Implementation of traceability requirements in the IVD Directive Report to the JCTLM

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European Diagnostic Manufacturers Association (EDMA)

EDMA

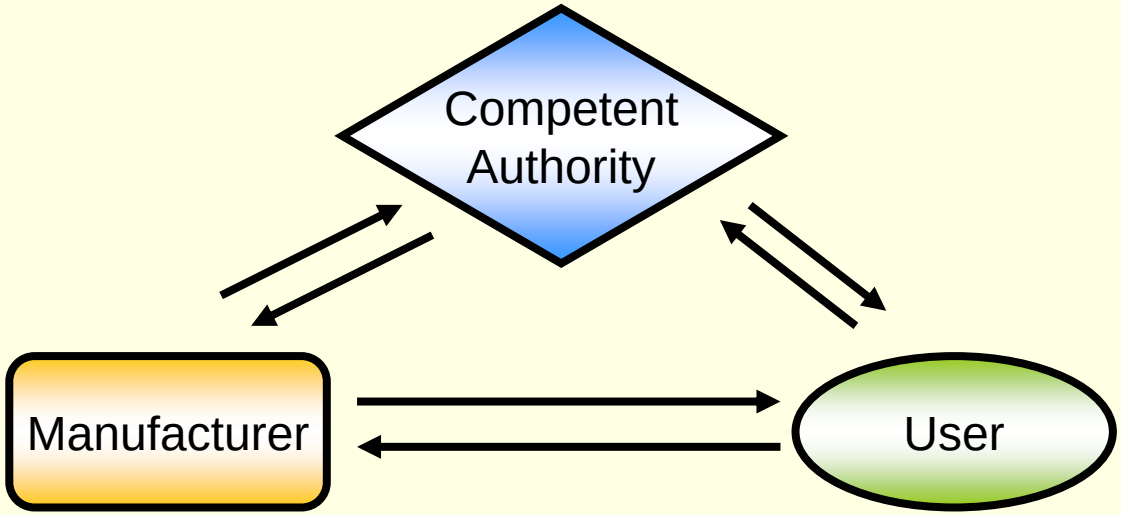
- European Diagnostics Manufacturers Association
- Represents IVD manufacturers in Europe – through its members 15 IVD companies and 21 National Associations
- One of the main pillars of EDMA is regulatory affairs – in particular ensuring compliance with the IVD Directive which includes the requirements of Traceability.

Directive 98/79/EC on *in vitro* diagnostic medical devices

Essential Requirements (Annex I)

"*The traceability of values assigned to calibrators and/or control materials must be assured through* ***available*** *reference measurement procedures and/or* ***available*** *reference materials of a higher order*"

Implementing Traceability in the IVD industry - concerned parties

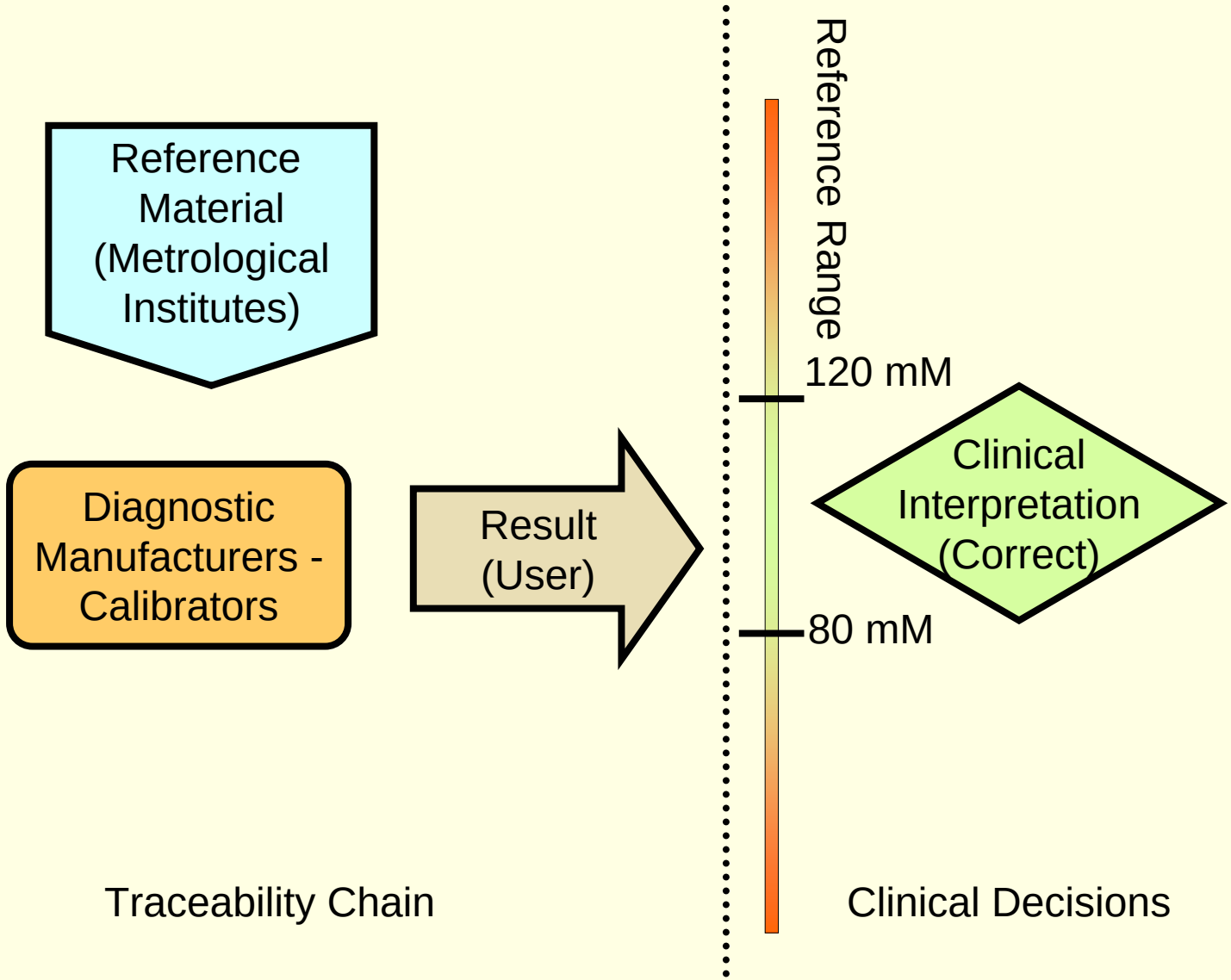


User – obtains the final value in the traceability chain

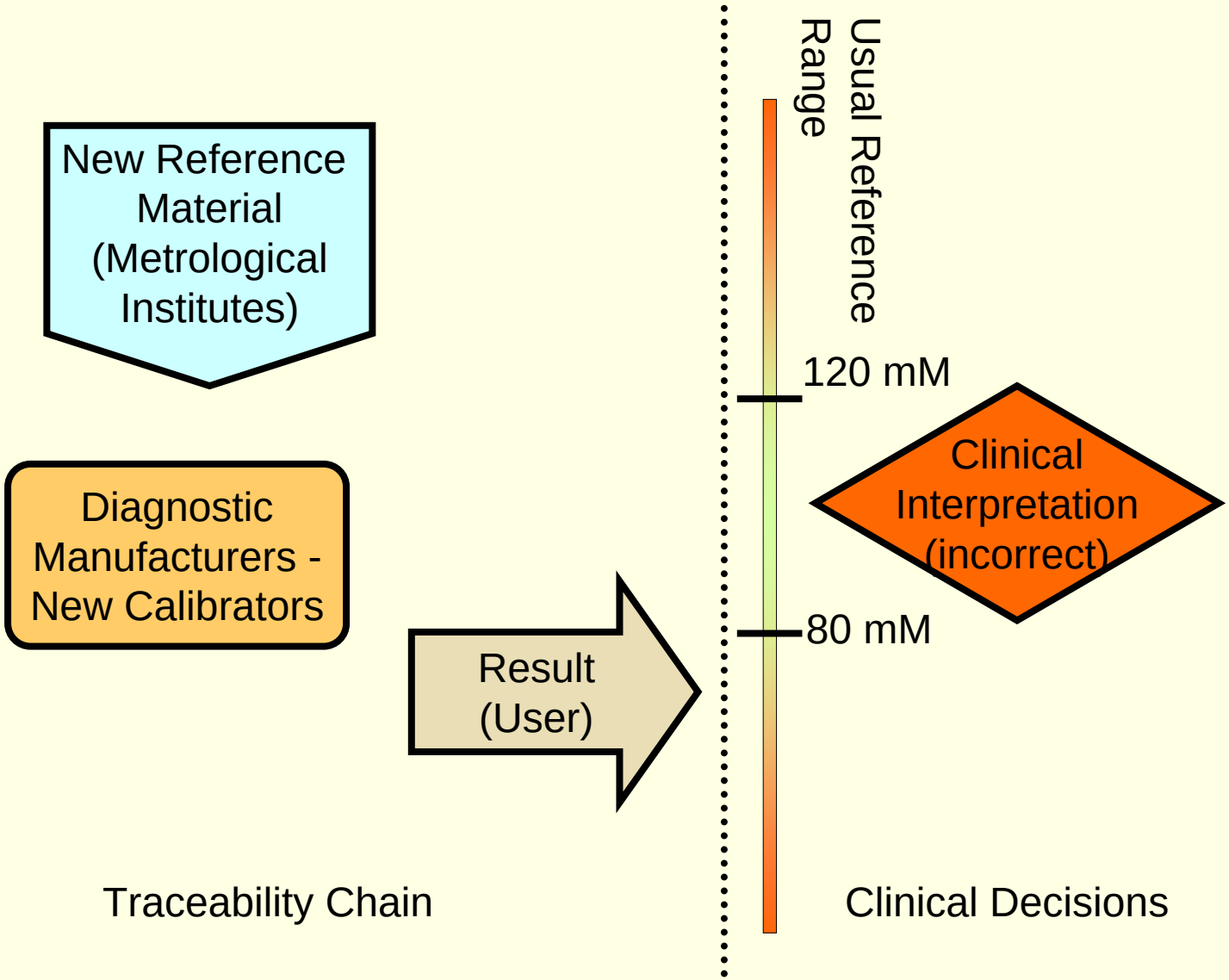
Manufacturer – Provides both the devices and the information to allow the user to obtain this value and ensure its traceability

Competent Authority – ensures that manufacturers and users comply with existing regulations. Provides guidance and performs inspections as appropriate.

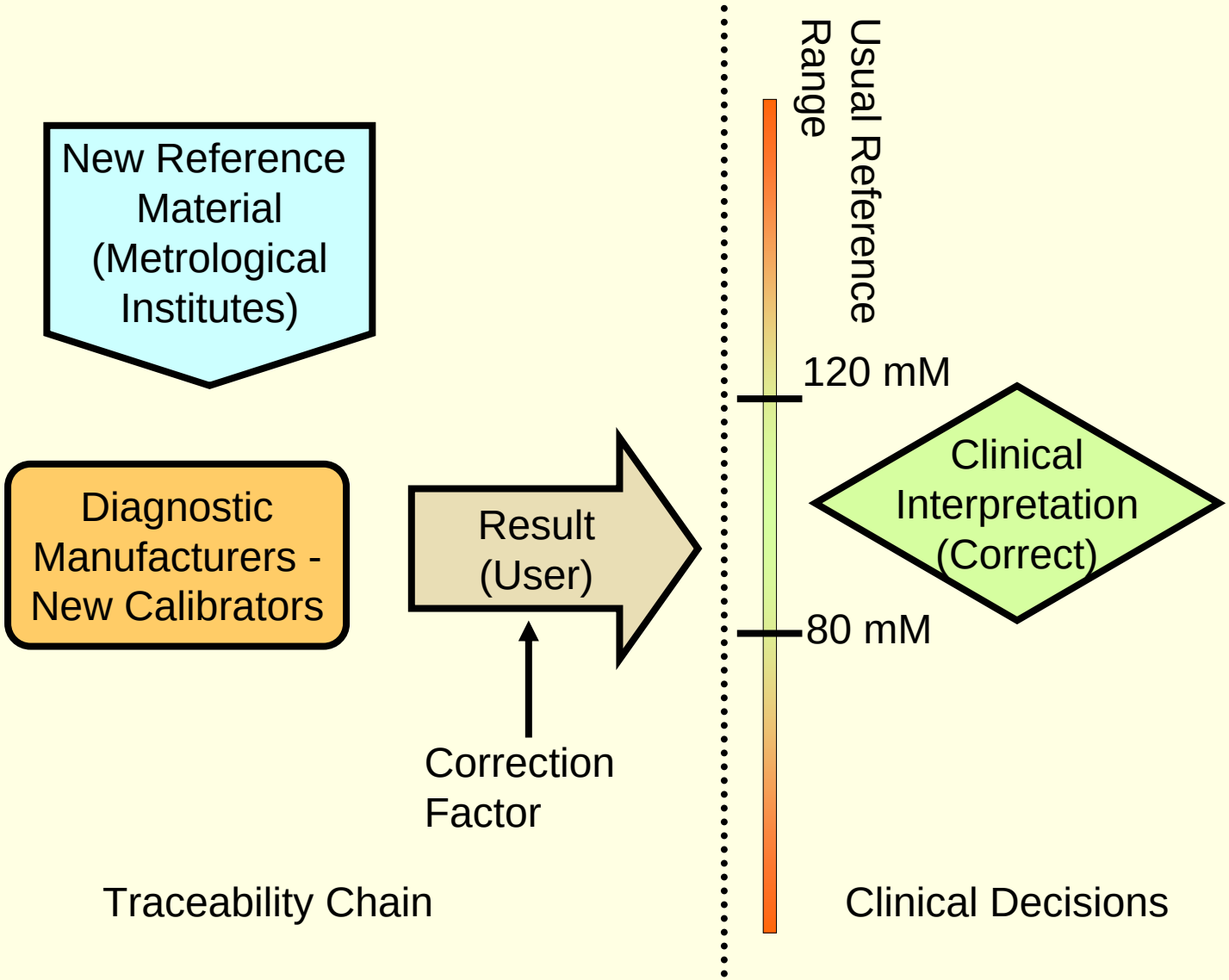
Values in Clinical Chemistry



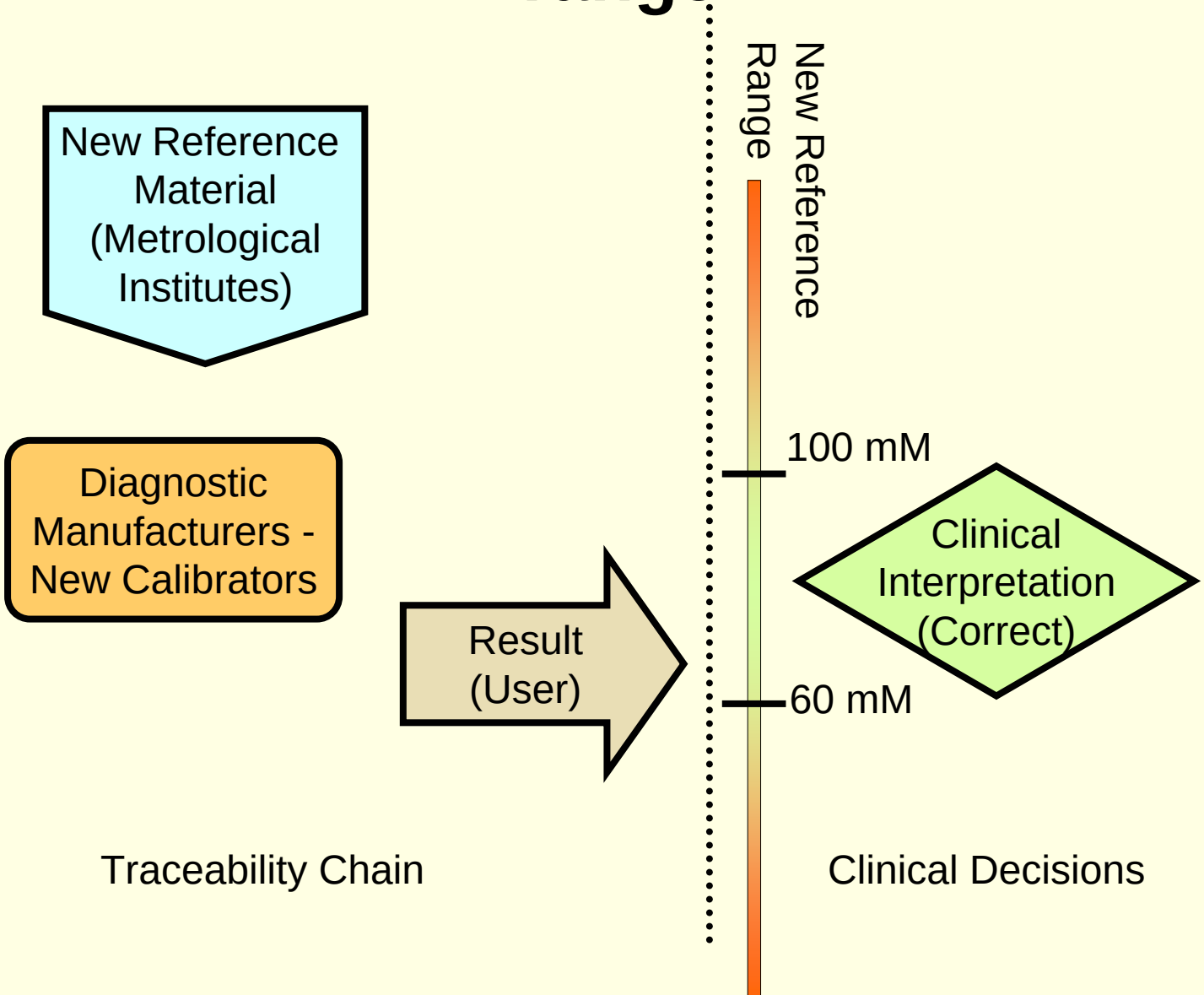
New reference material



One option– Correction factor



Second option: New reference range



Obtaining values in clinical chemistry

- When there is a change in reference materials this affects the final value. It is crucial that all concerned parties in both the traceability chain and the clinical decision chain are aware of this effect.
- Different parties are involved in obtaining a value: metrological institutes, manufacturers, and users.
- **The value in itself is of importance only insofar as it can be used to make a clinical decision.**
- There is often confusion between issues concerning the values and issues concerning the clinical decisions (interpretation of the values)
- Reference materials cannot be changed overnight! (EDMA received a request for a change in reference materials a week after the JCTLM lists were published!)

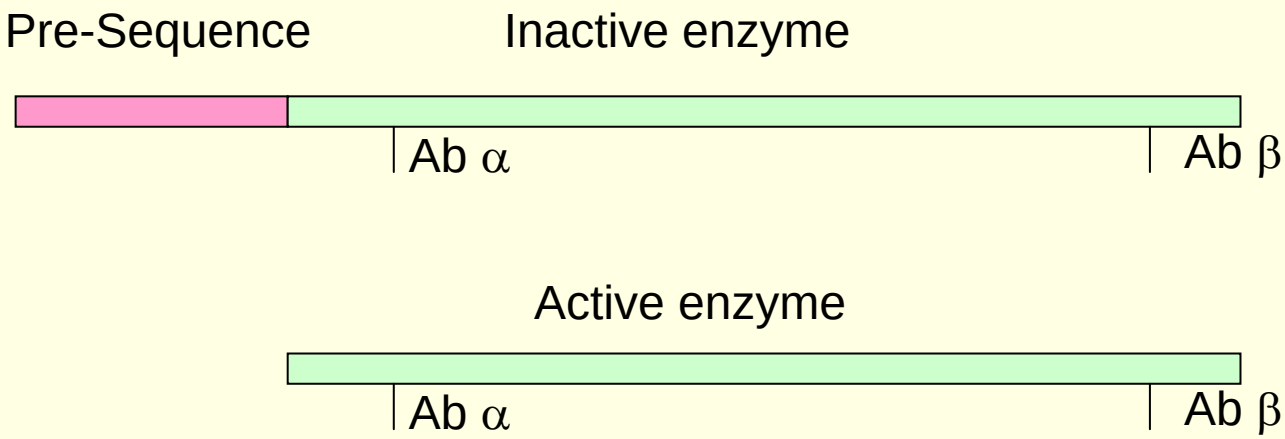
Traceability in practice

"If traceability to a higher order reference material or reference procedure is ensured, then the values will be the same for all kits measuring a given analyte."

Do you agree with this statement?

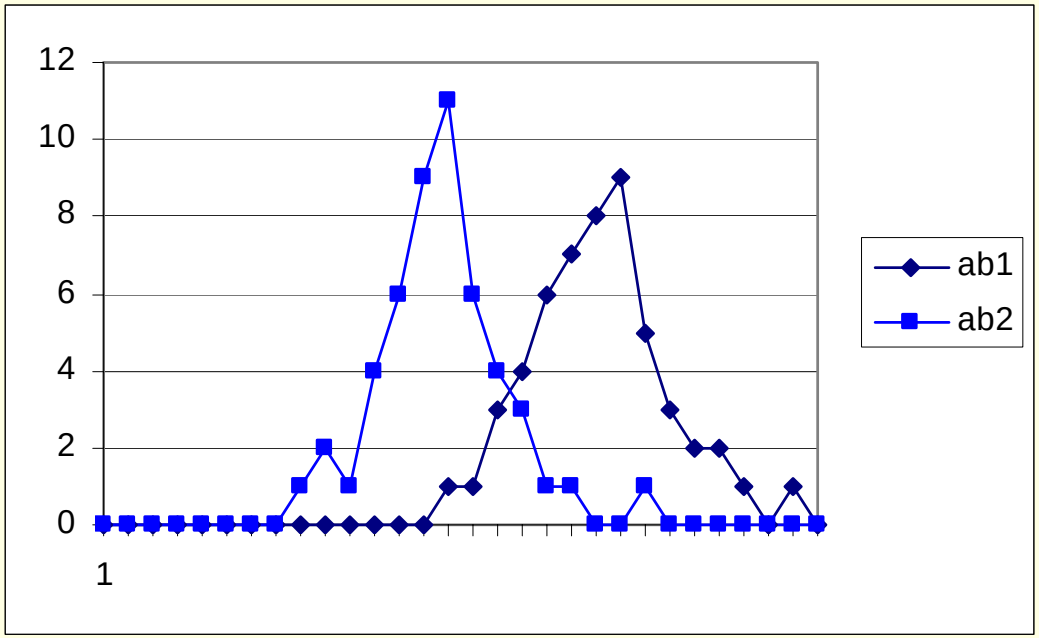
That is the expectation of many users and competent authorities. Consequently they argue that if the values are not the same, manufacturers are not in compliance with the IVD Directive.

Example of a problem



- Single gene
- Single transcript
- One active and one inactive form of an enzyme
- No post transcriptional modification
- Both Ab α and Ab β can detect only a single epitope yet perform identically on the control material (purified recombinant enzyme) which contains both epitopes
- Both kits reach the market at the same time – but results on patient sera are different.

Results in practice

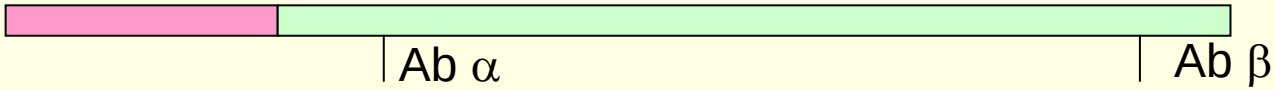


Clearly on the field the two kits will not perform in the same way

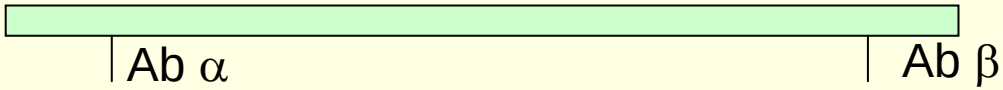
Reason?

Pre-Sequence

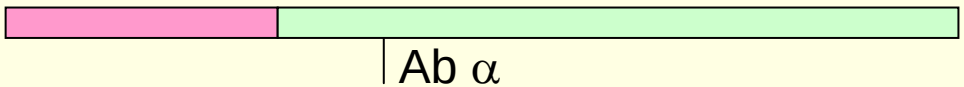
Inactive enzyme



Active enzyme



Truncated pre-enzyme



Issue – enzyme isoform pre-truncated

Which antibody gives the correct value then?

Why this discrepancy?

- Both kits are giving a metrologically correct result
- However their measurand is different – two different epitopes, even though both measurands are present in the reference material.
- Further studies will be needed to find out what is clinically relevant.
- **Issue is not related to metrology but the sample to be measured (different isoforms, different matrix) and the consequential clinical interpretation.**

Discrepancies in Values

- Generally accepted that traceability does not result in identical values. *"Traceability does not make the results identical; […] But traceability through calibration permits meaningful comparison by ensuring 'consistency' of measurement units."* (EURACHEM guide)

- In the case of traceability in clinical laboratories many factors contribute to making values non-identical, eg poorly characterized measurands, matrix effects, etc.

- In a clinical setting it is essential to interpret values in a clinically relevant fashion.

Great expectations

Oft expectation fails, and most oft there
Where most it promises; and oft it hits
Where hope is coldest, and despair most fits.
All's Well That Ends Well II, i, 145-147

- **Different stakeholders in the implementation of traceability have different expectations of which effect the fact of ensuring traceability will have in the clinical setting.**

- **EDMA is actively working to inform concerned parties on the work of the JCTLM and the importance of traceability.**

EDMA - Information

- EDMA informs its members (manufacturers) on the work of the JCTLM to ensure a transition to reference materials of higher order, where these are available. – Publishing of newsletters and position papers.

- In response to numerous inquiries and letters by CAs, EDMA always refers to the published JCTLM lists for higher order reference materials and methods.

Conclusions

- Traceability – involves various groups in its correct implementation – Metrological laboratories, manufacturers, users, and competent authorities – critical partnership
- Ensuring traceability to a higher order reference material or higher order reference procedure does not guarantee convergence of values amongst the various assays for a given analyte – even though this is what is expected from it by some of the concerned parties
- Sufficient time is needed to ensure a smooth transition from one reference material to another without compromising the correct reference ranges and therefore patient safety
- EDMA is working to promote both the importance of traceability and the work of the JCTLM
- Metrological Traceability is only part of the process that leads to a clinical decision

Thank you

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Questions?

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