ADVANCING 3Rs IMPLEMENTATION: BADAN POM STRATEGY FOR ANIMAL TESTING REPLACEMENT IN VACCINE QUALITY CONTROL

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1. Strategic Context and Global Regulatory Imperative

a. Alignment with Global 3Rs Principles
The transition toward non-animal testing strategies is a globally recognized imperative, driven equally by ethical considerations, scientific innovation, and the urgent need for more accurate, consistent, and timely quality control (QC) outcomes

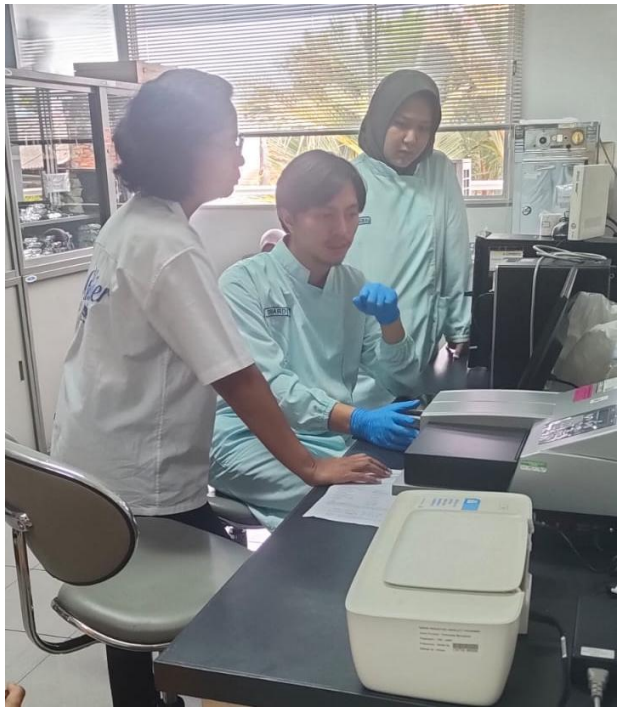
b. Efficiency Through Ethical Innovation
The migration from traditional *in vivo* animal testing to advanced *in vitro* is not merely an ethical mandate but a strategic economic necessity. Non-animal testing strategies have been demonstrated to reduce the substantial delays and associated costs inherent in conventional lot release testing

2. NCL’s Replacement Strategy 1: Modernizing Pyrogen Testing

Transition from Rabbit Pyrogen Test (RPT) to Monocyte Activation Test (MAT)

- Badan POM is preparing to implement the Monocyte Activation Test (MAT) a key step in replacing the traditional rabbit pyrogen test.
- In-House Training & Trial Test (with principle) in May 2025. Outcomes : Successful, yielding reliable and positive results.
- MAT Method Verification for NCL planned in 2026

3. NCL's Replacement Strategy 2: Optimizing Endotoxin Detection using Recombinant Methods



An initial trial utilizing recombinant endotoxin reagents was conducted in September 2025. This trial uses Recombinant Cascade Reagents (rCR) with existing microplate reader. The outcome of this initial execution was unfortunately deemed **invalid**

Root Cause Analysis (RCA) and Strategic Troubleshooting

A detailed Root Cause Analysis (RCA) revealed that the invalid results were not attributable to a failure of the core technology itself, but rather to critical deficiencies in procedural control and human factors

a. Procedural Accuracy and Personnel Overload: The presence of an excessive number of personnel during the assay led to compromised accuracy in the highly critical steps of liquid transfer (such as pipetting), directly impacting the precision necessary for kinetic assays

b. Homogeneity Failure Due to Delay: The essential homogeneity required for the solution during the kinetic measurement was compromised because the assay procedure suffered a delay during a mandatory rest period

Proposed Corrective Actions and Upcoming Trials

a. Trial Schedule: re-trial test for Recombinant Cascade Reagen (rCR) and Recombinant Factor C (rFC) trial tests are scheduled in January 2026

b. Dual Vendor Evaluation: These trials also designed to compare the performance of reagents from two major principles to determine the most robust and reliable protocol under the NCL's specific operational environment

c. Instrumental Flexibility and Open System Strategy

The existing microplate reader instrument operates as an **open system.** This means the instrument is capable of performing quantitative endotoxin analysis using various reagent chemistries from different manufacturers

4. NCL's Replacement Strategy 3 : Next Generation Sequencing (NGS) for Complex Vaccine QC

Two Badan POM personnel successfully participated in specialized training in India and Thailand during 2025 conducted by PATH. The training focused on Next-Generation Sequencing and QC Assays for Polio Vaccines

4. NCL’s Replacement Strategy 3 : Next Generation Sequencing (NGS) for Complex Vaccine QC

a. NGS Ecosystem Acquisition

The 2026 plan prioritizes securing the necessary equipment (NGS, PCR, Qubit) and, critically, ensuring long-term operational viability through mandatory software subscriptions and multi-year service contracts

b. International Capacity Building and Knowledge Sharing

- **Further Training:** The plan includes continued engagement with international bodies for highly specialized training related to NGS, concentrating on the technical nuances of data interpretation and preparation of regulatory submissions
- **Workshop Hosting:** The planned 2026 event, the "Workshop on Implementation of Next Generation Sequencing for Quality Control of Novel Polio Vaccines," signifies the NCL’s intention to disseminate its specialized expertise and potentially lead regional efforts for harmonizing these advanced QC methodologies,

5. Translating Global Mandates into National Policy by Standardization Division of Badan POM

1. **Elevating Quality by Design (QbD)**
   Badan POM Regulation No. 7/2024 on GMP embracing Quality by Design (QbD) principles through Real-Time Release Testing allows us to grant lot release based on a combination of in-process controls and real-time monitoring

2. **The Role of NCL and Standardization Division as NRA: Verification and Nationalization**
   - **Verification**: When an official international guideline for a specific *in vitro* method becomes available (e.g., MAT), our NCL first conducts verification studies to ensure the method is suitable for the diverse products registered in Indonesia
   - **Policy Formalization** : The method may then be incorporated into the Indonesian Pharmacopeia or introduced via an amendment to existing Badan POM regulations (e.g Badan POM Regulation No. 1/2023, Guideline on Batch/Lot Release Certification for Vaccines).

3. **Building a Flexible National Roadmap**

6. The Regulatory Stance: Directorate of Registration of Badan POM is Proactively Engaged

1. **Open to Variation:** The Directorate of Registration is already open and receptive to processing registration variation requests from companies seeking to replace *in vivo* methods.
2. **Concrete Progress:** Several companies have already initiated variation requests to switch to *in vitro* methods for their existing products. For new product submissions, several manufacturers are registering products whose In-Process Control (IPC) schemes no longer utilize *in vivo* tests.
3. **The Regulatory Requirement:** The company must provide robust validation study data for the proposed *in vitro* method. This data must clearly demonstrate that the new method meets the necessary Quality Control needs in terms of Critical Quality Attributes (CQAs) supported by clear scientific justification and results.

7. Conclusion

Badan POM is not waiting for global consensus; we are contributing to it. Our NCL provides the scientific proof, our Directorates as a NRA provide the regulatory mechanism.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