Medicines & Healthcare products Regulatory Agency

NIBSC
Confidence in Biological Medicines

Are all assays equal?

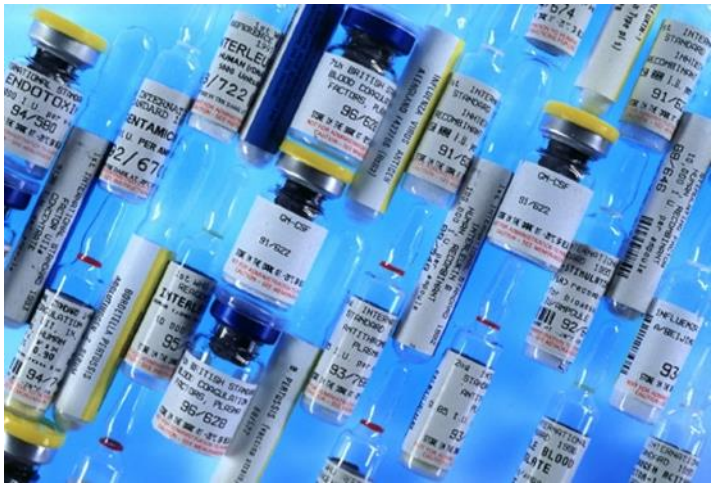
Mark Page

The National Institute for Biological Standards and Control

- UK government Institute funded by DoH
- 300 employees (70% scientific staff)
- WHO International Standards
- Serum, antigen, viruses, bacteria, allergens, cytokines, stem cells etc

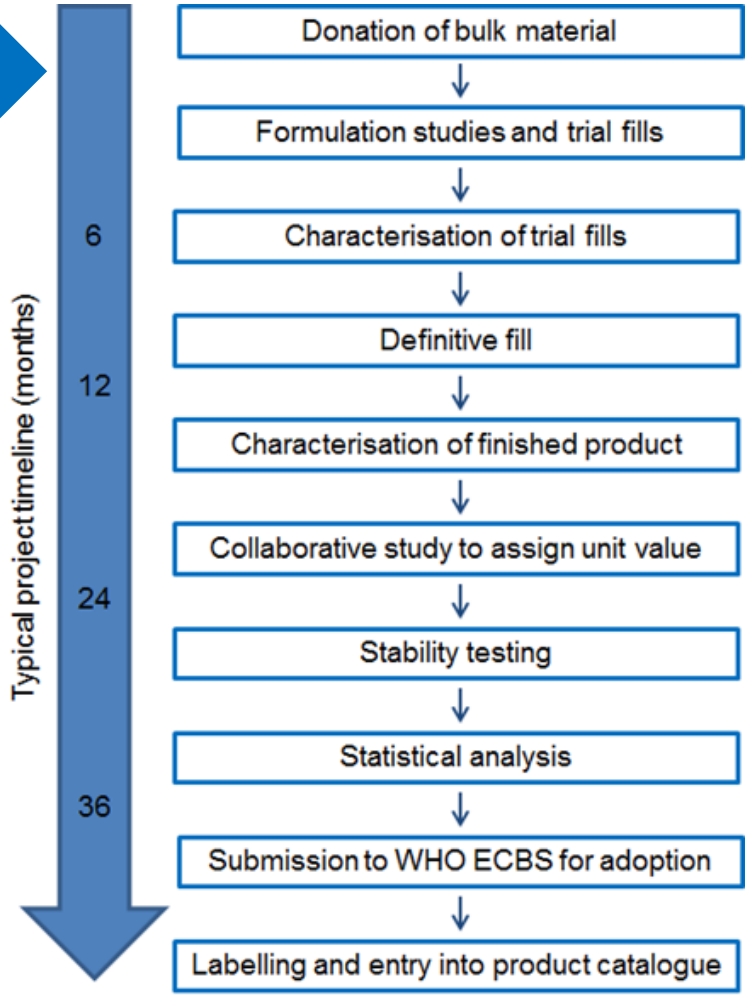
Types of standard

- **WHO International Standard**
  - highest order standard
  - established and endorsed through WHO Expert Committee on Biological Standardisation
  - 2 year time frame
  - assigned activity in international units
- **Working standards**
  - calibrated against the International Standard
  - routine use, high throughput assays
- **In vitro diagnostic standards**
  - assay monitors, in run controls
  - CE marked
- **>700 in NIBSC catalogue**
- **95% of world's standards**

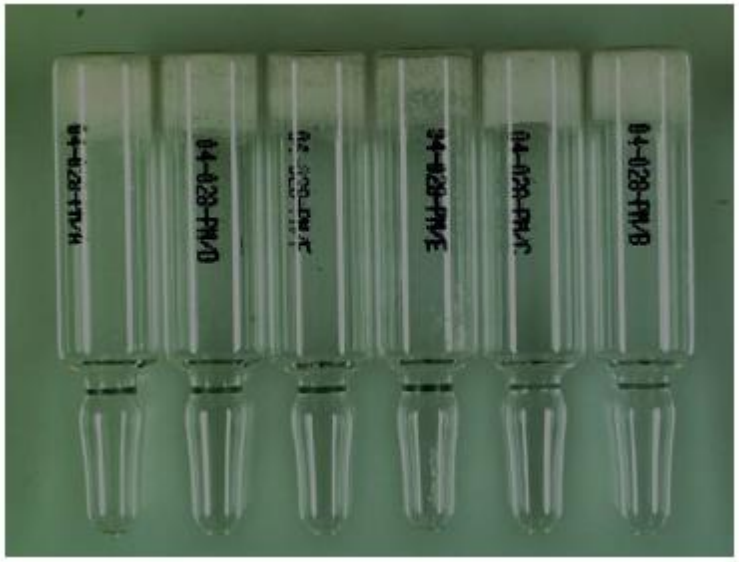


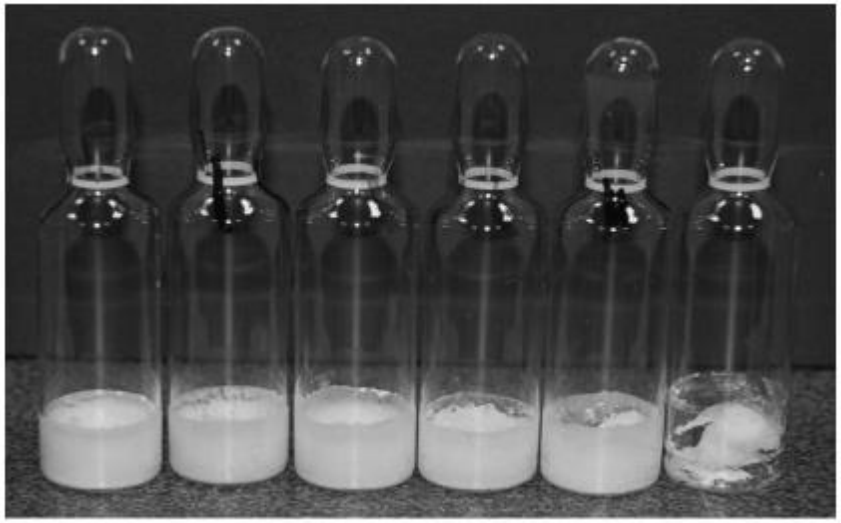
Standards projects - overview

Project endorsement
- NIBSC
- WHO ECBS



Process development (trial fills)





Internal run controls

Control material provided with the assay typically:

- Optimised for that assay
- Has a wide acceptable range
  - Less good at highlighting subtle changes
- Does not allow comparison of results between different assays
- Changes with every kit batch - does not show assay variability

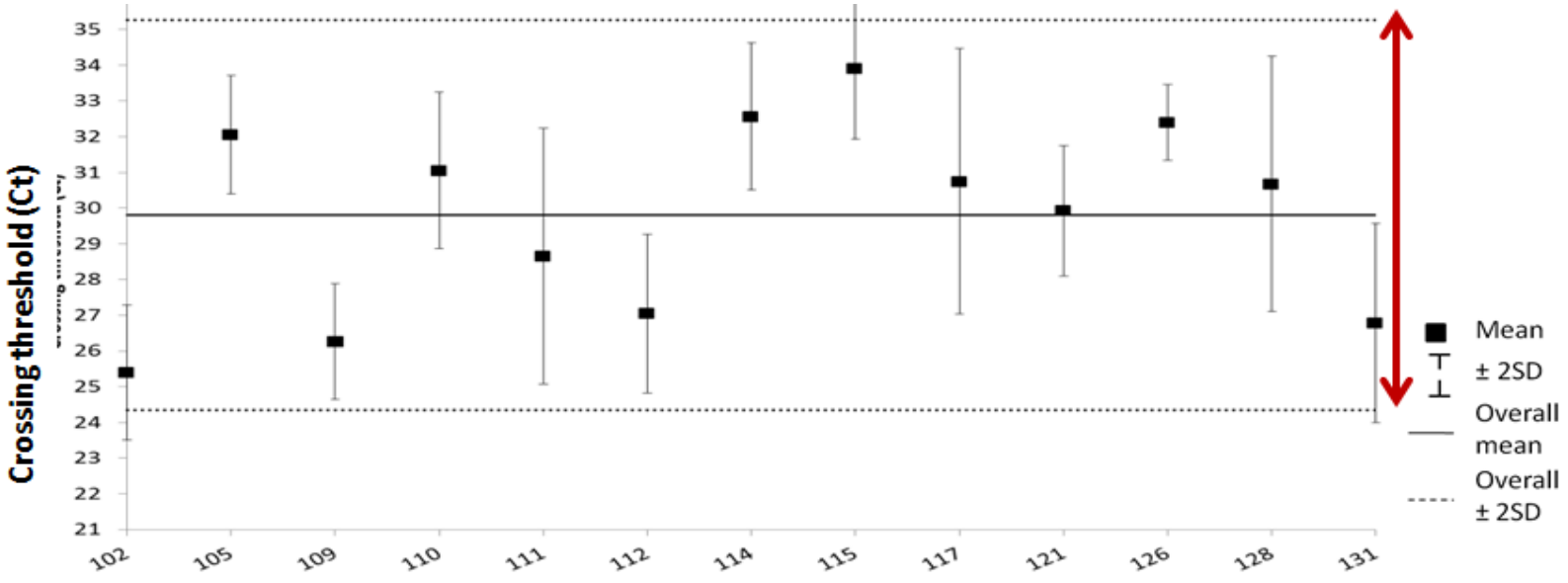
External run controls

- Controls that are not included in the kit
- Inclusion of a run control, EXTERNAL to assay controls, placed in every test permits regular monitoring of data for trends that indicate:
- Lot to lot variation in kit performance
- Early degradation of kit components
- Early evidence of equipment failure
- Variable operator performance

- **Leads to improved quality control of assay data**

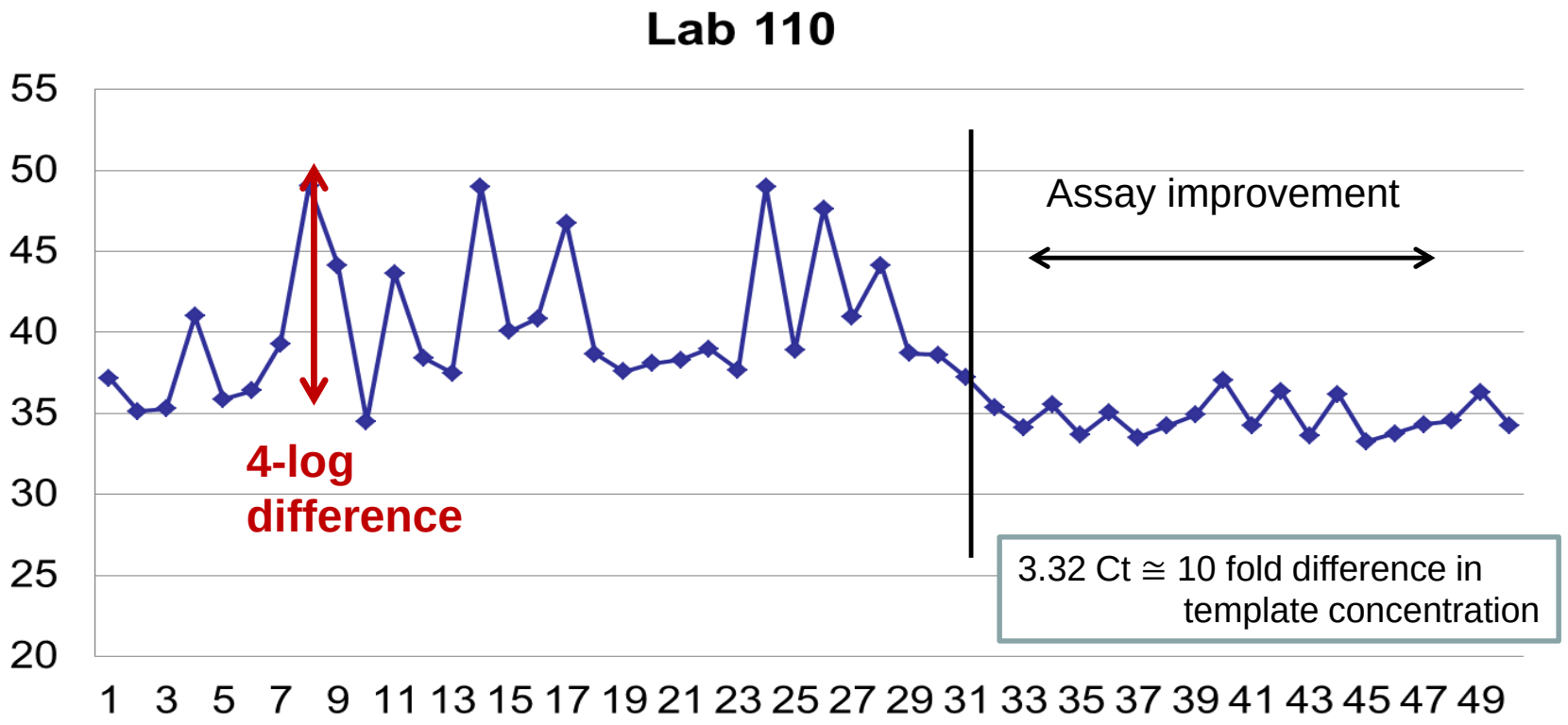
External run controls

- In 2008, 12 laboratories were sent tubes containing Norovirus, every tube contained identical material. Each lab was asked the same question:
- How much Norovirus is present?



The overall Ct difference between ± 2SD was 10.93. Given 3.32 Ct equates to ~ 10 fold difference in template concentration, that's a 1000 fold variation in results—for the **same** material.

Monitoring external run controls



Observing data over time highlights inconsistencies in early experiments, prompting changes for improved performance in later assays

External run controls

Typically labs will use a positive patient sample as an external control, however whilst that gives some consistency, there is no consistency between batches.

Traceability is needed!

Data from monitoring external run controls is good but values provided in copies or ct's are not comparable across assays.

BUT WITHOUT COPIES, HOW DO YOU QUANTIFY DATA?

WHY WOULD YOU WANT TO?

Anyone for coffee?

19.95 francs

498 pesetas

3.6 dollars

5.70 marks

Which coffee is the most expensive?

3 Euro

Biological standardisation

Providing laboratories with a means of comparison using the same unit of measurement

- Improve comparability between different lab data regardless of the assay
- In turn leads to better clinical management of patients.

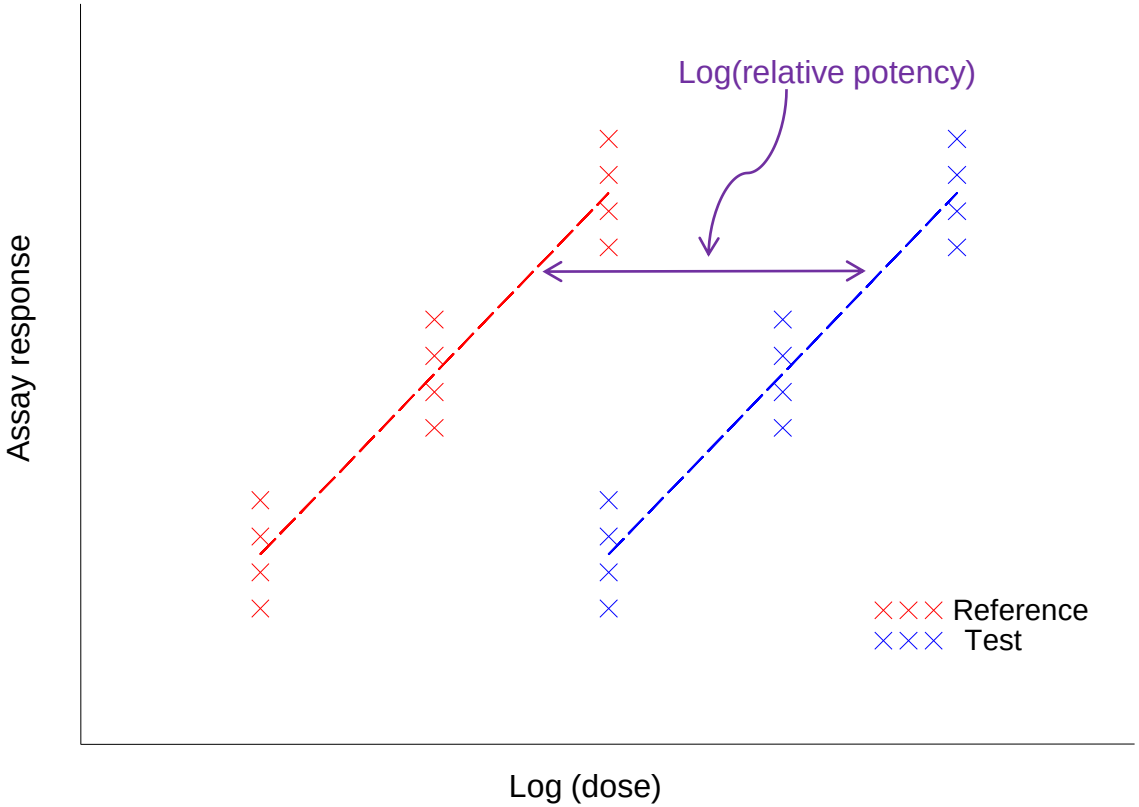
Biological Standardisation

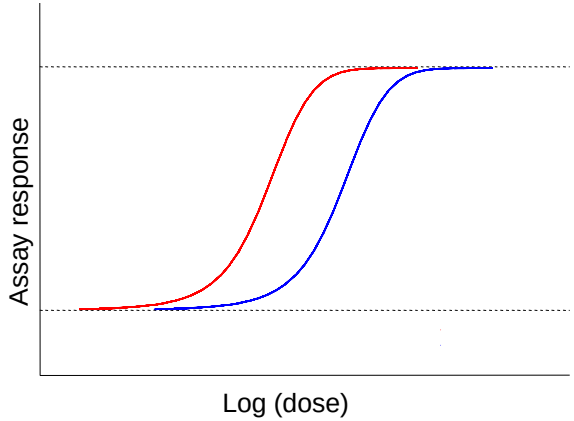
- By providing the same high level reference material to all laboratories enables the results to which all other controls can be compared and calibrated.

- International standards

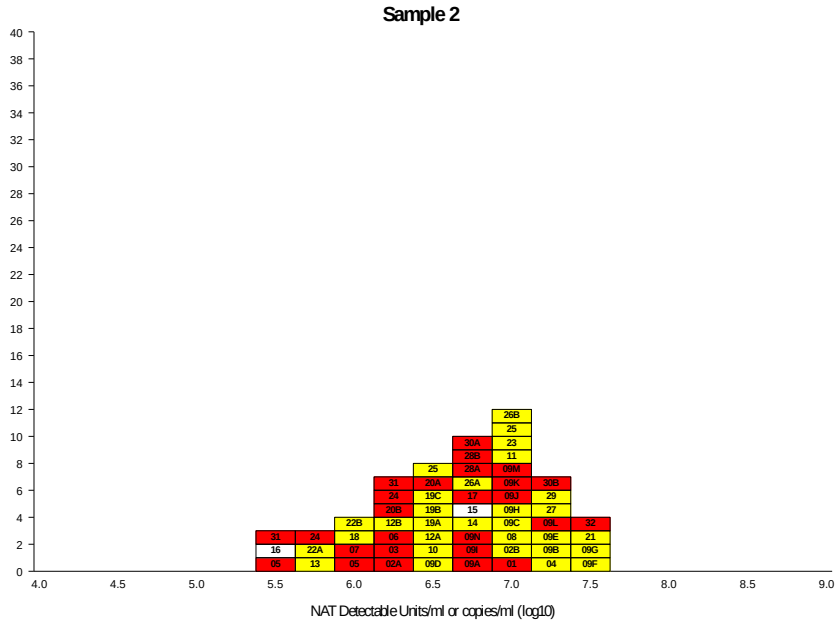
Statistical models

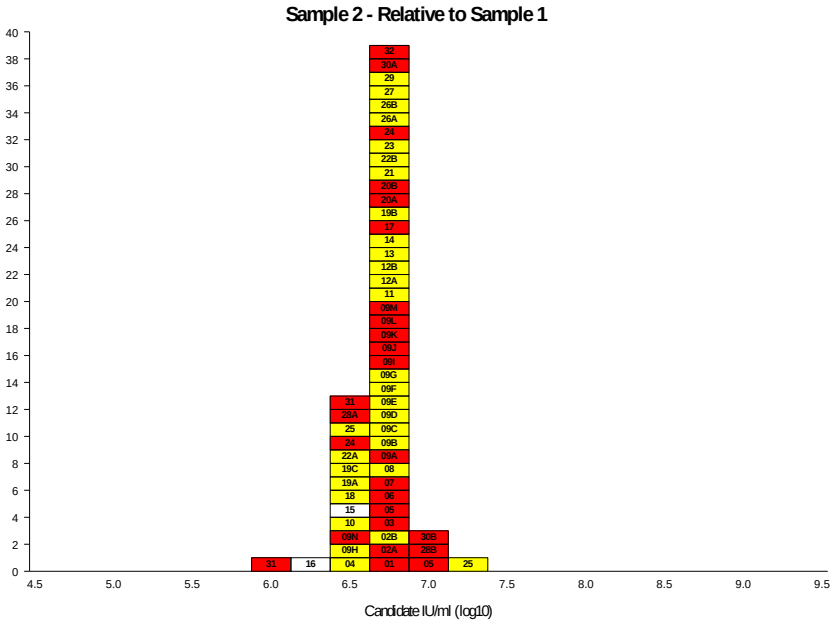
•Commonly used example: parallel-line model, “parallel” sigmoid curves - used to determine relative potency



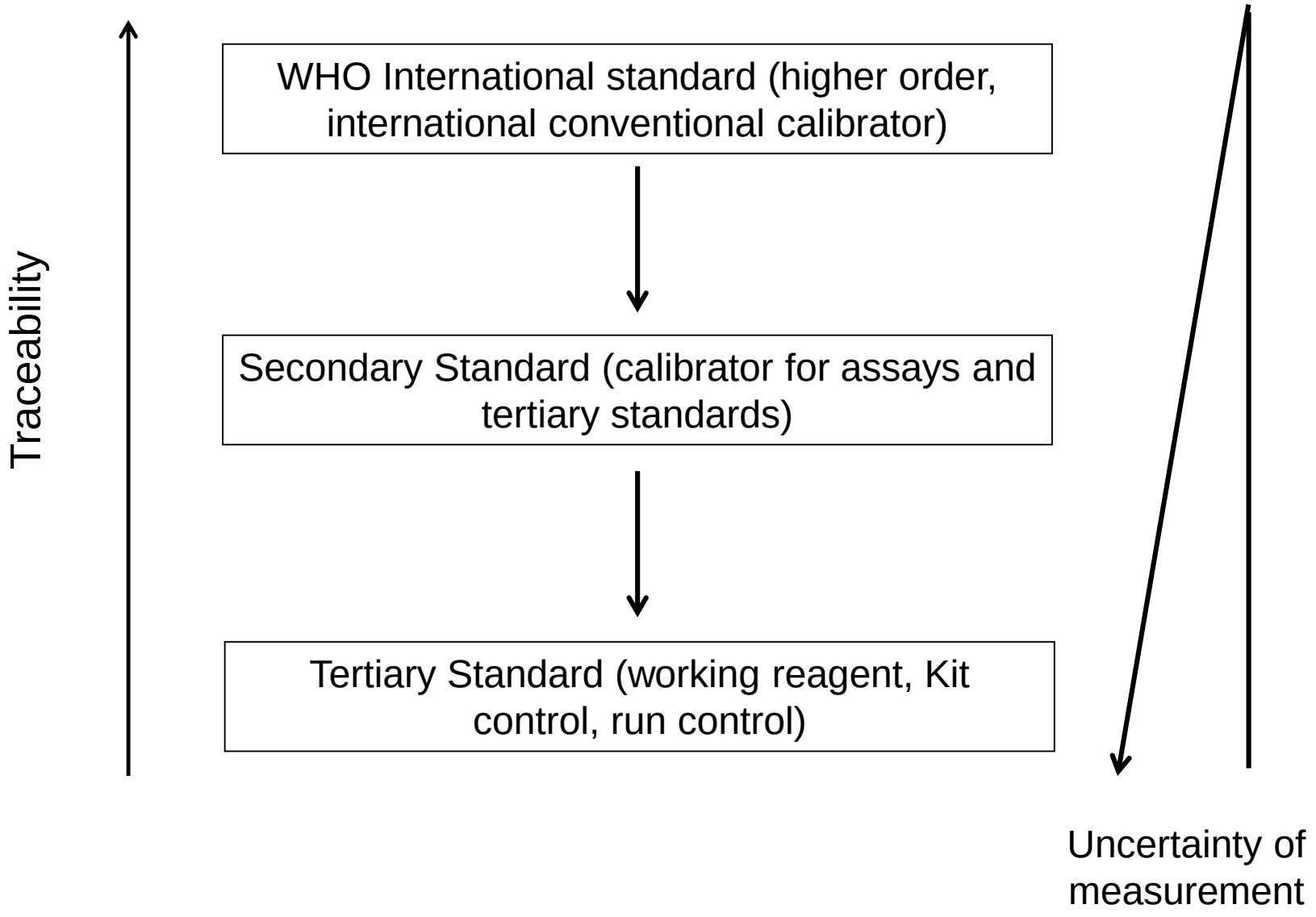


Reduction in inter-laboratory variability





Hierarchy of standards



Can any material act as a standard?

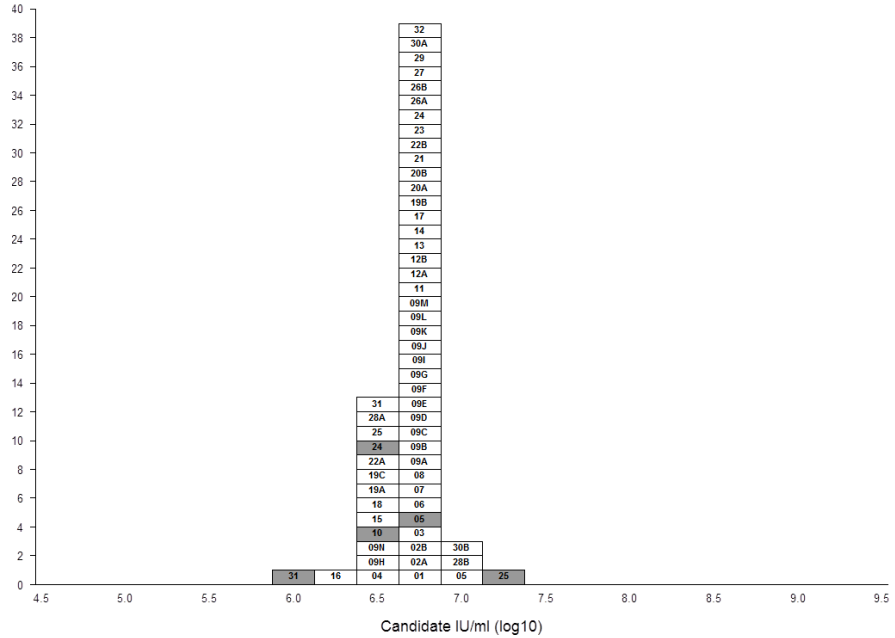
- NO! A standard must behave in a the same was as the clinical analyte it is measuring. Important considerations when designing a standard are:

*Analyte *Diluent *Concentration *Strain *Stability *Homogeneity *Specificity

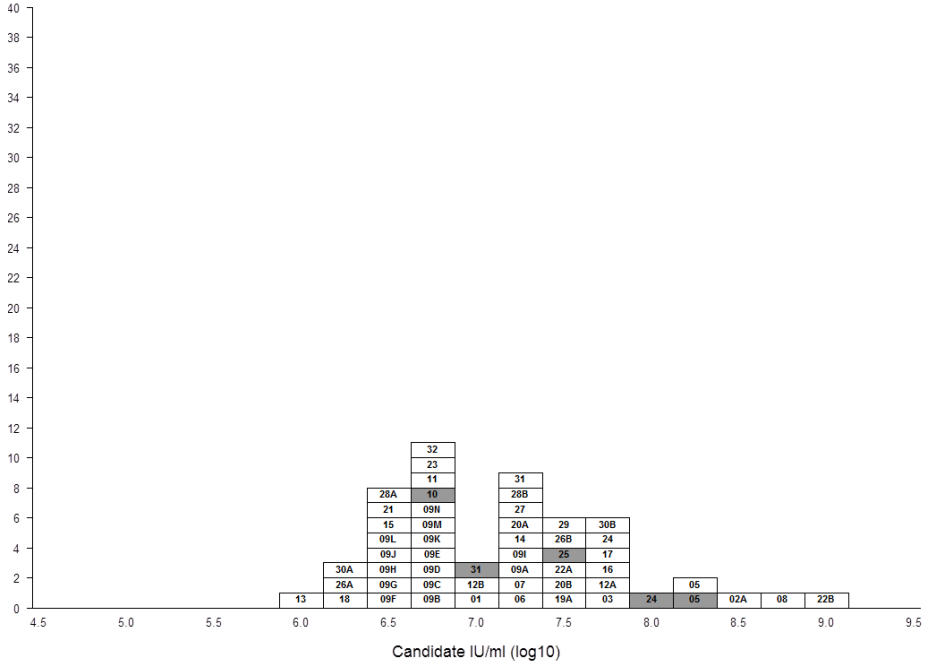
A standard should improve agreement between different assays

Good vs better

CMV - Whole Virus



CMV - Plasmid



- One size doesn't fit all
- In most cases a standard is better then no standard, but in some cases the wrong type of standard can make the situation worse

Conclusions

- External control material is essential to ensure the accuracy of results.
- The result provided by one assay is not comparable with another unless they are calibrated to a common standard.
- Different controls may have different applications, but they complement each other in the overall assurance of a test result.
- Controls must be calibrated correctly and formulated from appropriate materials if they are to yield meaningful results.