South African example on the application of the reliance principle

South African National Control Laboratory for Biological Products

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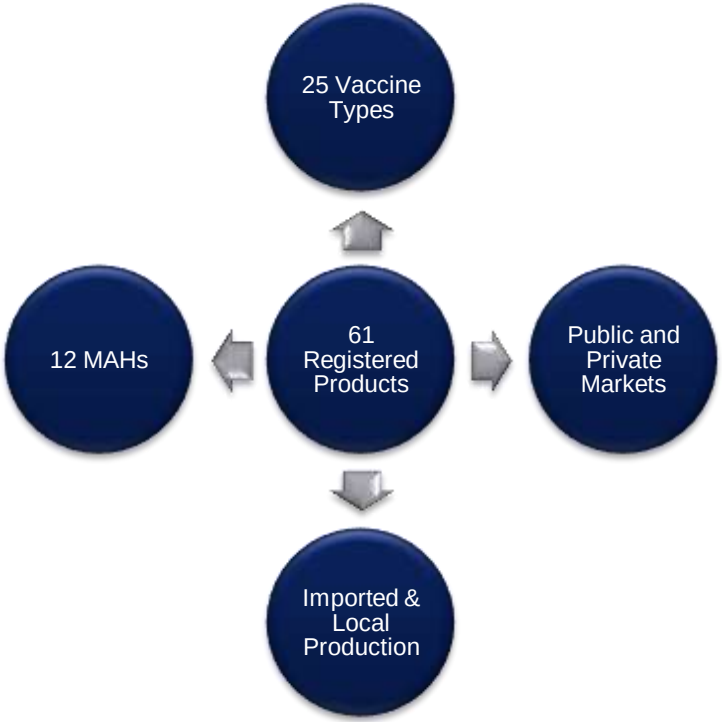
Overview

- South African vaccine market & Local production
- Lot release process & Rationale for reliance
- Risk based testing & Examples of reliance approaches
- New developments - Reliance on the African continent
- Critical reagent challenges and strategies

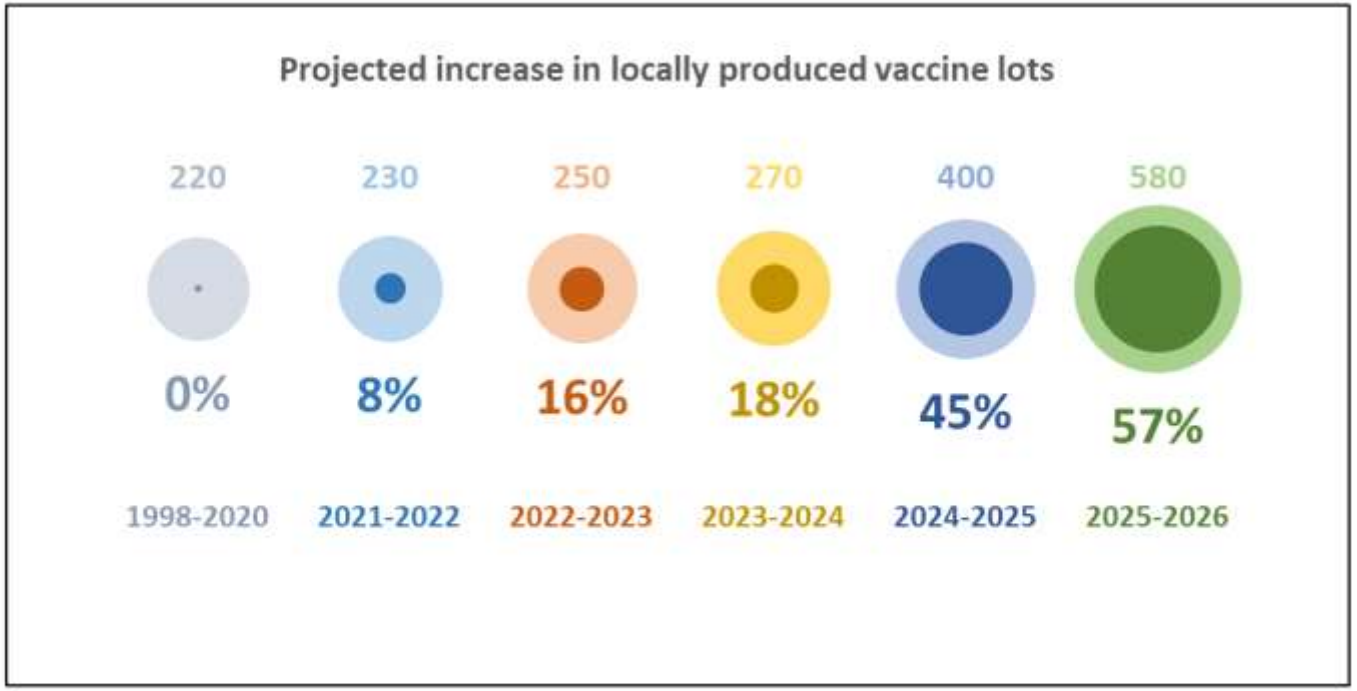
Overview of the RSA Vaccine Market



Imported from 14 international manufacturers

11 countries - Netherlands, Canada, Denmark, Indonesia, India, Cuba, Belgium, South Korea, USA, France, China

2 Local MNFs


Projected increase in locally produced vaccine lots
220
230
250
270
400
580
0%
8%
16%
18%
45%
57%
1998-2020
2021-2022
2022-2023
2023-2024
2024-2025
2025-2026

Elements of the LR Process

LSP Review

- Compliance with registration conditions

Testing

- Product specific based on risk assessment

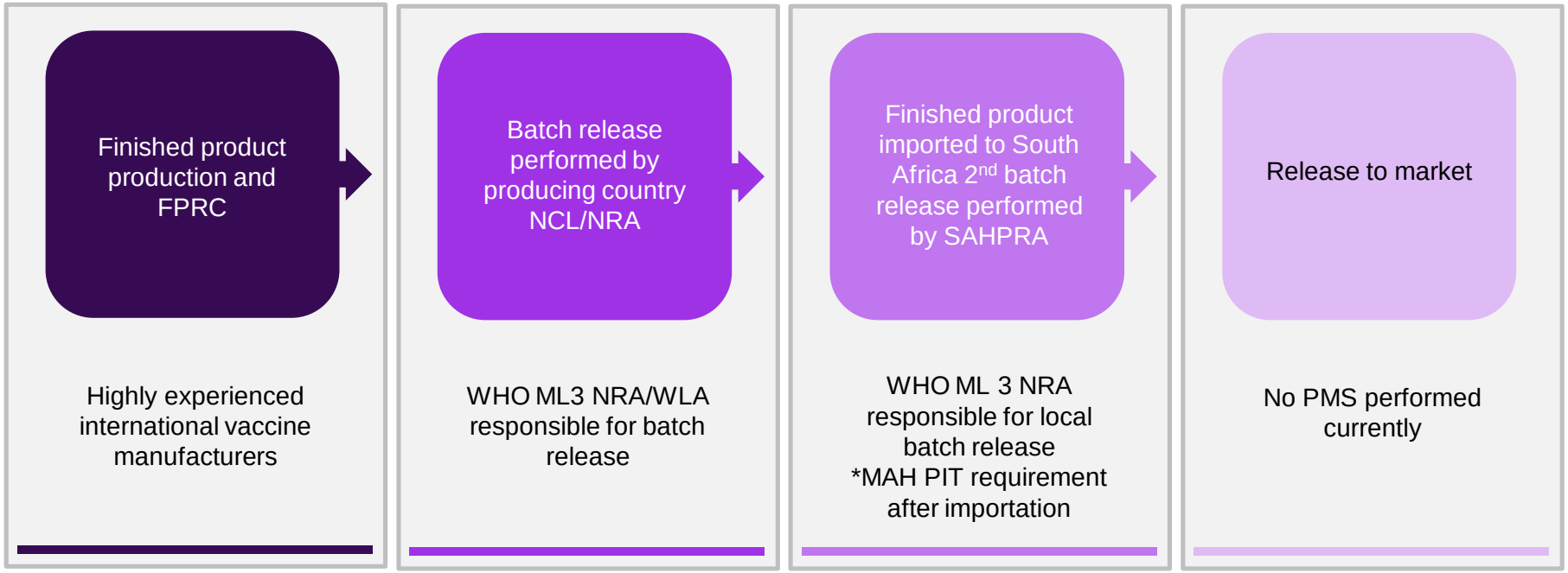
VAR Review

- Confirm cold chain integrity

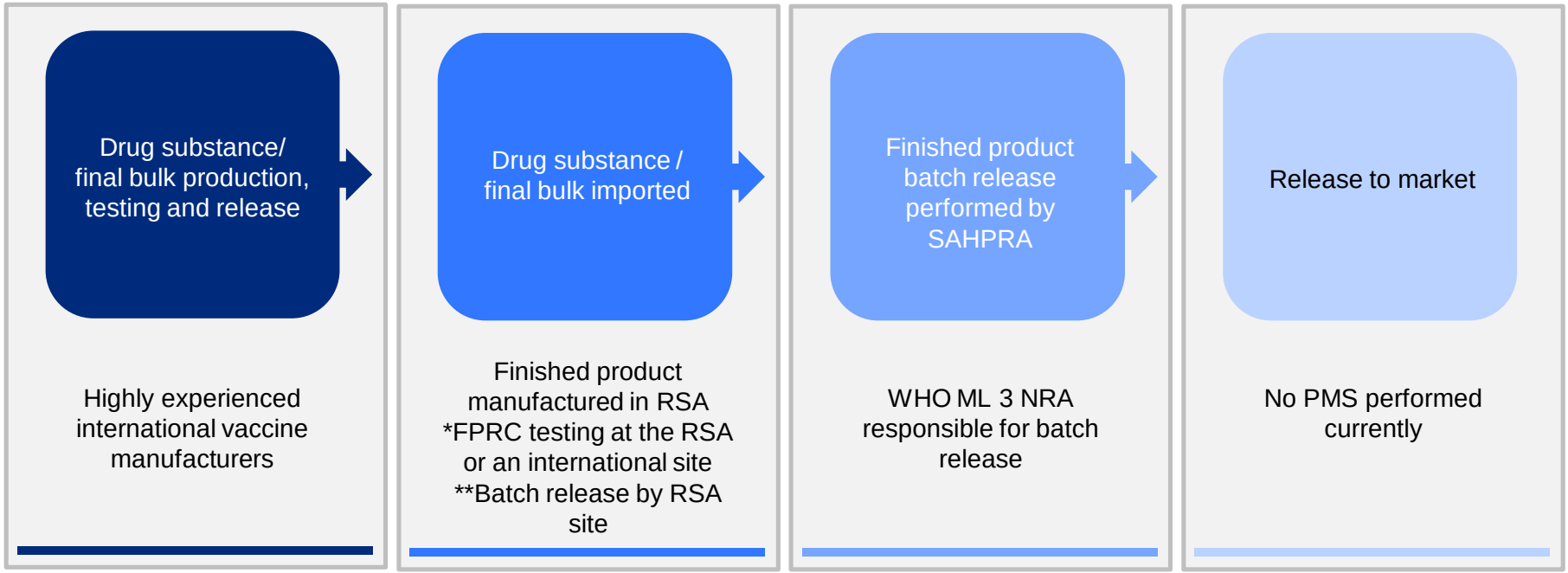
Packaging & Labelling Review

- Compliance with applicable regulations

Role as NRA/NCL of importing country



Role as releasing NRA of a producing country



Risk-based testing approach

Key risk evaluation considerations

Regulatory status and pathway

- Registered / Emergency use

Manufacturing process and controls

- Manufacturer experience
- Production history
  - Number of batches released since registration
  - Evidence of consistency of production (manufacturers trending data)
  - Evidence of consistency of production (SANCLBP test results)
  - History of product non-compliance and lot rejection
  - Nature and complexity of the quality control methods
  - GMP inspection outcome

Imported

- Testing requirements based on risk evaluation
- Adopted OCABR guidelines for test scope
- SAHPRA approves product-specific risk-based testing requirement

Implement reliance where possible

Locally manufactured

- All batches are tested
- Adopted OCABR guidelines for test scope
- SAHPRA approves product-specific risk-based testing requirement

Use of reliance – Example 1
No testing – Availability of OMCL results

Influenza (QIV & TIV)

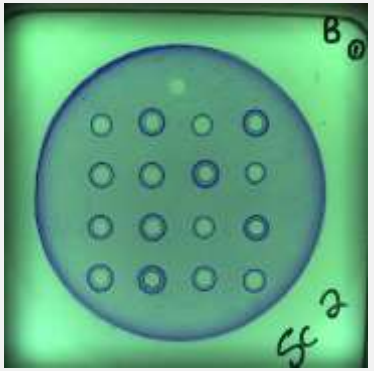
- SRID assay for HA content
- Seasonal change to product formulation
- Tested all batches (< 8 batches/year)
- No retesting since 2021
- Reliance to avoid redundant retesting

Challenges

- Reagent importation (time, import permits, cold chain)
- Assay verification
  - Time, available materials for a timely verification study
  - MNFs use different combinations of HA Standards & serums (different suppliers NIBSC/MHRA/TGA)
- Low uptake of vaccine < 4 batches/year/manufacturer *i.e.* trending not informative

Rationale for reliance

- Receive test reports and LR certificates issued by OMCLs
- LR process evaluates cold chain integrity – the main risk to product quality



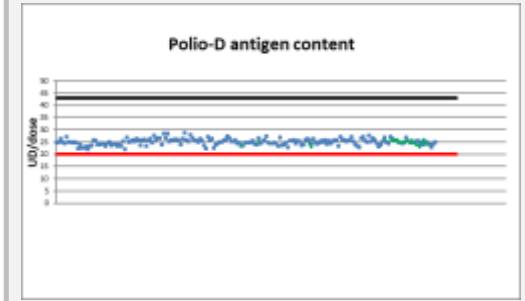
Use of reliance – Example 2
Reduced testing – Imported vs Locally produced

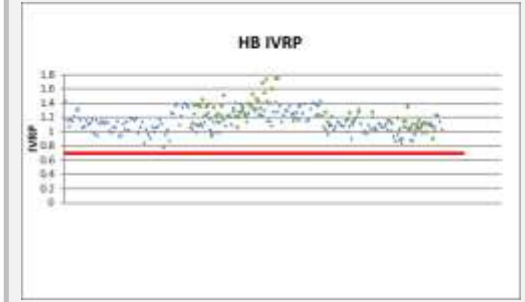
Hexavalent vaccine

- Product used in Pvt market & EPI
- Imported and locally produced (F&F)
- HB, HiB and IPV components tested
- Tested all imported and locally produced batches
- Historically tested > 80 batches
- Reduced testing for imported batches from 2022 (1/5)
- Still allows a comparison of imported vs locally produced product
- Assay designs allow for testing multiple batches in a single assay run

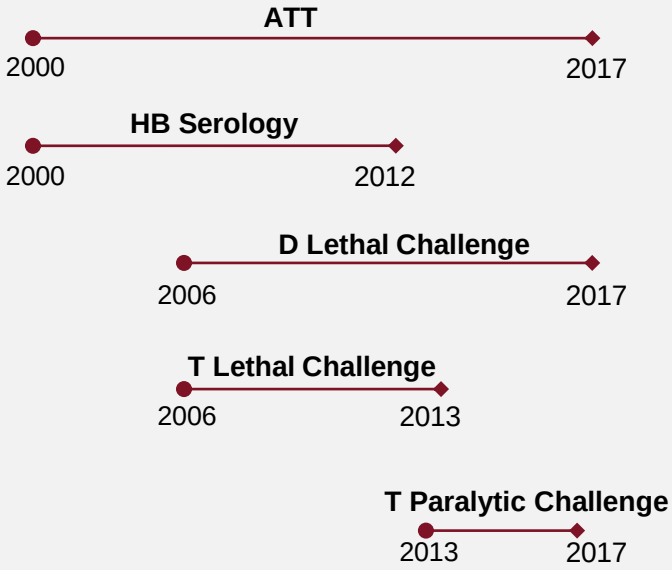
The rationale for reliance and reduced testing

- Evidence of consistency of production across all parameters tested by the manufacturer since 2013
- Evidence of consistency of production across all parameters tested since 2018
- No non-compliant batches





Use of reliance – Example 3
3Rs - Termination of *in vivo* testing



Rationale for termination of *in vivo* testing

- Animal supply challenges
  - One supplier in RSA was not reliable
  - Animals shipped 400 km by plane and truck
- Husbandry
  - Animal facility not up to standard
  - Energy-intensive, temp/hum control
- High assay variability
  - Not optimal for monitoring the consistency of production
  - 95% LCL well above specification limits – unlikely to detect marginally sub-potent batches
- Specialised skills
  - Need veterinarian and animal technologists
  - Ethics approval is required for *in vivo* testing
- Logistics and assay management
  - Coordinate animal receipt and vaccine submission
  - Need for reagents from manufacturers e.g. toxins
- High cost but limited added value

Network of African Reliance Laboratories (NARL)

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

7. Governance Structure of the Network

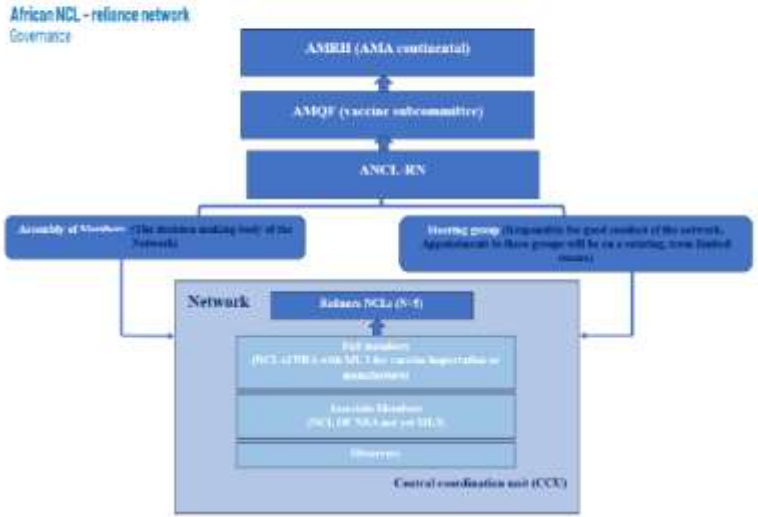
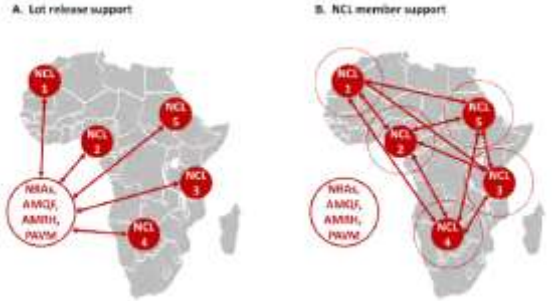


Table 2. ANCL-RN membership categorization

Category	Membership Description
Reliance Laboratories	Expert hubs of NCLs, operating at international standards, with the authority to carry out testing and lot release of vaccines and or biological products. The NCLs will be drawn from NRAs that have achieved WHO GBT ML3 status of either vaccine producing or vaccine importing African countries. Tenure as reliance NCL will be term limited.
Full members	NCLs from NRAs which have attained WHO GBT ML3 status of either vaccine producing or vaccine importing African countries. These NCLs may also be one of the Reliance NCLs hubs.
Associate members	NCLs from NRAs which have not yet attained WHO GBT ML3 status
Observers	Any organization invited at the discretion of the ANCL-RN or the AMQF vaccines sub-committee. Invitation will be based on consensus and observers will not participate in decision-making process. Observers may include organizations with an interest and involvement in the development, assistance, monitoring and evaluation of the NCL, NRA and regulatory systems of African countries. Observers may also include academic institutions, professional bodies, multinational pharma, other regulatory networks, development partners and donors.

Figure 1: Hub and spoke model of ANCL-RN

The Reliance Laboratories are integral to the functioning of the ANCL-RN as they interact with both (A) the external African continental regulatory system to facilitate lot release and (B) the Network members (other Reliance Laboratories as well as NCL membership).



Critical reagent supply

- Reagent importation (time, import permits, veterinary health certificates, cold chain integrity)
- Limited availability e.g. for staff training
- Sourcing commercially available reagents
  - Reserved for vaccine manufacturers e.g. ELISA conjugates
  - Local supplier import restrictions (animal-derived materials)
- Changes introduced by manufacturers (standards/internal controls/antibodies)
  - Short notice/no notice - Impact release testing
  - Access to qualification reports & updated SOPs

Strategies to optimize use of critical reagents

- Apply reliance to reduce/prevent retesting of imported products
- Method technology transfer
  - Ensure assays are under control
  - False OOS retesting and invalid assays drain on reagent stock
- Communication with MNF regarding supply
  - planning, stock control
- Bulking of batches
  - Test multiple batches in a single run (if assay layout permits)
- Procure the same batches of commercially available reagents e.g. ELISA conjugates
  - Rely on manufacturer material qualification reports
  - Avoid local requalification e.g. working concentrations

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