Considerations for Implementing Tests Approved by Another National Regulatory Authority

2nd International Workshop

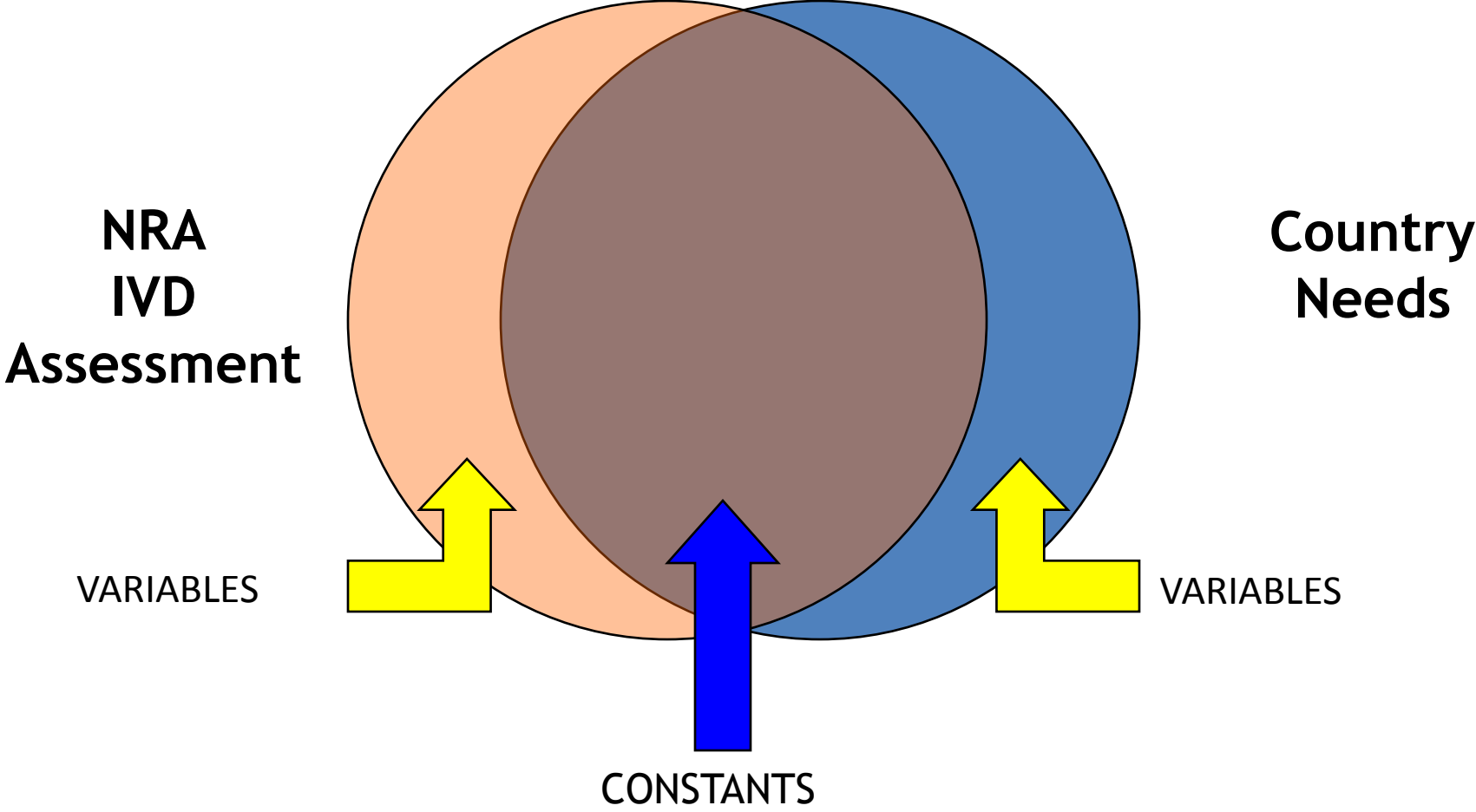Accessible and Quality Assured In Vitro Diagnostic Tests for Public Health Programs

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Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Considering Tests Approved by an NRA

$$R = \rho^l \, e^{-\frac{1}{2}\rho} \, H(\rho)$$

$$R' = \left(\frac{l}{\rho} - \frac{1}{2}\right) R + \rho^l \, e^{-\frac{1}{2}\rho} \, H'$$

$$\rho^2 R' = \left(l\rho - \frac{1}{2}\rho^2\right) R + \rho^{l+2} \, e^{-\frac{1}{2}\rho} \, H'$$

$$(\rho^2 R')' = (l - \rho)R + \left(l\rho - \frac{1}{2}\rho^2\right)\left[\left(\frac{l}{\rho} - \frac{1}{2}\right) R + \rho^l \, e^{-\frac{1}{2}\rho} \, H'\right]$$
$$+ \left(\frac{l+2}{\rho} - \frac{1}{2}\right) \rho^{l+2} \, e^{-\frac{1}{2}\rho} \, H' + \rho^{l+2} \, e^{-\frac{1}{2}\rho} \, H''$$

$$\frac{\frac{1}{\rho^2}(\rho^2 R')'}{\rho^l \, e^{-\frac{1}{2}\rho}} = \left(\frac{l}{\rho^2} - \frac{1}{\rho}\right) H + \left(\frac{l}{\rho} - \frac{1}{2}\right)\left[\left(\frac{l}{\rho} - \frac{1}{2}\right) H + H'\right]$$
$$+ \left(\frac{l+2}{\rho} - \frac{1}{2}\right) H' + H''$$
$$= \left[\frac{l(l+1)}{\rho^2} - \frac{l+1}{\rho} + \frac{1}{4}\right] H + \left[\frac{2l+2}{\rho} - 1\right] H' + H''$$

CONSTANTS

Constants?
Design and Manufacturing

- Product description
- Product design
- Design overview
- Formulation and composition
- Biological safety
- Key suppliers

- Documentation of design changes
- Manufacturing process
- Overview of manufacture
- Site of manufacture

Constants?
Product Performance

- Analytical studies
- Specimen types
- Analytical performance characteristics
- Accuracy of measurement
- Analytical sensitivity

- Analytical specificity
- Metrological traceability of calibrators and control material values
- Measuring range of assay
- Validation of assay cutoff
- Software verification and validation

Constants?
Other

- Commercial history (countries of supply)
- Quality Management System
  – Quality manual
  – Quality management system documents
- Inspection

VARIABLES

$$R = \rho^l\, e^{-\frac{1}{2}\rho}\, H(\rho)$$

$$R' = \left(\frac{l}{\rho} - \frac{1}{2}\right) R + \rho^l\, e^{-\frac{1}{2}\rho}\, H'$$

$$\rho^2 R' = \left(l\rho - \frac{1}{2}\rho^2\right) R + \rho^{l+2}\, e^{-\frac{1}{2}\rho}\, H'$$

$$(\rho^2 R')' = (l - \rho)R + \left(l\rho - \frac{1}{2}\rho^2\right)\left[\left(\frac{l}{\rho} - \frac{1}{2}\right) R + \rho^l\, e^{-\frac{1}{2}\rho}\, H'\right]$$

$$+ \left(\frac{l+2}{\rho} - \frac{1}{2}\right) \rho^{l+2}\, e^{-\frac{1}{2}\rho}\, H' + \rho^{l+2}\, e^{-\frac{1}{2}\rho}\, H''$$

$$\frac{\frac{1}{\rho^2}(\rho^2 R')'}{\rho^l\, e^{-\frac{1}{2}\rho}} = \left(\frac{l}{\rho^2} - \frac{1}{\rho}\right) H + \left(\frac{l}{\rho} - \frac{1}{2}\right)\left[\left(\frac{l}{\rho} - \frac{1}{2}\right) H + H'\right]$$

$$+ \left(\frac{l+2}{\rho} - \frac{1}{2}\right) H' + H''$$

$$= \left[\frac{l(l+1)}{\rho^2} - \frac{l+1}{\rho} + \frac{1}{4}\right] H + \left[\frac{2l+2}{\rho} - 1\right] H' + H''$$

Variables

- What does FDA approval/clearance of an IVD address?
  - Safety and effectiveness for marketing in the US
  - Test performance in predominantly US populations
  - Consistency of manufacturing at specific manufacturing sites
  - Test design for US users
  - Test design for US testing environments

Variables
Test Performance

- Testing in US populations
  - Population/region differences in test performance
  - Sensitivity/specificity/predictive values may vary by country/region/disease prevalence
  - Confounding factors (co-infections, environmental, other)

Variables
Manufacturing Site

- Manufacturing facility evaluated with product

- Same controls in place at manufacturing site not approved with product?

- Potential for significant impact on product performance

- Product design

Variables
Product Design

- US approved/cleared test designed for US operators and US conditions
  - Storage requirements (temperature/humidity) and stability
  - Instructions for use
  - Trained personnel
- Resource-limited settings
  - Temperature and humidity outside of validated range
  - Lack of trained personnel
  - Lack of special storage conditions
  - Unreliable power sources
  - Need for studies to demonstrate test shelf-life, shipping stability, etc.

Variables
Product Design, cont.

- "Regulatory versions" of products
  - Manufacturers produce different versions of the same test for use in different markets
    - Manufacturing site
    - Product quality
    - Different NRA degree of oversight
  - May lead to assumption that all tests by that name are the same

Variables
Risk

- Risk/benefit consideration may differ from region to region
- Nevertheless, it is critical for:
  - Performance parameters to be well characterized
  - Performance to be consistent from lot to lot
  - Labeling to be truthful

SUMMARY

- There are elements of that evaluation by an NRA that may be taken into account by countries who adopt a test previously approved by an NRA (constants).

- However, there are also critical elements that do not necessarily transfer (variables) and should be taken into account to assure maximum public health benefit in specific settings.

AN ANALOGY

Evaluating Previously Approved Diagnostics:
Reinventing the Wheel?

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Reinventing the Wheel?
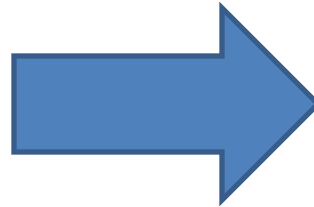

ROBUSTNESS

Matching the Wheel to the Terrain
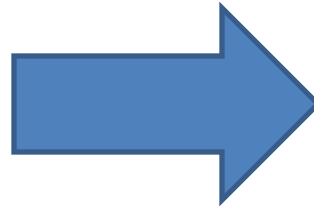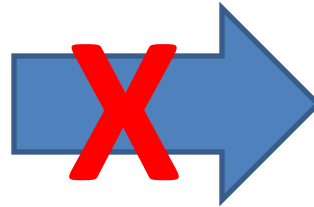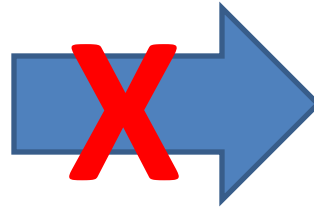
Matching the Wheel to the Terrain

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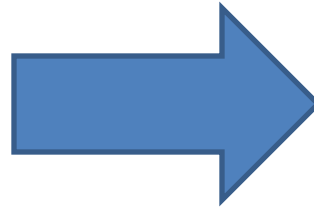# Matching the Wheel to the Terrain

Matching the Wheel to the Terrain

Where We Run into Problems…

Looks great, but won'

Where We Run into Problems...

Limited applicability

Where We Run into Problems...

Inappropriate adaptation

Ultimately leading to…

Obrigado!