

Advancing 3Rs in Quality Control of Immunobiologicals

Butantan's Strategy for Implementing MAT and Recombinant Endotoxin Testing

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Analytical R&D

Regulatory Landscape in Brazil

MINISTRY OF
HEALTH



Brazilian Health Regulatory Agency

MINISTRY OF SCIENCE,
TECHNOLOGY AND INNOVATION



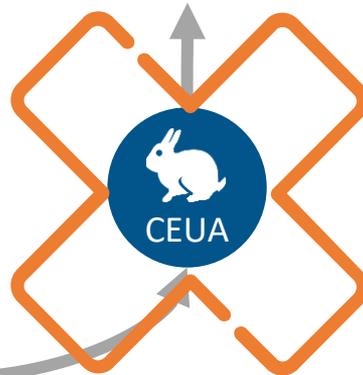
National Council for the Control
of Animal Experimentation



**Brazilian
Pharmacopoeia
7th ed (Dec/2024)**

5.5.2.7.1 MAT
5.5.2.7.2 RPT

MANUFACTURER



**Normative Resolution
N° 45 (Oct/2019)**

Deadline to stop
using rabbits for RPT:
Oct/2024



**Normative Resolution
N° 68 Oct/2024**

Deadline extended to
Oct/2025

Brazilian Health Regulatory Agency



RDC N° 511 of 2021

- I – German Pharmacopoeia;
- II – United States Pharmacopoeia;
- III – Argentine Pharmacopoeia;
- IV – British Pharmacopoeia;
- VI – European Pharmacopoeia;
- VII – International Pharmacopoeia (World Health Organization);
- VIII – Japanese Pharmacopoeia,
- IX – Mexican Pharmacopoeia.
- X – Portuguese Pharmacopoeia.



IN N° 65 of 2020 Post registration changes

Change from a pharmacopoeial monograph to a different pharmacopoeial monograph.



Minor change

These have a minimal potential impact and can be **implemented immediately**. Must be documented and included in the manufacturer's next **Annual Report**.

- ❖ Analytical validation Report
- ❖ Updated specifications of the product
- ❖ Comparability study between the current and the proposed methodology

Implementation of MAT at Butantan

EQUINE IMMUNOGLOBULINS



Antivenoms

- Bothropic antivenom
- Bothropic and lachetic antivenom
- Crotalic antivenom
- Bothropic and crotalic antivenom
- Elapid antivenom
- Scorpion antivenom
- Arachnid antivenom
- Lonomia antivenom



Antitoxins

- Diphtheria antitoxin
- Tetanus antitoxin
- AB Botulinum antitoxin



Antivirus

- Rabies antiviruses

EQUINE IMMUNOGLOBULINS



Antivenoms

Bothropic antivenom

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Antitoxins

Diphtheria antitoxin

Tetanus antitoxin

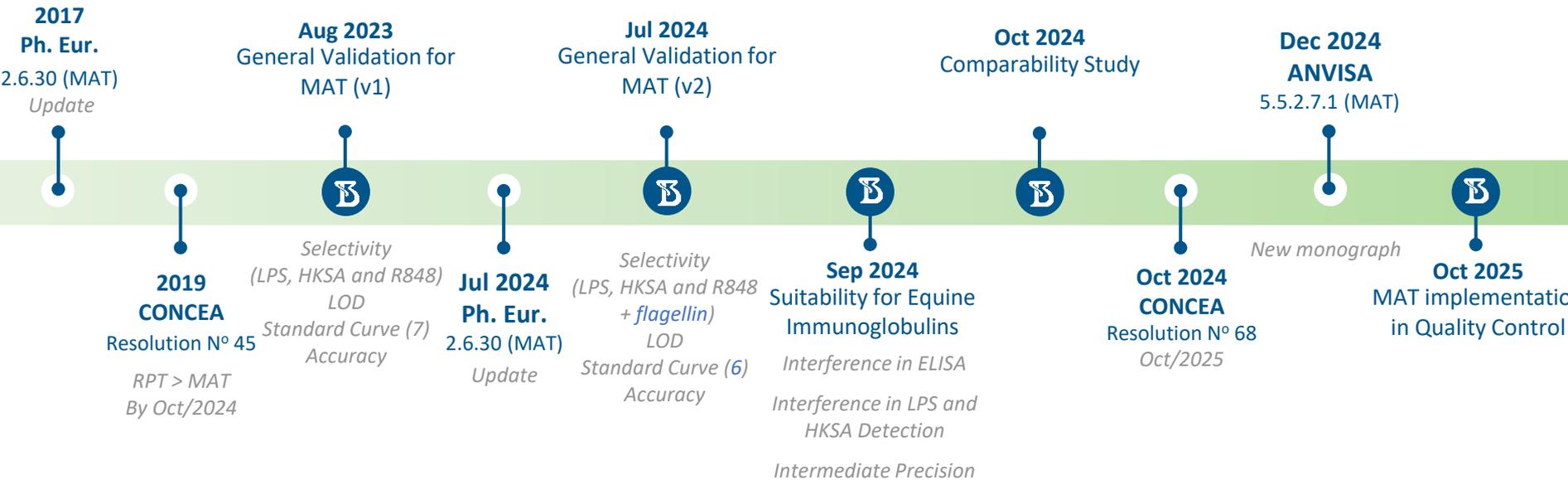
AB Botulinum antitoxin



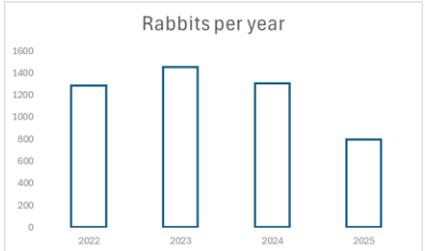
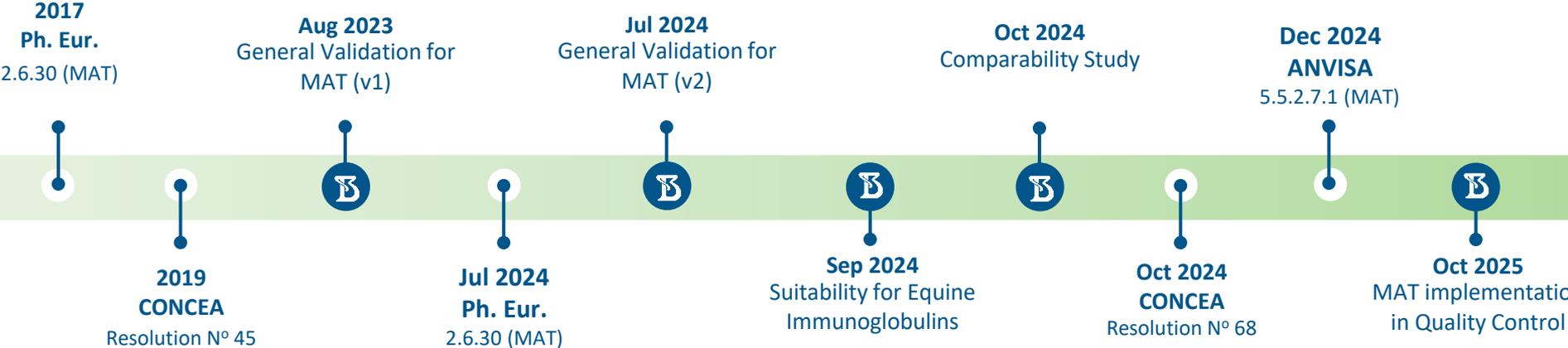
Antivirus

Rabies antiviral

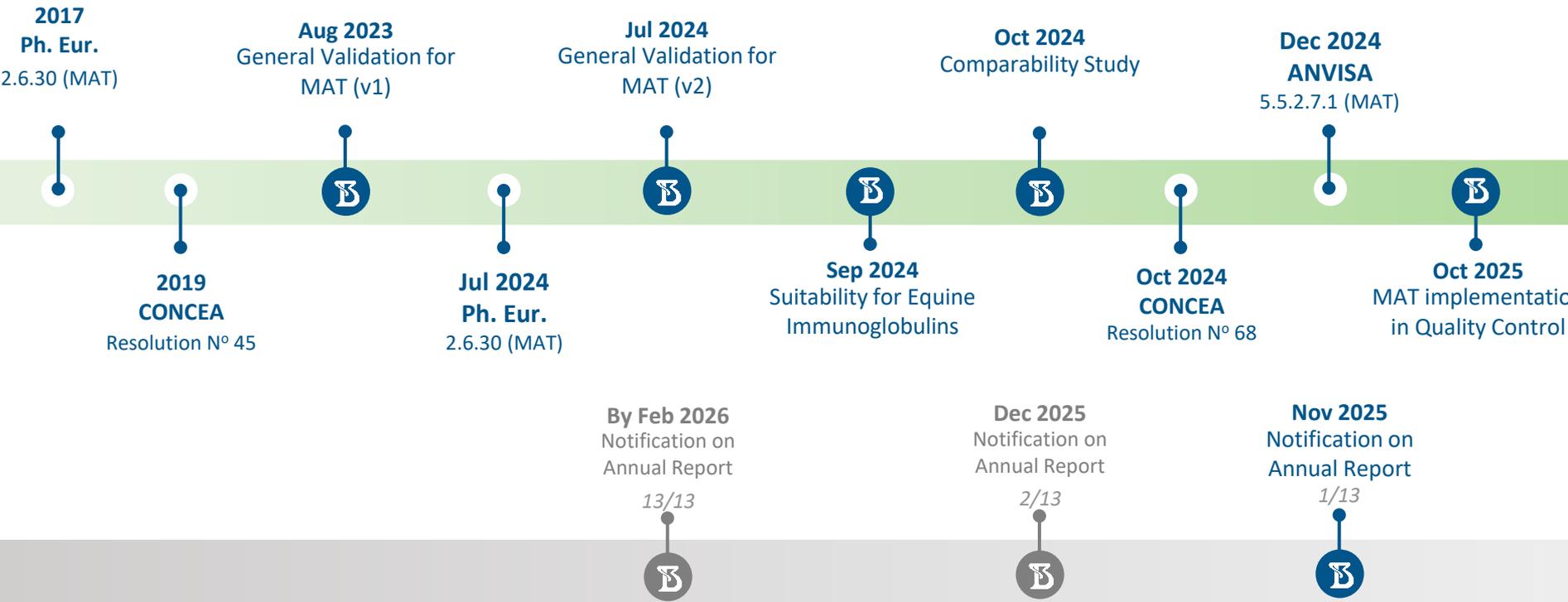
Implementation of MAT at Butantan



Implementation of MAT at Butantan



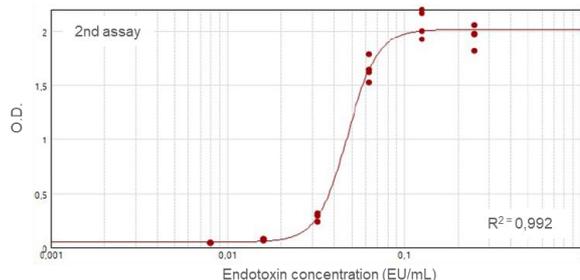
Implementation of MAT at Butantan



General information about MAT at Butantan



Standard Curve



6 concentration: 0.008 – 0.250 EU/mL

LOD \leq 0.016 EU/mL

4 Parameter Logistic (4PL) Model:

- Estimated Parameters (*superior asymptote, slope and inflection point*) were statically significant ($p < 0,05$);
- $r^2 \geq 0.975$;
- Lack of fit ($p > 0,05$);
- Variance of residual were homoscedastic ($p > 0.05$).



Accuracy and Precision

Recovery: 50-200%

RSD: 30%



Equine immunoglobulins

Specification: 1.75 – 23.33 EU/mL

MDV: 109 - 1458

LPS spike: 0.03 EU/mL

Sample dilutions:

1/20

1/40

1/80

Implementation of Recombinant endotoxin testing at Butantan



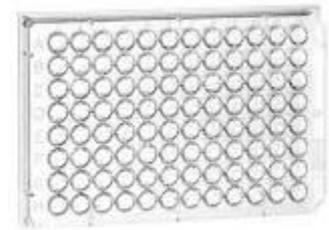
Gel-Clot



**LAL Cartridge
Kinetic Chromogenic**



**LAL Kinetic Turbidimetric
Plate**





Gel-Clot

2



**LAL Cartridge
Kinetic Chromogenic**

44



**LAL Kinetic Turbidimetric
Plate**

44

Implementation of Recombinant endotoxin testing

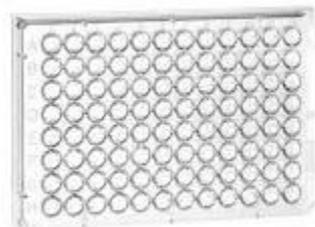
rCR Cartridges

Kinetic Chromogenic



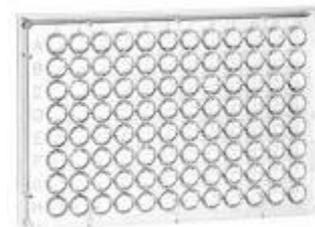
rCR Plate

Kinetic Chromogenic

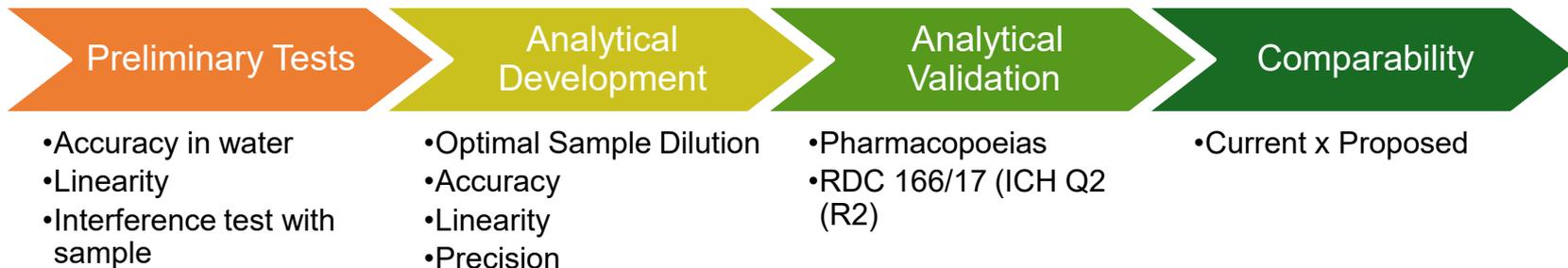


rFC Plate

Kinetic Fluorescence



Implementation of Recombinant endotoxin testing



Implementation of Recombinant endotoxin testing



	Preliminary Tests	Analytical Development	Analytical Validation	Comparability
rCR cartridge (chromogenic)	✓	✓	✓	3rd Trimester 2026
rCR plate (chromogenic)	✓	🚶	1st Trimester 2026	
rFC plate (fluorescence)	✓	2nd Trimester 2026	2nd Trimester 2026	



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Thank you!
Obrigada!

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BUTANTAN**
Gestão é uma ciência

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A serviço da vida



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GOVERNO DO ESTADO
SÃO PAULO SÃO TODOS