# The role of APS in international guidelines and standard dealing

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**JIB Paris November 17, 2023**

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# Defining analytical performance goals 15 years after the Stockholm Conference

**8th CIRME International Scientific Meeting**

Milan (IT)
24-25 November 2014

with the auspices of IFCC International Federation of Clinical Chemistry and Laboratory Medicine

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# Story of APS

Stockholm Conference 1999
General Conference Milano 2014
CELME Prague 2023

DE GRUYTER Clin Chem Lab Med 2015; 53(6): 833–835

**Consensus Statement**

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

**Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine**


CZECH SOCIETY
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EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE
5th Symposium CELME 2023
CUTTING EDGE OF LABORATORY MEDICINE IN EUROPE
ANALYTICAL PERFORMANCE SPECIFICATIONS: MOVING FROM MODELS TO PRACTICAL RECOMMENDATIONS
The aim of this conference is to go through and discuss the three different models agreed by the Milan 2014 EFLM Strategic Conference to set APS for the medical laboratory and to give practical examples on how this can be done.
Prague, Czech Republic, Charles University | October 12–13, 2023

# Analytical performance settings

**Better accurate tests for better patient outcomes improve**

- the diagnostic effect of a test - better, rapid, more appropriate diagnoses and decrease the rate of misdiagnosis
- the therapeutic effect of a test - support better treatment process

**Other impacts of the test on healthcare**

- test safety
- speed
- convenience and
- costs

# Analytical Performance Specification

**Criteria that specify the quality required for** analytical performance in order to deliver laboratory test information that would satisfy *clinical needs* for patients care and improving *health outcomes*.

***What amount or level* of quality we need and which uncertainty can be accepted for patient safety ???**

- an acceptable risk of harm from decisions based on a lab test result

| Stockholm Criteria 1999<br>*Scand J Clin Lab Invest 1999;49:475-585* | Outcome-related Criteria 2010<br>*Clin Chem 2010;56:714–22* | Milan Models 2014<br>*CCLM 2015;53:833-35* |
|---|---|---|
| 1. Effect of AP on clinical outcomes | | 1. Effect of AP on clinical outcomes |
| | | 1a. direct effect on outcomes |
| 2. Effect of AP on clinical decisions | Effect of AP on clinical decisions<br>APS based on: | 1b. indirect effect of AP on probable clinical outcomes |
| | D. guideline driven clinical decisions | - clinical decisions |
| | E. analysis of follow-up test ordering | - classification of patients |
| | F. decision analytic models | - simulation or decision analytic models |
| 2a. based on biological variation | B. APS based on biological variation | 2. APS based on biological variation |
| 2b. based on clinicians' opinion | C. APS based on surveying clinical needs | |
| 3. National or international recommendations | | |
| 4. APS set by external bodies | A. APS defined by external bodies | |
| 4a. Regulator | A1. Regulator | |
| 4b. EQA organiser | A2. EQA organiser | 3. State of the art |
| 5. State of the art | | |
| 5a. Data from EQA | | - Data from EQA |
| 5b. Publications | | - Literature |

# Models to set Analytical Performance

**Model 1. Clinical outcome - Based on the effect of analytical performance on clinical outcomes**

*1a. Direct outcome studies*

*1b. Indirect outcome studies*

**Model 2. Biological variability - Based on components of biological variation of the measurand**

**Model 3. State of the art**

# Model 1. Clinical outcome - Based on the effect of analytical performance on clinical outcomes

- **Applied when the measure and has a central and well-defined role in the decision making of a specific disease or a given clinical situation and test results should be interpreted through established decision limits.**
- **Pros**
  - Results influence patient care and affect clinical outcomes
- **Cons**
  - Requires a demonstrated relationship between the measurand, medical decisions and clinical outcomes
  - Few published examples because studies can be difficult to perform

# Model 1 – Clinical outcomes

***1a. Direct outcome studies***

Assess the impact of analytical performance of the test on clinical outcomes.

***1b. Indirect outcome studies***

Assess the impact of analytical performance of the test on the probability of clinical outcomes by assessing the impact on medical decisions and subsequent patient management as intermediates to patient health outcomes.

# Models 1a and 1b from 2014 to 2023

- more or less agree that model 1a is almost impossible
- Model 1b:
  - assess the impact of CV and bias on clinical classification;
  - do not directly translate to Model 1 APS; they just tell you what classification errors occur with a certain degree of imprecision and bias in a certain population.
  - Different simulation studies, either theoretical or by asking clinicians have been done.
  - The «bias formula» is actually (mainly) based on a Type 1b model

- Model 1b approaches, so far…

…BUT…

How much analytical error is tolerable without severely affecting disease classification, management decisions and health outcomes?

# Model 2. Biological variation (BV)

- **Applied to measurands with high homeostatic control or in a *"steady state"* status when a subject is in good health,**
- ***Steady state* is defined as:**
  - **a situation where a measuand has to be kept at a certain concentration level in the blood otherwise the body will suffer showing symptoms (the measurands is under strict homeostatic control, e.g., plasma ions);**
  - **a situation where a measurand has de facto a stable concentration, but deviations from this concentration will not in itself cause symptoms (e.g., serum creatinine, total protein).**
- Pros
  - Available for many measurands, with defined criteria for assessing study quality
- Cons
  - Many of the studies used to establish BV have limited population diversity
  - May not be realistic given current technology for some measurands
  - Multiple methods for calculating BV can yield different values

# Model 2. Based on components of biological variation of the measurand

This attempts to minimize the ratio of ‘analytical noise’ to the biological signal. The advantage is that it can be applied to most measurands for which population-based or subject-specific biological variation data can be established.

There are limitations to this approach, including the need to carefully assess the relevance and validity of the biological variation data, e.g., the presence of ‘steady state’, the appropriate time intervals, effect of inter-current illness and effect of measurand concentrations.

# The Model 2 – problems

- The model 2 should not be used for measurands having not sufficient homeostatic control (e.g., most hormones): not acceptable to use the BV-based model to derive APS for all measurands just because the BV information is now more easily obtainable.
- BV published data of varying quality and quite heterogeneous
- Safe application for deriving APS requires prior critical appraisal
- Need for standards (i.e., a set of attributes to enable the data to be effectively transmitted and applied)

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## WHAT'S NEW

**The EFLM Biological Variation Database is now live!** The database delivers updated evidence-based biological variation (BV) estimates to users worldwide. Click here to access the EFLM BV databse

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# EFLM Biological Variation Database

Search for analyte Search

| Meta - Analysis | List of all BV Estimates | Measurands |
| --- | --- | --- |
| List of BV estimates for all measurands<br>Go | View individual BV estimates<br>Go | Show all Measurands<br>Go |
| Overview of meta-analysis derived BV estimates with APS and RCV calculation | Overview of all BV records with publication details | Overview of BV data sets for each measurand |

DE GRUYTER

Clin Chem Lab Med 2023; 61(5): 741–750

**Review**

Sverre Sandberg*, Anna Carobene, Bill Bartlett, Abdurrahman Coskun, Pilar Fernandez-Calle, Niels Jonker, Jorge Díaz-Garzón and Aasne K. Aarsand

# Biological variation: recent development and future challenges

https://doi.org/10.1515/cclm-2022-1255
Received December 10, 2022; accepted December 12, 2022; published online December 20, 2022

**Abstract:** Biological variation (BV) data have many applications in laboratory medicine. However, these depend on the availability of relevant and robust BV data fit for purpose. BV data can be obtained through different study designs, both by experimental studies and studies utilizing previously analysed routine results derived from laboratory databases. The different BV applications include using BV data for setting analytical performance specifications, other standards for deriving and reporting BV data, the EFLM Biological Variation Database and new applications of BV data including personalized reference intervals and measurement uncertainty.

**Keywords:** biological variation; BIVAC; EuBIVAS; personalized reference intervals (prRI); reference change value.

## Background

# The Model 2

- **A huge effort has been done to establish reliable data for within- and between subject biological variation.**
- **Concept of model 2 is that analytical noise should be low compared to biological variation.**
- **During the CELME 2023 a new model for calculating optimum and minimum APS will be proposed.**

# Model 3: Based on the state of the art

- **When a measurand has neither central diagnostic role nor strict homeostatic control.**
- **This model does apply for urinary measurands, for which the concentrations varied.**
- **This model can be temporarily used also for those measurands still waiting for the definition of outcome-based APS or while waiting for robust biological variability data.**
- **State-of-the-art has been defined as:**
  - “the highest level of analytical performance technically achievable by field methods” (Milan conference, best option);
  - “the performance of the best 20% of laboratories in an EQAS” (Milan conference, alternate option);
  - “the mean performance declared for that test by the most relevant manufacturers”.

# Model 3. State-of-the-art

- **When models 1 and 2 do not fit.**
- **We have seen that this has been interpreted in different ways .**
- **It will be discussed what is actually meant by «state of the art» and how we can determine it.**
- **Pros**
  - Can be determined for any measurand and specimen type
  - Obtainable from PT / EQA surveys and by some accrediting agencies (eg, US CLIA)
- **Cons**
  - Not linked to patient health or clinical outcomes
  - PT/EQA samples not always commutable with patient specimens
  - Reflect current state – not aspirational and therefore may not drive improvement

# Problems with Model 3 - the state-of-the-art

- **No scientific background: how good the ‘highest’ is?**
- **Lack of neutrality (dependency on industry defined quality).**
- **There may be no relationship between what is analytically achievable and what is clinically needed.**
- **The myth of state-of-the-art as a ‘rescue’ model when APS correctly obtained with other more appropriate models for a certain measurand appear too stringent should be dismantled.**

# Interactions between Models 1

**Interaction between models 2 and 1**

- There cannot be a proven clinical need with precision $<CV_I$ criteria
- In this setting, more samples are needed, not better assays
- **Conclusion:** Good precision based on biological variation can be seen as a “limiting criteria”. There is no need to be better.

**Interaction between models 3 and 1:**

- Only current assays are in use to generate evidence
- Can it be assumed that better assays will improve outcomes?
- **Conclusion:** A model 1 approach cannot propose an APS tighter than Model 3

# Interactions between Models 2

**Interaction between models 3 and 1 & 2**

- **Setting APS based on assay performance that is not available is not useful in the routine lab**
- **If a better assay appears to be needed, this becomes a “testable hypothesis”**
- **For example, would a serum sodium assay with a desirable $CV_A$ (<0.25%) improve patient outcomes?**

# EFLM – Which Milan Model to Use?

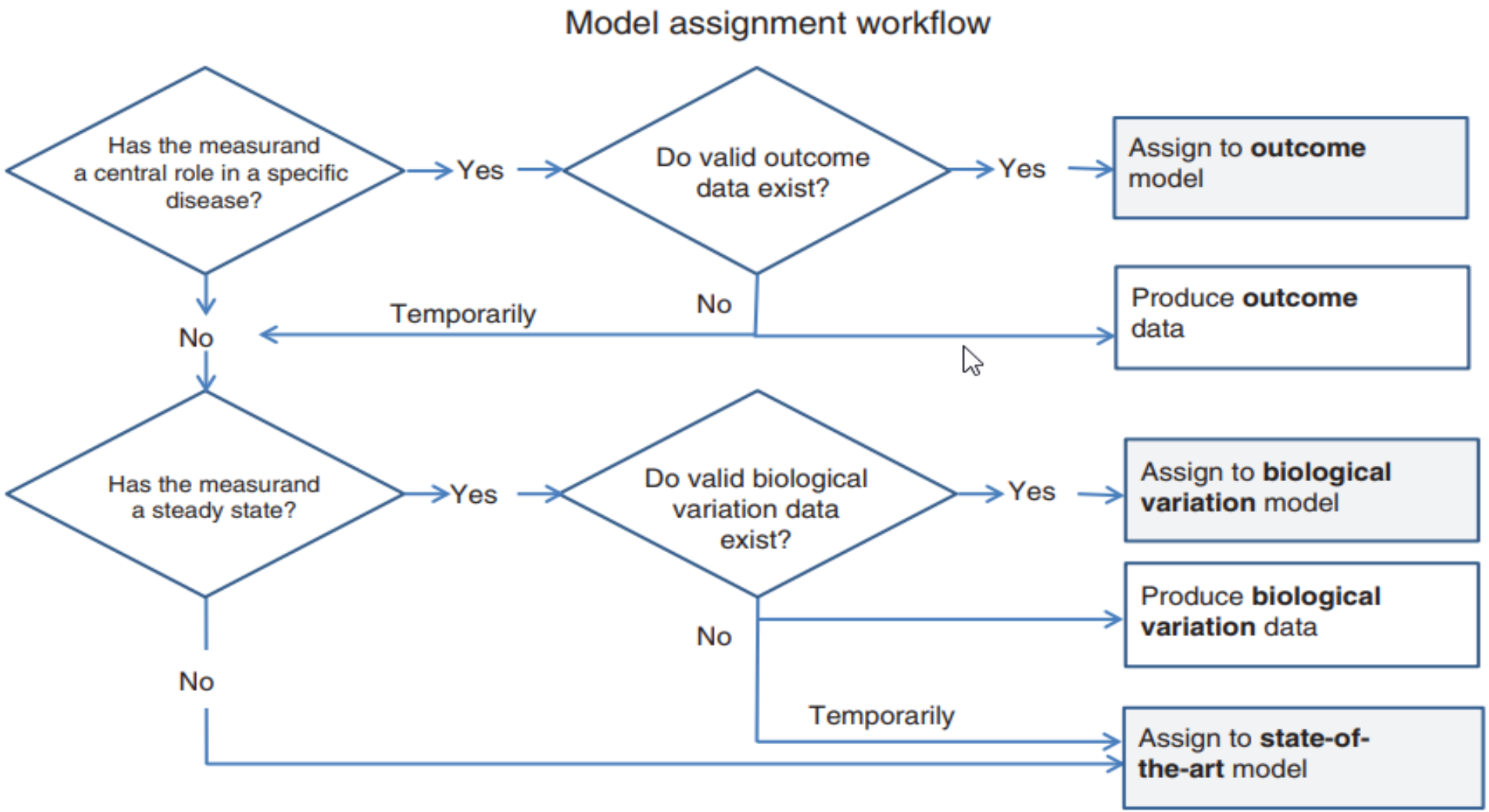



**Figure 1:** Workflow for assignment of a measurand to a defined analytical quality specification model.

CCLM 2017, 55 (2), 189-194

# EFLM – Which Milan Model to Use?

**Table 1:** Proposal for assignment of some commonly requested laboratory measurands to the three models for analytical performance specifications (APS) as defined in the Milan Consensus.[a]

| APS model 1: outcome-based | APS model 2: biological variation | APS model 3: state-of-the-art |
|---|---|---|
| P-Cholesterol+ester | P-Sodium ion | U-Sodium ion |
| P-Cholesterol+ester in LDL | P-Potassium ion | U-Potassium ion |
| P-Cholesterol+ester in HDL | P-Chloride | U-Chloride |
| P-Triglycerides | P-Bicarbonate | U-Calcium ion |
| P-Glucose | P-Calcium ion | U-Magnesium ion |
| B-Hemoglobin $A_{1c}$ | P-Magnesium ion | U-Phosphate (inorganic) |
| P-Albumin | P-Phosphate (inorganic) | U-Creatinine |
| P-Troponin T and P-troponin I | P-Creatinine | U-Urate |
| P-Thyrotropin | P-Cystatin C | |
| B-Hemoglobin | P-Urate | |
| B-Platelets | P-Proteins | |
| B-Neutrophil leukocytes | B-Erythrocytes | |
| | B-Erythrocyte volume fraction | |
| | B-Erythrocyte volume | |
| | P-Prothrombin time | |
| | P-activated partial thromboplastin time | |

[a]Some of the measurands can also have APS from other models depending on their clinical use. P and B denotes the system blood plasma or whole blood, respectively. Measurements might be performed in different types of sample matrices, such as serum, heparin plasma, citrate plasma, etc., as appropriate for the method.

CCLM 2017, 55 (2), 189-194

# Measurement uncertainty

**Uncertainties …… ??!!!**

# ISO 15189:2022
# Definition of measurement uncertainty

**3.19 measurement uncertainty MU**

- non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used
- Note 8 to entry: In medical laboratories, most measurements are performed in singleton, and are taken to be an acceptable estimate of the value of the measurand, while the MU interval indicates other results that are also possible.

# ISO 15189:2022
# requirements on measurement uncertainty

**7.3.4. Evaluation of measurement uncertainty (MU)**

a) The Mu of measured quantity values shall be evaluated and maintained for its intended use, where relevant. The Mu shall be compared against performance specifications and documented.

- NOTE ISO/TS 20914 provides details on these activities together with examples.

a) MU evaluations shall be regularly reviewed.

b) For examination procedures where evaluation of MUU is not possible or relevant, the rationale for exclusion from MU estimation shall be documented.

c) MU information shall be made available to laboratory users on request.

d) When users have inquiries on MU, the laboratory´s response shall take into account other sources of uncertainty, such as, but not limited to biological variation.

e) If the qualitative result of an examination relies on a test which produces quantitative output data and specified as positive and negative samples.

f) For examinations with qualitive results, MU in intermediate measurement steps or IQC results which produce quantitative data should also be considered for key (high risk) parts of the process.

g) MU should be taken into consideration when performing verification or validation pf a method, when relevant.

# ISO/FDIS 17511:2019 (E)

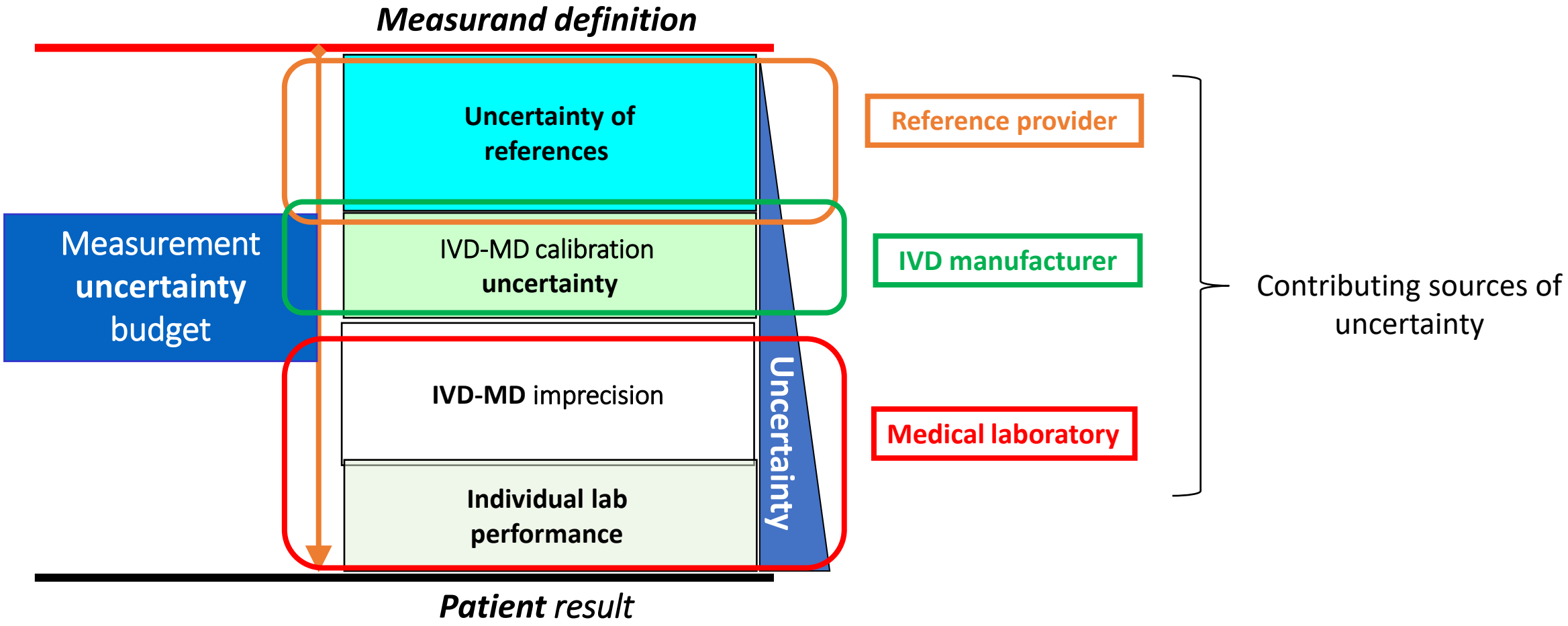
**4.3. Specifications for maximum allowable expanded measurement uncertainty, *Umax(y)***

The standard emphasizes that measurement procedures and materials used to establish metrological traceability should be ‘fit for purpose.’ The term ‘fit-for-purpose’ typically implies that a measurement procedure or reference material applied within a calibration hierarchy demonstrates a MU that is consistent with the MAU. This means that the combined MU calculated using the MU of each component used in the calibration hierarchy does not exceed MAU.

# Sources of bias (systematic error) and how to detect

1. Bias vs reference method, between methods:
- EQA
  - Commutable
  - Value assignment in reference method
  - Multi sample statistics
- Commutable reference material
2. Bias between lots within method:
- Patient samples or
- IQC, if commutable between lots

# Uncertainty budget in metrological traceability




[Braga F, Panteghini M. Clin Biochem 2018;57:7]

# Why - measurement uncertainty

- for giving objective information about the quality of individual laboratory performance;
- for serving as a management tool for the medical laboratory and IVD manufacturers;
- for identifying analytes that need analytical improvement for their clinical use and ask IVD manufacturers to work for improving the quality of assay performance;
- for abandoning assays with demonstrated insufficient quality.

# APS in routine laboratory

- EQA analysis
- Method selection
- Method verification
  - Interferences
  - Stability
  - Sample Type
  - Method comparison
- Method Validation or verification

- QC
- Result change
- MU assessment
- (Sigma values)
- Error Budget
- Accuracy Utility balance
- Hidden APS

# APS is complicated and should be specified for labs use

- Uncertainty $umax_{CS}$ assumes any bias is identified and corrected
  - appropriate for metrological traceability

- an acceptable risk of harm needs to consider all sources of errors
  - bias from calibrator lot changes, and other measuring system sources
  - bias from inadequate/inconsistent metrological traceability among different measurement procedures
  - bias from differences in selectivity for the measurand among different measurement procedures
  - bias from pre-analytical considerations

# Which APS to use?

- APS can be used to guide many decisions affecting laboratory performance
- Need to understand them, what they mean, where they come from, strengths and limitations
- Sample commutability should be considered when setting APS.
- Chosen APS should be based on the impact of the performance of the measurand on patient management.
- Most practical specifications are based on biological variation and state-of-the-art.
- Select Model based on:
    - Available data
    - Quality of evidence
    - Fit with analyte

# Conclusions 1

- APS could be different for different test applications and different criteria should be selected for each measurand
- Different APS may be needed for different questions
- Estimating uncertainty for end-user measuring system results is difficult
- State-of-the-art and Biological Variation are the data most commonly used to set APS
- Unacceptable bias should not be accepted
- Laboratory professionals are responsible for acceptance criteria

# Conclusions 2

- APS should be chosen based on the impact of the laboratory test performance of the measurand on patient management - medical decisions and actions
- APS based on intended use and medical need
- APS should represent an acceptable risk of harm for medical decisions, but risk of harm is difficult to estimate
- The meaning of APS is still not well known, most of the “professionals” did not know the topic
- There is uncertainty in an APS

# Clinical decision procecess and APS

- No clearly defined
- How precise data need MDs  for decision making
  - Diagnostic
  - Therapeutic
- What uncertainty is acceptable for different analytes in clinical processes
- APS shoud be move to clinical concept from labs, analytics characteristics and IVD manufactures
- Preanalytical and postanalytical variations, uncertainities
- Matrix effects

# Clinical decisions need equivalent lab results from different measurement procedures

Equivalent means within an uncertainty consistent with an acceptable risk of harm from decisions based on a lab test result.

There is a need to disseminate understanding of APS to whole laboratory community.


Thank you very much
Merci
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