

# DEVELOPMENT & IMPLEMENTATION OF THE MAT

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## THE NBI EXPERIENCE

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**N**NATIONAL  
**B**BIOPRODUCTS  
**I**INSTITUTE NPC

*Committed to providing safe, cost effective,  
quality medicinal products.*



# AGENDA

- Introduction
- Pyrogen Testing at NBI
- Development of the MAT
- Validation
- Implementation
- Challenges



# COMPANY OVERVIEW



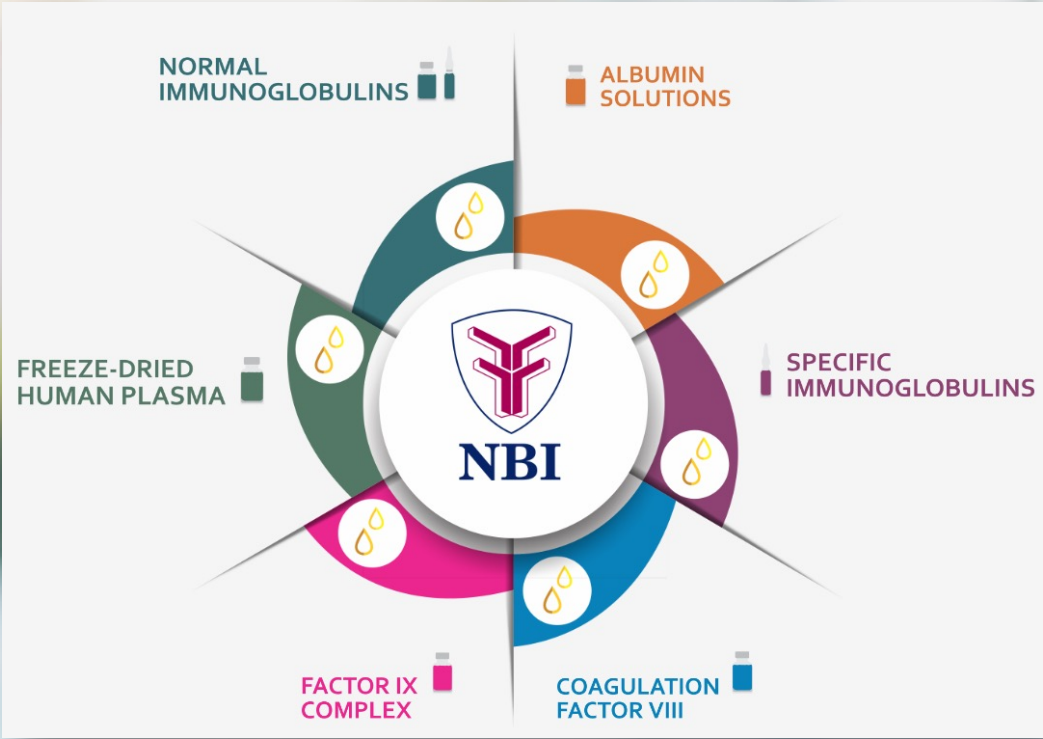
**Based in Pinetown, South Africa**  
approximately 20 km from Durban  
Situating at **10 Eden Road** in **Paradise Valley**



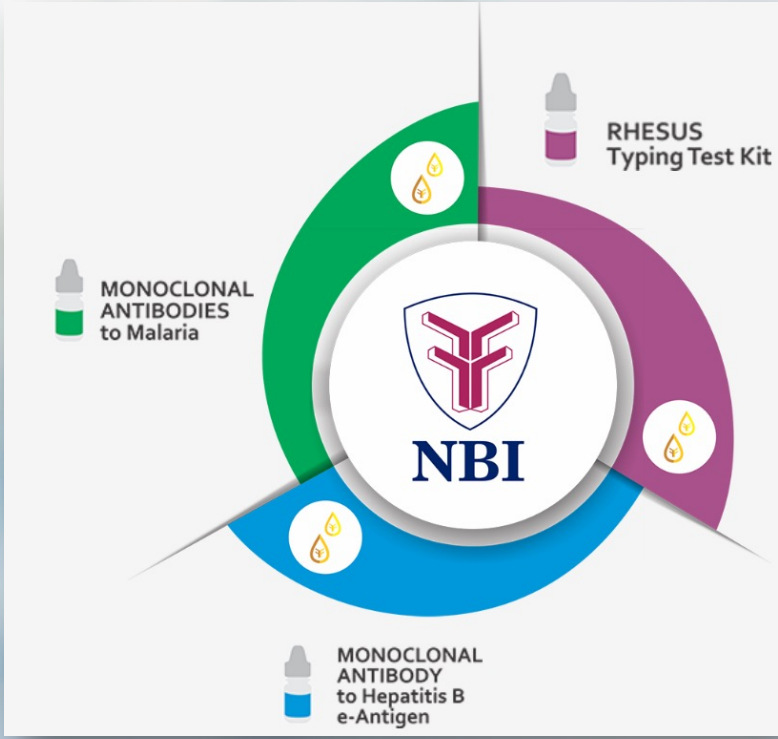
NBI is a private, non-profit, pharmaceutical company that manufactures plasma-derived medicinal products (PDMPs) from fresh/frozen plasma of human origin, using the process of cold ethanol fractionation. Our products are marketed, sold and distributed to reach South and Southern African patients. The company's manufacturing site and head office are located in Pinetown, KwaZulu-Natal, South Africa.

# Overview of NBI's Product Range

## Pharmaceuticals (PDMPs)



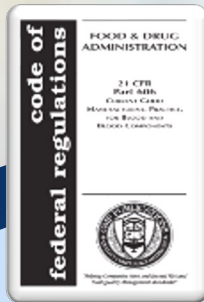
## Diagnostics



# Compliance with Local and International Regulatory Requirements

## Pharmacopoeias

FDA  
CFR



PICS  
Annex 1 & 14



Council  
of Europe



EMA Note  
for Guidance

NMRC



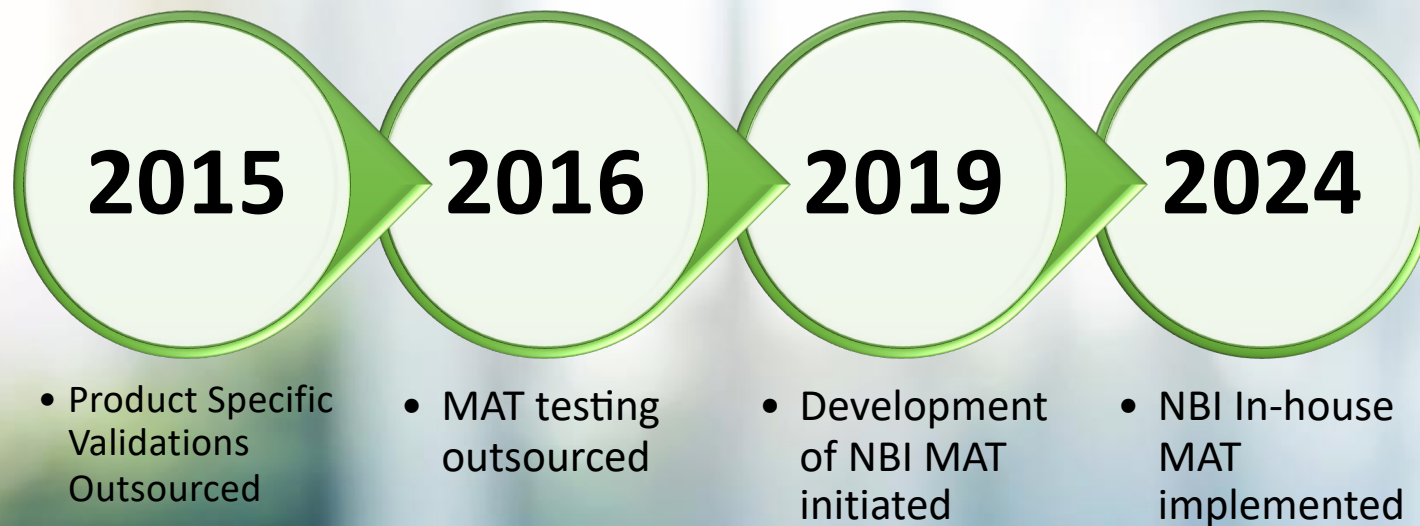
European Law  
Blood Directive



WHO Technical  
Report series

**SAHPRA**  
SOUTH AFRICAN  
HEALTH PRODUCTS  
REGULATORY AUTHORITY

# MAT TESTING OF NBI PRODUCTS



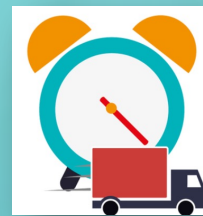
**Why develop an in-house MAT when off the shelf kits are available?**

# WHY DEVELOP A MAT WHEN THERE ARE COMMERCIAL MAT KITS AVAILABLE?

**Cost**



**Delivery Time**



**Regulatory Red Tape**



**In-house Capability**



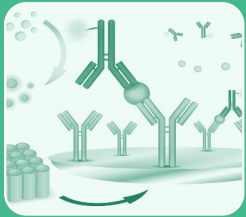
# DEVELOPMENT OF THE NBI MAT



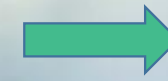
**1. Monocyte Activation**  
(Immunological Response)



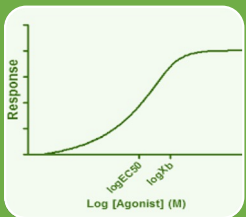
**Cell Source**



**2. ELISA**



**Interleukin  
Detection**

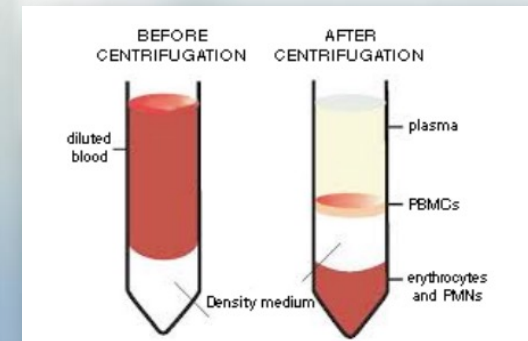


**3. Analysis**  
(Quantification of pyrogenic  
contamination)



# Cell Source

- Cryopreserved PBMCs
- Pool of 4 donors
- Donors – group of NBI volunteers
- South African National Blood Service (SANBS) assists with blood draw
- Density gradient isolation
- Long-term storage –liquid nitrogen vapour phase
- Qualification of cryopreserved pool



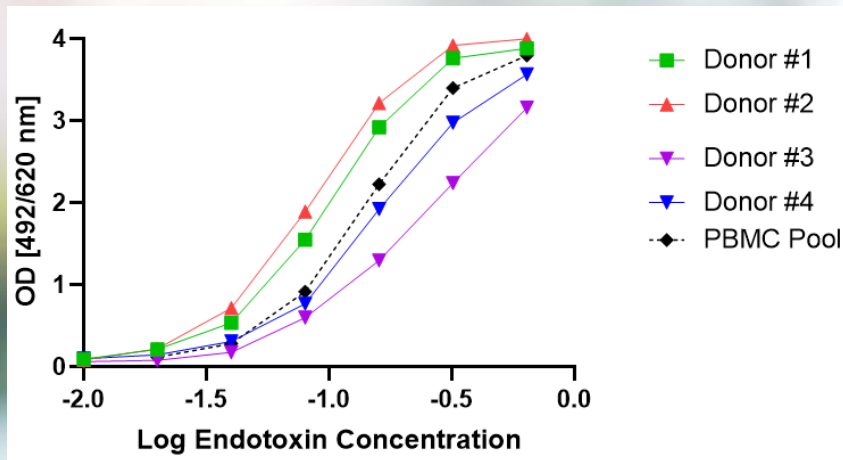
# Challenges

- Technical expertise
- Labour intensive
- Processing time
- Facility capacity/capabilities (e.g. centrifugation; rate-controlled freezing)

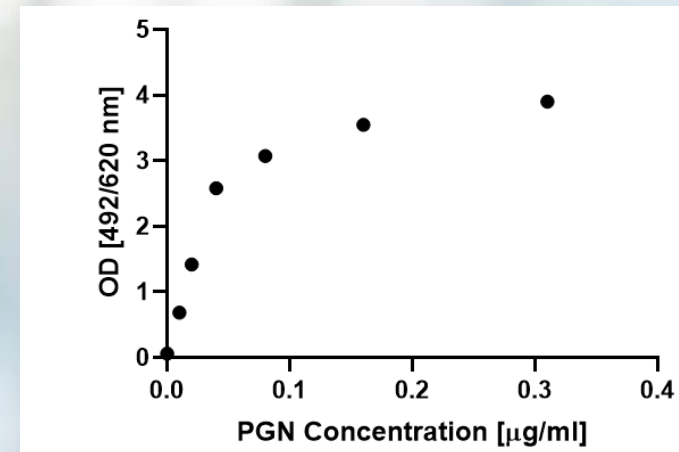


# Qualification of Cryopreserved PBMCs

- Pooling of PBMCs from 4 donors overcomes donor variability



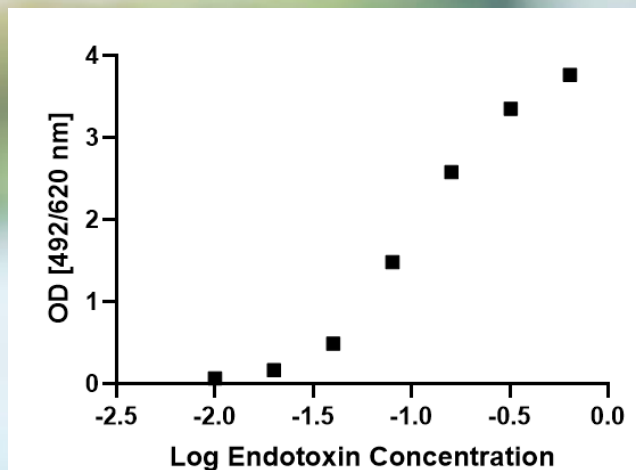
- Non-endotoxin detection



- Peptidoglycan (PGN)
- Flagellin (FLA)

# Interleukin Detection

- PBMCs respond to endotoxin & NEPs by releasing pro-inflammatory cytokines e.g. Interleukin-6 (IL-6), IL-1 $\beta$  or tumour necrosis factor (TNF)
- IL-6 – shown to have higher sensitivity
- Opted for commercial IL-6 ELISA & adapted it for use in the NBI-MAT



# Product Specific Validations

## Interference Testing



- Endotoxin International Standard

## Detection of NEPs

- PGN

## Interference in the Detection System

## Submission to Regulator



- All PDMPs except for 1 tested using Method 1 (previously known as Method A)
- 1x PDMP tested using Method 2 (previously know as Method C)

# Implementation

- Regulatory Approval – SAHPRA
- Training of QC Analyst
  - Theory
  - Hands-on Practical
  - Competency
- Setup & equipping of testing laboratory



# Challenges

- **Technical**
  - PBMC processing
  - Technically challenging assay – requires excellent pipetting skills and knowledge of cell culture and proper handling of cells
  - Method 1 is more technically demanding, however, we have had more issues with the implementation of Method 2 but we are currently working on this
- **Training**
  - 7-8 months, ideally more is required
  - Critical that analysts are not only capable of performing the MAT but that they have an excellent theoretical understanding of the assay and knowledge of why certain steps are performed the way that they are.
- **Laboratory Facilities & Equipment**
  - PBMCs – centrifugation capacity, rate-controlled freezer/containers, liquid nitrogen vapour phase storage
  - Performing the MAT
    - Ergonomic Pipettes - Reduce Repetitive Stress Injuries
    - Good quality, compatible pipette tips for accuracy
- **Products**
  - 1x product that is particularly challenging – significant interference with the MAT

*Thank You*



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