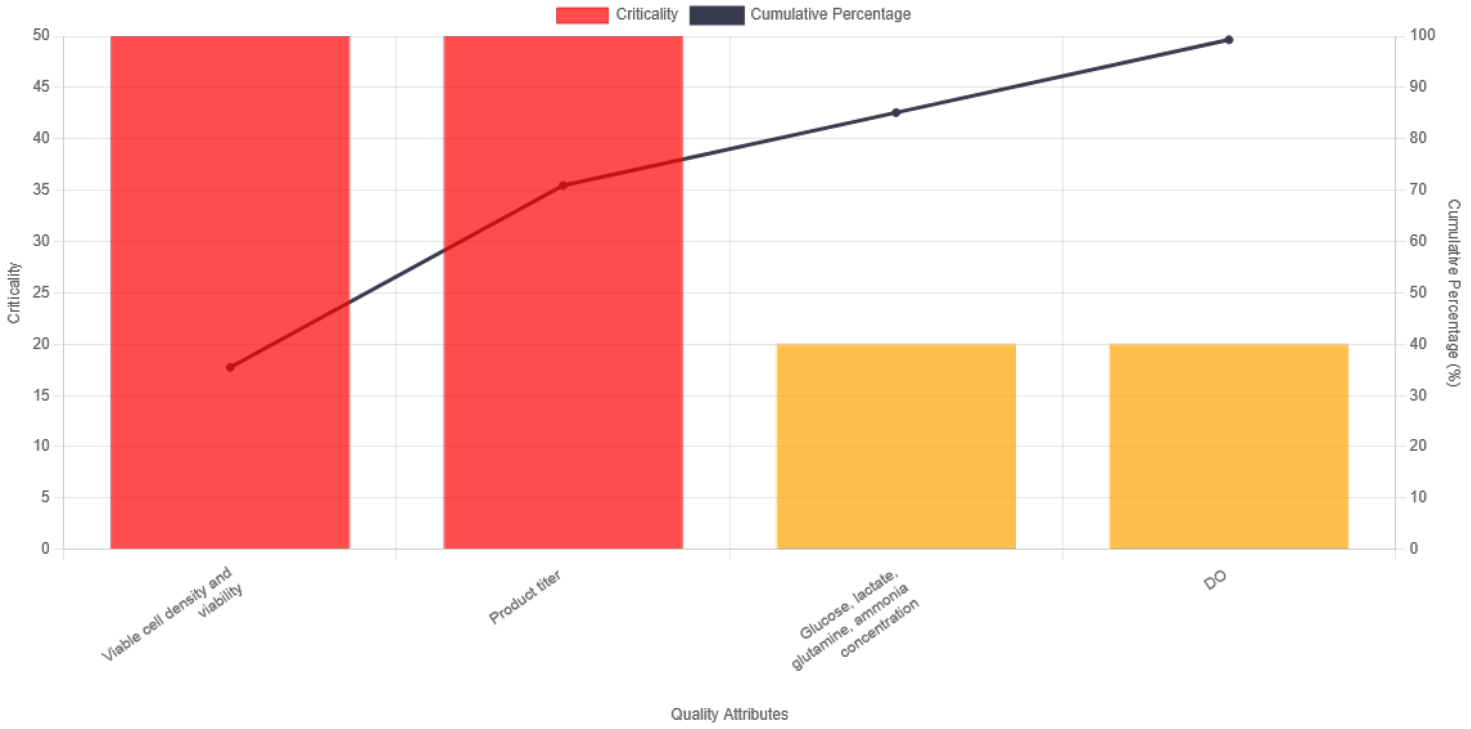
Process Analytical Technology (PAT) for mAb-X clinic

OUTPUT NAME	PROCESS ANALYTICAL TECHNOLOGY	TYPE	TIMING MEASUREMENT	SPECIFICATION (TARGET)	ANALYTICAL PROCEDURES	COMMENT	PROCESS IMPROVEMENTS via PAT
Viable cell density and viability	*No PAT available*	*N/A*	*N/A*	*N/A*	***No Analytical Procedures defined***	*N/A*	*N/A*
Glucose, lactate, glutamine, ammonia concentration	*No PAT available*	*N/A*	*N/A*	*N/A*	***No Analytical Procedures defined***	*N/A*	*N/A*
Product titer	*No PAT available*	*N/A*	*N/A*	*N/A*	***No Analytical Procedures defined***	*N/A*	*N/A*
DO	*No PAT available*	*N/A*	*N/A*	*N/A*	***No Analytical Procedures defined***	*N/A*	*N/A*

FMECA Results Interpretation

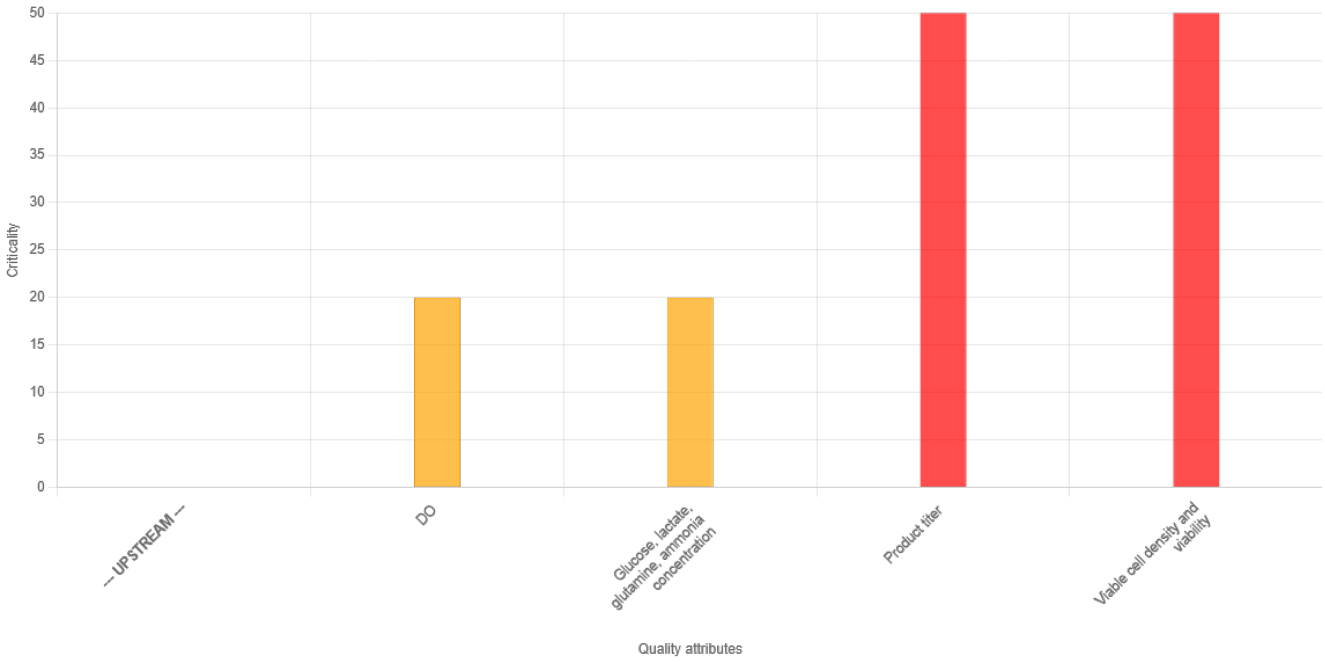
Criticality Analysis : Pareto Diagram

High Criticality Threshold : 25 **Low Criticality Threshold : 9**



Criticality Analysis : Histogram

High Criticality Threshold : 25 **Low Criticality Threshold : 9**

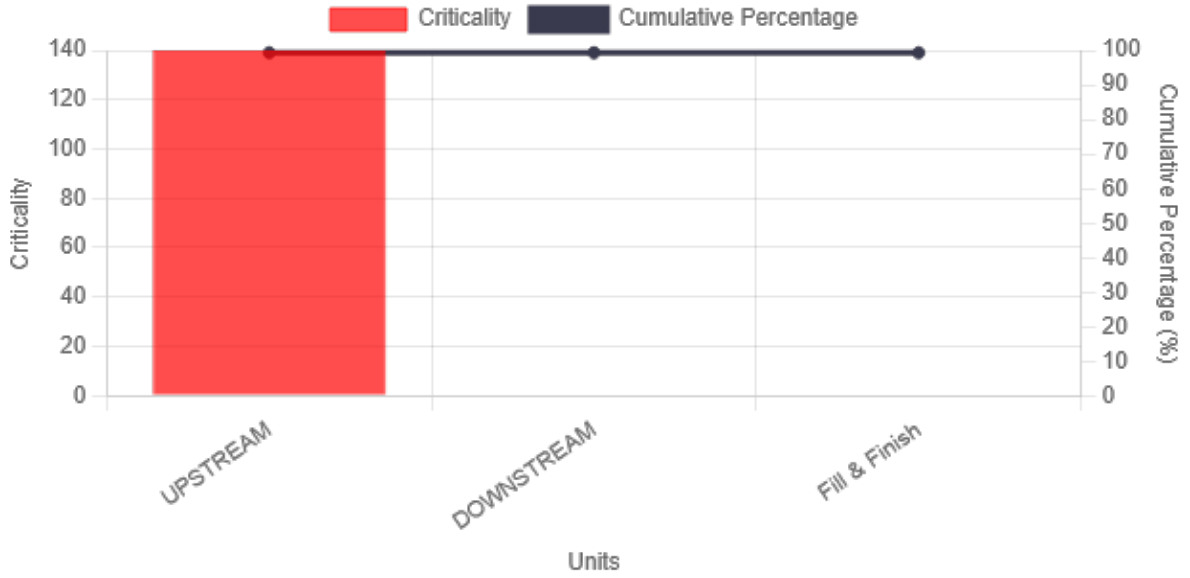


Critical Step Identification for project mAb-X clinic

High Criticality Threshold : 25
Low Criticality Threshold : 9

Project Units	Total Criticality
UPSTREAM	140
DOWNSTREAM	0
Fill & Finish	0

Criticality Analysis for Project



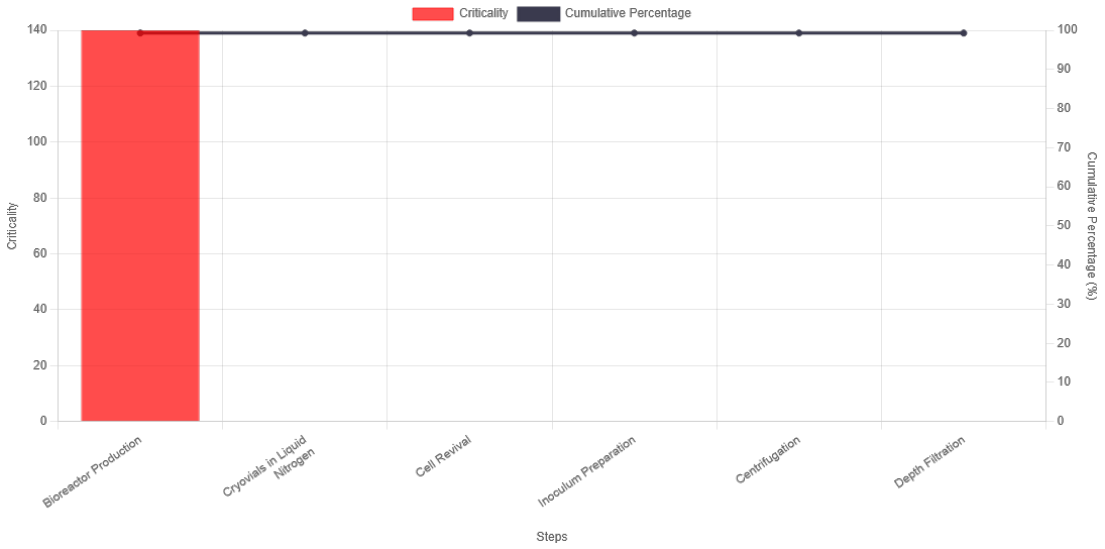
Critical Step Identification per Unit

Unit Name: UPSTREAM
Total Criticality of the Unit: 140

High Criticality Threshold : 25
Low Criticality Threshold : 9

Step Name	Total Criticality
Cryovials in Liquid Nitrogen	0
Cell Revival	0
Inoculum Preparation	0
Bioreactor Production	140
Centrifugation	0
Depth Filtration	0

Criticality Analysis for Selected Unit



Unit Name: DOWNSTREAM
Total Criticality of the Unit: 0

High Criticality Threshold : 25
Low Criticality Threshold : 9

Step Name	Total Criticality
Capture Chromatography	0
Viral Inactivation	0
Intermediate Chromatography	0
Polishing Chromatography	0
Viral Filtration	0
Concentration / Diafiltration (TFF)	0
Sterile Filtration (0.22 µm)	0

Criticality Analysis for Selected Unit

Pareto Diagram step/unit

Unit Name: Fill & Finish
Total Criticality of the Unit: 0

High Criticality Threshold : 25
Low Criticality Threshold : 9

Step Name	Total Criticality
Formulation & Sterile Filtration	0
Filling	0

Step Name	Total Criticality
Quality Control & Packaging	0

Criticality Analysis for Selected Unit

Pareto Diagram step/unit

Inputs Informations :

Process Parameters

INPUT NAME	UNIT	STEP	COMMENT
pH	UPSTREAM	Bioreactor Production	*N/A*
Aeration rate & Oxygen flowrate	UPSTREAM	Bioreactor Production	DO*=30% NOR=[10;100]%
Feeding mode	UPSTREAM	Bioreactor Production	(batch, fed-batch, perfusion). Finally--> fed-batch (bolus)
Feed rate and schedule	UPSTREAM	Bioreactor Production	J3, J6
Culture duration	UPSTREAM	Bioreactor Production	Récolte à J10
Headspace pressure of the bioreactor	UPSTREAM	Bioreactor Production	(bar)
Agitation speed	UPSTREAM	Bioreactor Production	(rpm)
Temperature	UPSTREAM	Bioreactor Production	(°C)
Flowrate of surface air	UPSTREAM	Bioreactor Production	To control the amount of foam on the surface. (NL/min), NL=Normo-Litres

Material Attributes

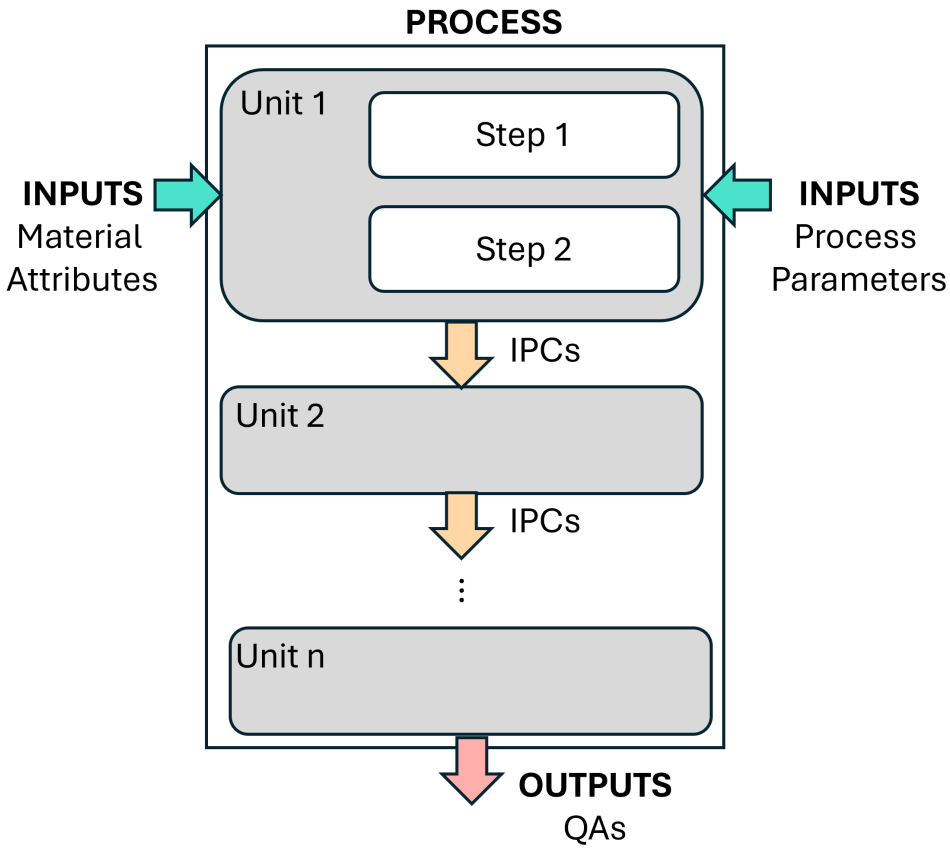
INPUT NAME	UNIT	STEP	COMMENT
Feed composition	UPSTREAM	Bioreactor Production	Nutrients, glucose, amino acids, etc. Finally, only glucose.
Basal medium quality	UPSTREAM	Bioreactor Production	Composition of the initial medium (standard)
Bioreactor type	UPSTREAM	Bioreactor Production	(glass, single-use)

Cause/Effect Matrix

The Cause/Effect Matrix helps identify relationships between inputs and outputs in the manufacturing process. It highlights critical factors influencing product quality, performance and safety. The table below summarizes key parameters that will be analyzed in the upcoming section.

- Identification of key process inputs
- Correlation between inputs and outputs
- Risk prioritization for process optimization

Input	Impact on Process	Output
Material Attributes	Critical for drug stability	Dissolution profile, potency
Process Parameters	Influence on bioavailability	Tablet hardness, weight uniformity
Material Attributes	Critical for drug stability	Dissolution profile, potency



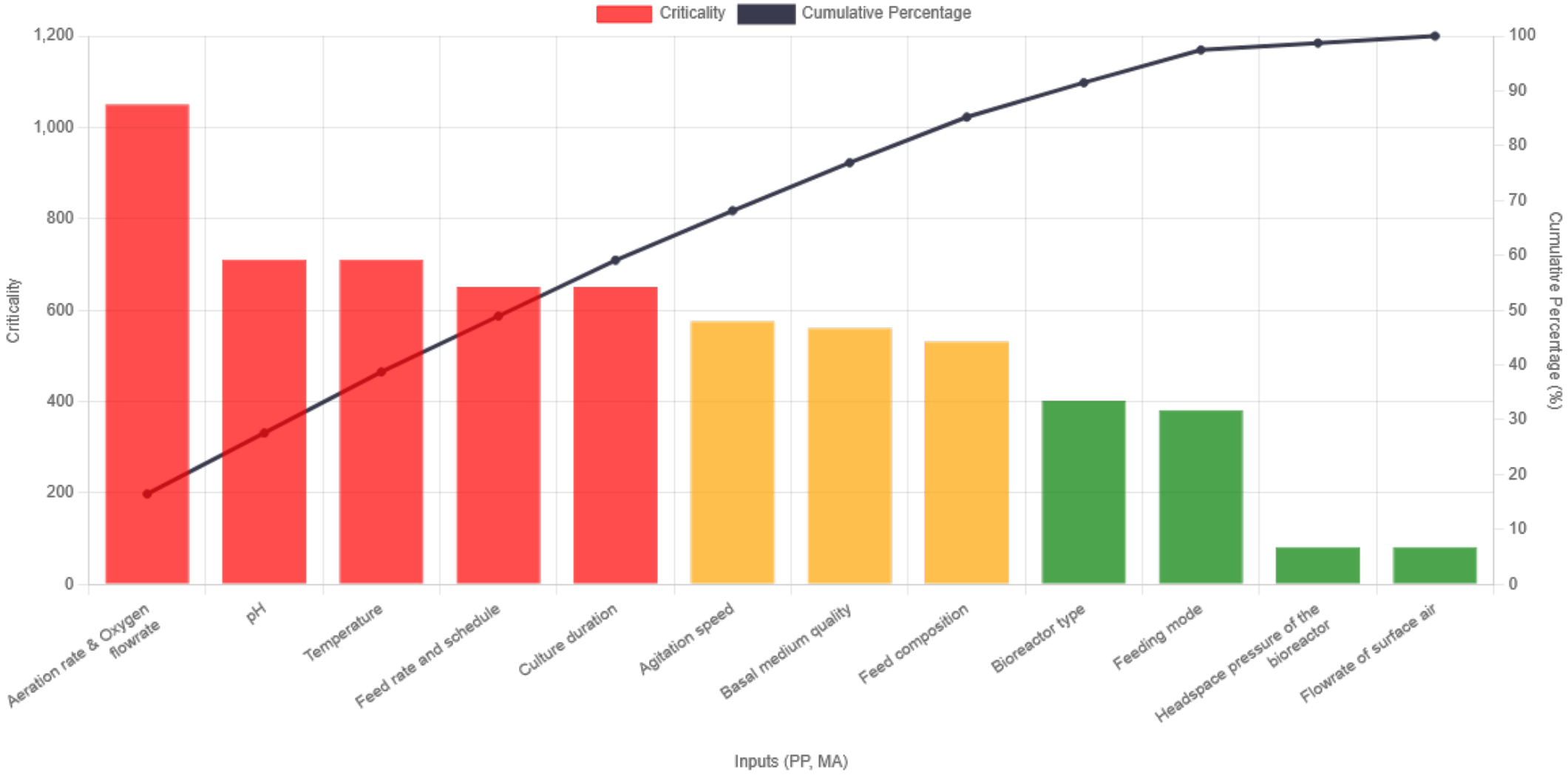
Visual representation of process interactions.

Cause-Effect Matrix Analysis for mAb-X clinic

INPUT NAME	UNIT	STEP	TYPE	Viable cell density and viability (50)	Product titer (50)	RPN	COMMENT	OPERATIONAL RANGE	CONTROL METHOD
Feed composition	UPSTREAM	Bioreactor Production	N/A			531	Nutrients, glucose, amino acids, etc. Finally, only glucose.	Feed is only composed of glucose	Fixed
Basal medium quality	UPSTREAM	Bioreactor Production	N/A			561	Composition of the initial medium (standard)	Composition of a standard medium	Fixed
Bioreactor type	UPSTREAM	Bioreactor Production	N/A			401	(glass, single-use)	Single-use bioreactor	Fixed
pH	UPSTREAM	Bioreactor Production	N/A			711	*N/A*	pH* in [6.8 ; 7.2]	Driven by a PID controller
Aeration rate & Oxygen flowrate	UPSTREAM	Bioreactor Production	Quantitative			1051	DO*=30% NOR=[10;100]%	Air: [15-30] NL/min O2: [1-5] L/min	Controlled by Mass Flow Controllers (MFC PID)
Feeding mode	UPSTREAM	Bioreactor Production	N/A			381	(batch, fed-batch, perfusion). Finally--> fed-batch (bolus)	Fed-batch mode	Fixed
Feed rate and schedule	UPSTREAM	Bioreactor Production	N/A			651	J3, J6	Glucose bolus administred J3 and J6	Fixed scheme
Culture duration	UPSTREAM	Bioreactor Production	Quantitative			651	Récolte à J10	Cell harvest at J10	Fixed
Headspace pressure of the bioreactor	UPSTREAM	Bioreactor Production	N/A			81	(bar)	P*=0.35 bar	Driven by PID controller
Agitation speed	UPSTREAM	Bioreactor Production	N/A			576	(rpm)	S* in [90-110] rpm	driven by a PID controller
Temperature	UPSTREAM	Bioreactor Production	N/A			711	(°C)	T* in [36.5 ; 37.5] °C	Driven by a PID controller
Flowrate of surface air	UPSTREAM	Bioreactor Production	N/A			81	To control the amount of foam on the surface. (NL/min), NL=Normo-Litres	200 NL/min	fixed value controlled by a MFC

Cause-Effect Analysis & Pareto Prioritization for mAb-X clinic

RPN Threshold : 600



Input - Output Relation per Input

Input: Feed composition

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Feed composition	Strong link	Strong link
Justifications	No justification provided	No justification provided

Input: Basal medium quality

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Basal medium quality	Perhaps strong or Unknown	Perhaps strong or Unknown
Justifications	No justification provided	No justification provided

Input: Bioreactor type

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Bioreactor type	Moderate	Moderate
Justifications	No justification provided	No justification provided

Input: pH

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
pH	Strong link	Strong link
Justifications	No justification provided	No justification provided

Input: Aeration rate & Oxygen flowrate

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Aeration rate & Oxygen flowrate	Strong link	Perhaps strong or Unknown
Justifications	No justification provided	No justification provided

Input: Feeding mode

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Feeding mode	Perhaps strong or Unknown	Perhaps strong or Unknown
Justifications	No justification provided	No justification provided

Input: Feed rate and schedule

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Feed rate and schedule	Strong link	Strong link
Justifications	No justification provided	No justification provided

Input: Culture duration

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Culture duration	Strong link	Strong link
Justifications	No justification provided	No justification provided

Input: Headspace pressure of the bioreactor

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Headspace pressure of the bioreactor	No relationship or small	No relationship or small
Justifications	No justification provided	No justification provided

Input: Agitation speed

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Agitation speed	Strong link	Perhaps strong or Unknown
Justifications	No justification provided	No justification provided

Input: Temperature

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Temperature	Strong link	Strong link
Justifications	No justification provided	No justification provided

Input: Flowrate of surface air

INPUTS	OUTPUTS	
	Viable cell density and viability	Product titer
Flowrate of surface air	No relationship or small	No relationship or small
Justifications	No justification provided	No justification provided