L15 Validation

Basis to accreditable measurement methods

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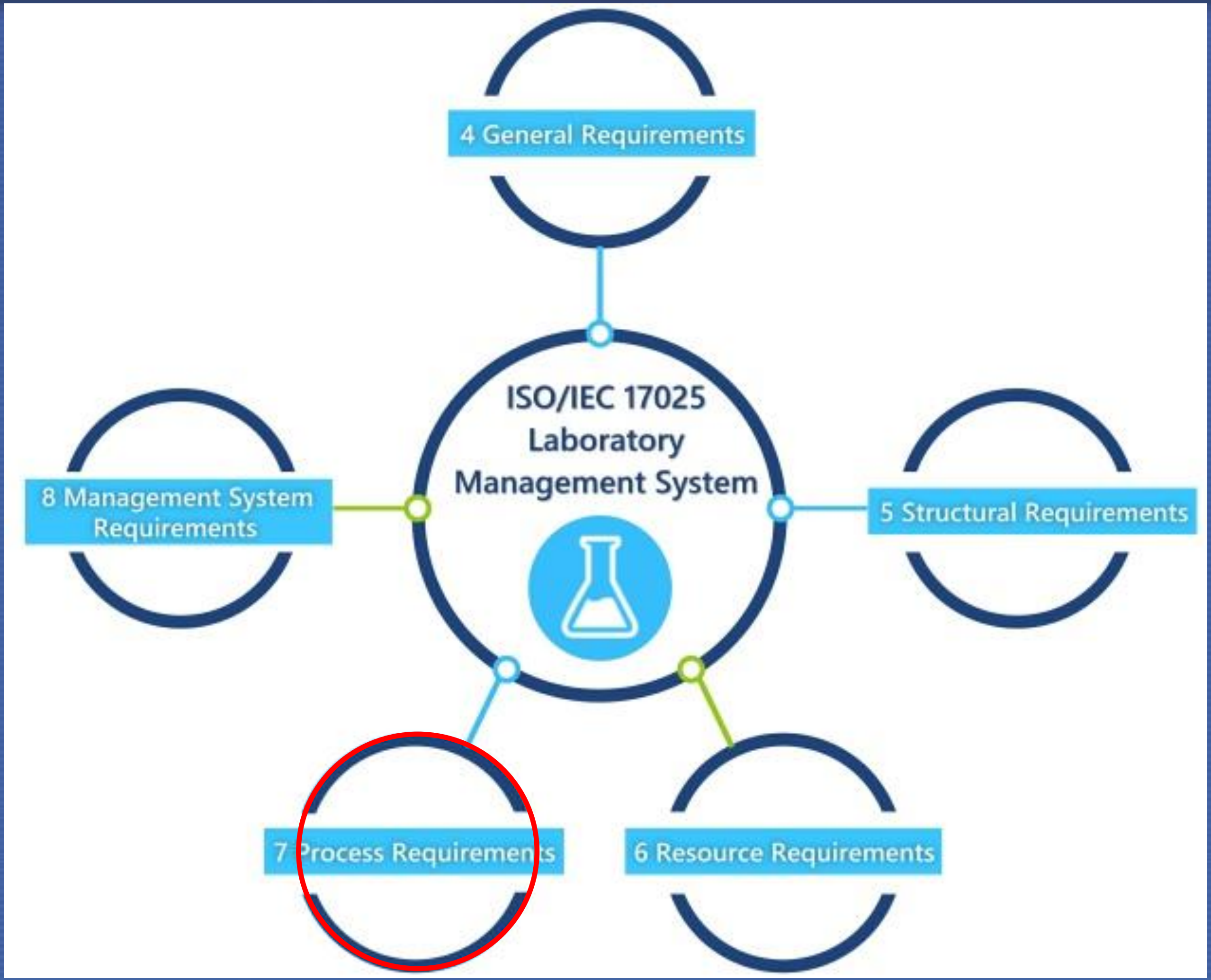
International Atomic Energy Agency

7 Process Requirements



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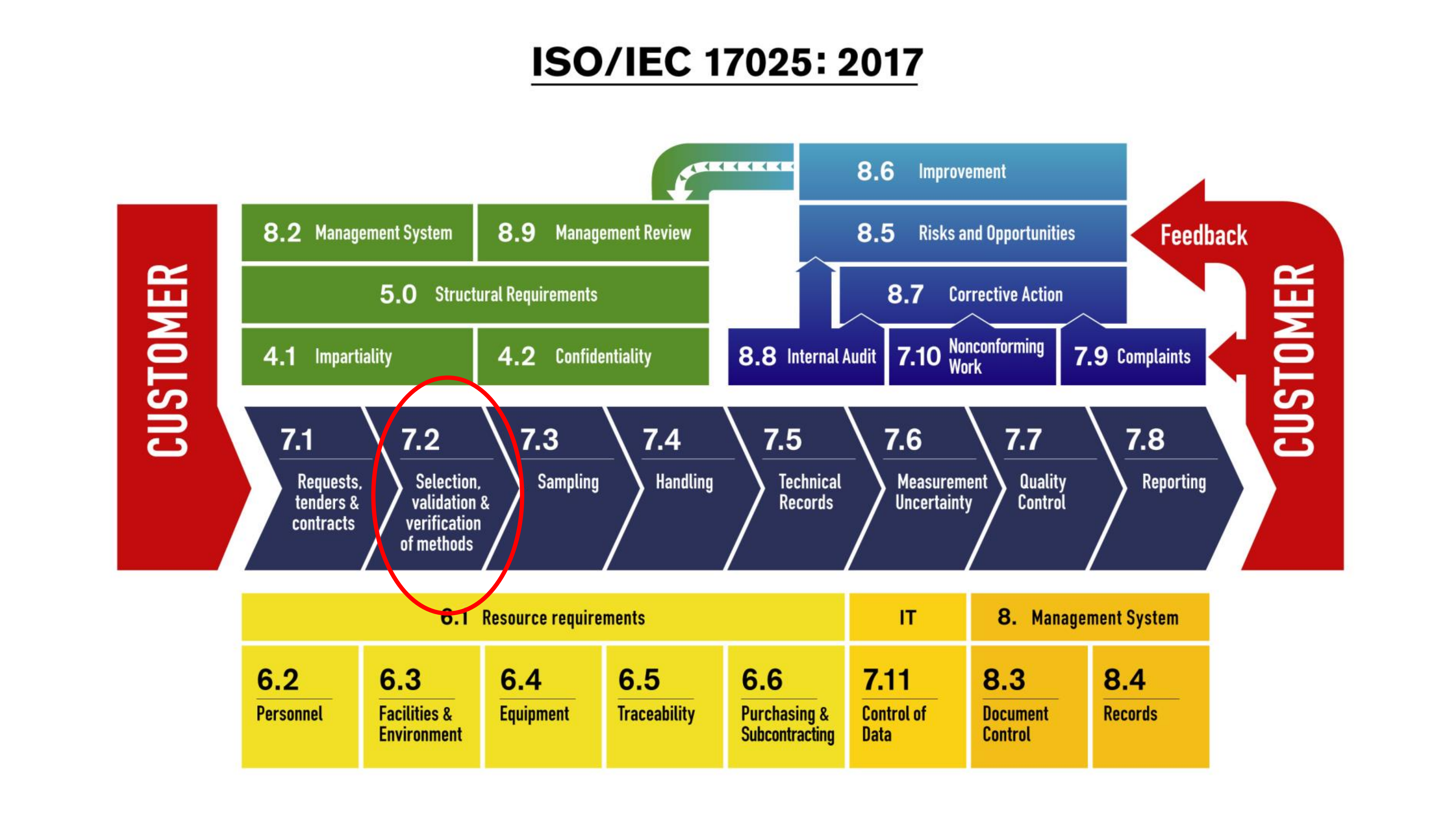
Structure


ISO/IEC 17025: 2017
8.6 Improvement
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8.9 Management Review
8.5 Risks and Opportunities
Feedback
5.0 Structural Requirements
8.7 Corrective Action
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CUSTOMER
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Methods: Validation

VIM: Validation: **verification,** where the specified requirements are adequate for an intended use

- EXAMPLE TLD dosimetry Hp(10) with an accuracy within ISO 14146 and with e.g. a detection limit < 50 µSv as required by national legislation by your regulator for photons of e.g. 20 keV to 6 MeV.

VIM: Validation: Validation is the **confirmation by examination** and the provision of **objective evidence** that the **particular requirements of a specific intended** use are fulfilled.'

Proof that the testing method is acceptable for solving a user requirement.

7.2 Selection, verification and validation of methods

7.2.1 Selection and verification of methods - The term "method" in the standard is used to identify calibration method, testing/measurement procedure, sampling procedure.

- Use appropriate methods and procedures
- All methods, procedures and documentation are kept up to date and available
- Ensure use of the latest valid version of a method and supplemented with additional details
- If customer not specify the method, the laboratory select an appropriate method and inform customer and use any published or lab developed method

7.2 Selection, verification and validation of methods (2)

- Verify laboratory can properly perform methods before introducing them by ensuring that it can achieve the required performance and maintain records of verification. Follow same step after revision
- Method development is planned activity by competent personnel with adequate resources and periodic review. The modifications to the development plan shall be approved and authorized
- Deviations from methods allowed, if the deviation has been documented, technically justified, authorized, and accepted by the customer

List of applicable standards

- IEC 62387:2020 Radiation protection instrumentation - Passive integrating dosimetry systems for personal and environmental monitoring of photon and beta radiation.
- ISO 14146:2018 Radiological protection - Criteria and performance limits for the periodic evaluation of dosimetry services
- IEC TR 62461:2015 Radiation protection instrumentation - Determination of uncertainty in measurement
- ISO 15382:2015 Radiological protection - Procedures for monitoring the dose to the lens of the eye, the skin and the extremities
- ISO 15690:2013 Radiological protection - Recommendations for dealing with discrepancies between personal dosimeter systems used in parallel

List of applicable standards

- ISO 21909-1:2015 Passive neutron dosimetry systems - Part 1: Performance and test requirements for personal dosimetry
- ISO 15690:2013 Radiological protection - Recommendations for dealing with discrepancies between personal dosimeter systems used in parallel ISO 20553:2006 Radiation protection - Monitoring of workers occupationally exposed to a risk of internal contamination with radioactive material
- ISO 16637:2016 Radiological protection - Monitoring and internal dosimetry for staff members exposed to medical radionuclides as unsealed sources
- ISO 27048:2011 Radiation protection - Dose assessment for the monitoring of workers for internal radiation exposure

Source: EURADOS Report 2015-04

7.2 Selection, verification and validation of methods (3)

7.2.2 Validation of methods

- The laboratory shall validate:
  1. Non standard methods
  2. Laboratory designed / developed methods
  3. Standard method used outside the intended use
  4. Amplification and modifications of standard methods
- When changes are made to a validated method, the influence of such changes is determined and if affect the original validation, a new method validation to be performed
- The performance characteristics of validated methods is assessed for the intended use, relevant to the customers' needs and consistent with specified requirements
- Maintain records of validation

7.2 Selection, verification and validation of methods (4)

Techniques used for method validation (Any one or more methods from listed below to be used) :

1. Calibration or evaluation of bias and precision using reference standards or reference materials
2. Testing method robustness through variation of controlled parameters such as time temperature, volume dispensed, etc.
3. Comparison of results achieved with other validated methods;
4. Inter laboratory comparisons;
5. Evaluation of measurement uncertainty of the results based on an understanding of the theoretical principles of the method and practical experience of the performance of the test method
6. Systematic assessment of the factors influencing the result

The validation is done for procedure of sampling, testing, handling and transportation of test or calibration items.

Influencing factors

Results of testing depend on

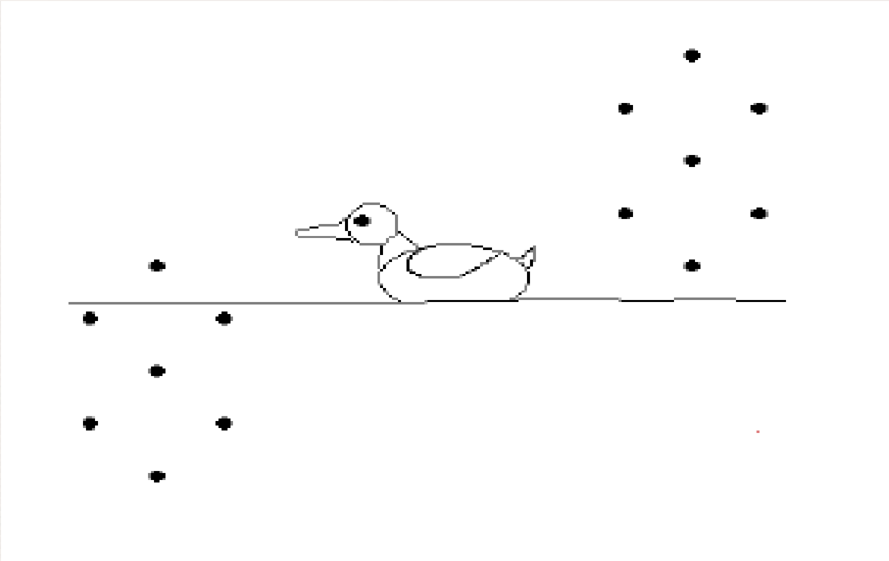
- Instrumental and technical factors
    - Test method
    - Equipment
- Human factors
- Environmental factors
- ….

Ultimate goal

- The goal of a analytical method: quantify as good as possible any quantity that the lab needs to evaluate

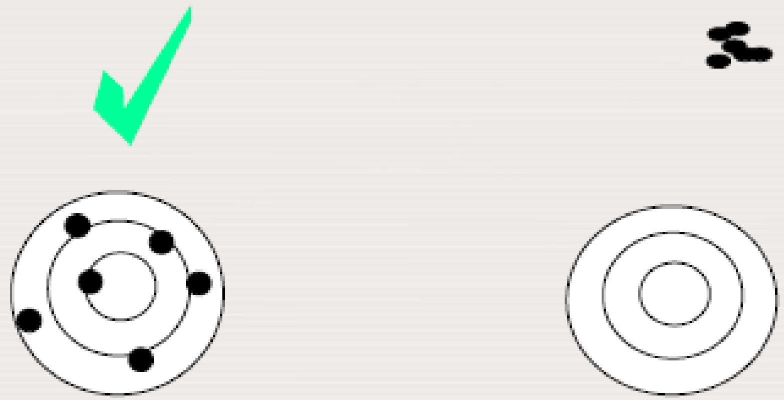
- The goal of validation: to give to the lab and the authorities sufficient guarantees that the results issued by the lab with the validated method, once used in routine, will be sufficiently close to the real value

Methods and validation



On the average the duck is dead ....

Is this true?



"It is better to be roughly right than precisely wrong."

The validation process

Development (5.4.1 -5.4.4/5.6)

- Select your method: normalized, manufacturer, self developed
- Draft procedure to an experienced analyst
- Use/Buy adequate calibrated instruments, chemicals, reagents, reference materials, well choosen samples, …
- Perform pre-validation tests on the instrument!

Selection – know how (5.4.1)

- Appoint a good researcher responsible for supervising the validation
- Perform literature study, review any existing method performance data
- Define the method: matrix, measurand,
- Find out the intended use/purpose - client, authorities, …. Pre-validation criteria> **validation report**

Intra-lab Validation (5.4.5), Validate if relevant

Trueness
Specificity/Selectivity
Linearity / range
Intermediate precision/ repeatability
Sensitivity
Detection /Quantification limit
Robustness

if it fulfills pre-validation criteria, fit for purpose > **validation report**

Routine use- <u>based upon validation data</u>

- Internal Quality Control 5.9
- External Quality Control 5.9
- Calibration / Verification 5.5/5.6
- Qualify the analysts who participated in the validation (auto-qualification)

Measurement uncertainty (5.4.6)
Fit for purpose > **Validation report**

Inter-lab validation (5.9)
Trueness/reproducibility
fit for purpose > **Validation report**

What to validate

accuracy

repeatability

trueness

linearity

bias

random error

precision

reproducibility

uncertainty

systematic error

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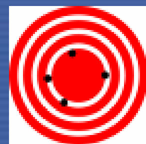
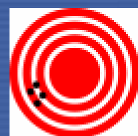
What to validate

- Accuracy 
- Precision 
- Repeatability
- Reproducibility
- Limit of detection
- Reporting level
- Range of applicability
- Linearity
- Uncertainty
- Robustness
- Selectivity
- Sensitivity

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Methods – Verification & Validation – example of IMS (Individual Monitoring Service)

- Validation of external monitoring, using TLD batches, or similar devices can be done by:

➢ **Verification:** of the reader/dosemeter combination by irradiating at a SSDL, mainly for precision and trueness for a **limited** set of (a few well chosen doses e.g. 0,1 – 1 and 50 mSv) and energy eg. Cs-137

➢ **Type Testing:** according to IEC 62387, mainly for demonstrating in the whole range of doses from detection limit to accidental doses, from low energies to high energies, for different angles, for photons and beta's, and a mix of these. But also for temperature, humidity, fading, residual dose, memory effects, dropping, ….

➢ Both **Verification and Type Testing** together validate your method taking into account regulatory requirements, IAEA GSG No.7: 2018 & ISO 14146:2018 Radiological protection — Criteria and performance limits for the periodic evaluation of dosimetry services

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Performance criteria - example of IMS

- IEC 62387: 2012: Radiation protection instrumentation -Passive integrating dosimetry systems for personal and environmental monitoring of photon and beta radiation
  - IEC 62387:2012 applies to all kinds of passive dosimetry systems that are used for measuring the personal dose equivalent (for whole body dosimetry), the personal dose equivalent (for eye lens dosimetry), the personal dose equivalent (for both whole body and extremity dosimetry), the ambient dose equivalent (for environmental dosimetry), or the directional dose equivalent (for environmental dosimetry).

- Occupational Radiation Protection, IAEA GSG No.7 (2018)

- ISO 14146:2018 Radiological protection — Criteria and performance limits for the periodic evaluation of dosimetry services

Example: ISO 14146

7 Performance limits

7.1 Limits

7.1.1 Personal, workplace dosemeters and environmental dosemeters

For each irradiated dosemeter, the quotient R between the measured dose value G and the conventional quantity value H_{ref}, given by the response

$$R = \frac{G}{H_{ref}}$$

shall meet the following criteria between H_0 and H_{top} (see 6.3):

— Criterion 1) For photon radiation with a mean energy of $\bar{E}_{ph}$ > 65 keV and for beta radiation with a mean energy of $\bar{E}_{beta}$ > 0,2 MeV (easier-to-measure):

$$0{,}71 \cdot \left(1 \quad \frac{2 \cdot H_0/1{,}33}{H_0/1{,}33 + H_{ref}}\right) \leq R \leq 1{,}67 \cdot \left(1 + \frac{H_0}{4 \cdot H_0 + H_{ref}}\right);$$

— Criterion 2) For neutron radiation, for photon radiation with a mean energy of $\bar{E}_{ph}$ ≤ 65 keV, and for beta radiation with a mean energy of $\bar{E}_{beta}$ ≤ 0,2 MeV (harder-to-measure):

$$0{,}5 \cdot \left(1 \quad \frac{2 \cdot H_0/1{,}5}{H_0/1{,}5 + H_{ref}}\right) \leq R \leq 2\,.$$

If mixtures of two or more radiation qualities and or types are used and the above-mentioned harder-to-measure components contribute more than 20 % of the total dose, criterion (2) applies to total dose. Criterion (1) applies for a contribution below 20 %.

NOTE 1 The factors 0,71 and 1,67 (criterion 1) and 0,5 and 2 (criterion 2) limit the maximum error of the dosimetry system at high dose values. At the lower limit of the dose range, −90 % and +100 % deviation is allowed.

NOTE 2 The factors 0,71 and 1,67 were chosen according IEC 62387[4] and are similar to the corresponding factors in ICRP 75 (0,67 and 1,5)[5].

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Requirements from IEC 62387 - Scope

Table 1 – Mandatory and maximum energy ranges covered by this standard

Measuring quantity	Mandatory energy range for photon radiation	Maximum energy range for testing photon radiation	Mandatory energy range for beta-particle radiation[a]	Maximum energy range for testing beta-particle radiation[a]
$H_p(10)$, $H^*(10)$	80 keV to 1,25 MeV	12 keV to 10 MeV	–	–
$H_p(3)$	30 keV to 250 keV	8 keV to 10 MeV	0,8 MeV almost equivalent to an E_{max} of 2,27 MeV	0,7 MeV[b] to 1,2 MeV almost equivalent to E_{max} from 2,27 MeV to 3,54 MeV
$H_p(0,07)$, $H'(0,07)$	30 keV to 250 keV	8 keV to 10 MeV	0,8 MeV almost equivalent to an E_{max} of 2,27 MeV	0,06 MeV[c] to 1,2 MeV almost equivalent to E_{max} from 0,225 MeV to 3,54 MeV

a The following beta radiation source are suggested for the different mean energies: For 0,06 MeV: ^{147}Pm; for 0,8 MeV: $^{90}Sr/^{90}Y$; for 1,2 Mev: $^{106}Ru/^{106}Rh$.

b For beta-particle radiation, an energy of 0,7 MeV is required to reach the radiation sensitive layers of the eye lens in a depth of about 3 mm (approximately 3 mm of ICRU tissue).

c For beta-particle radiation, an energy of 0,07 MeV is required to penetrate the dead layer of skin of 0,07 mm (approximately 0,07 mm of ICRU tissue).

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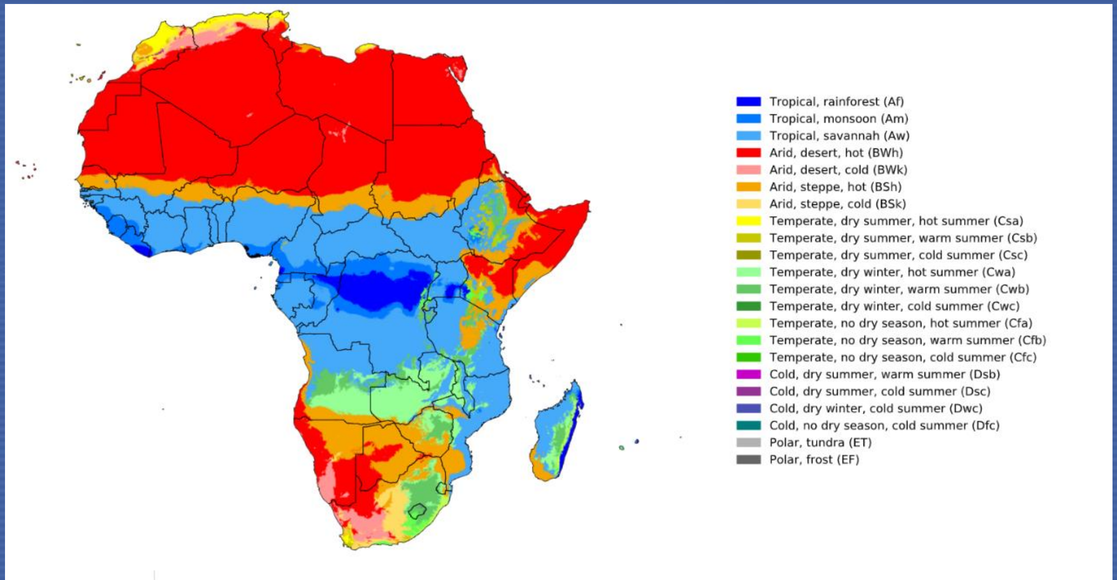
Linearity, energy, accuracy, … tests

7	Relative response due to non-linearity	0,1 mSv $\leq H \leq$ 1 Sv	–9 % to +11 %	11.3
8	Overload, after-effects, and reusability	10 times the upper limit of the measuring range: $10 \cdot H_{up}$, however at maximum 10 Sv. Reused dosemeters shall fulfil the requirements	Perception to be off-scale on the high end side of the measuring range, after-effects may not cause fault measurements and $v(H_{low})$ shall be according to line 6	11.4
9	Relative response due to mean photon radiation energy and angle of incidence	80 keV to 1,25 MeV and 0° to ± 60° from reference direction	For 12 keV $\leq E_{ph} <$ 33 keV: r_{min} = 0,67 to r_{max} = 2,00 and for 33 keV $\leq E_{ph} <$ 65 keV: r_{min} = 0,69 to r_{max} = 1,82 and for $E_{ph} \geq$ 65 keV: r_{min} = 0,71 to r_{max} = 1,67	11.5.1
10	Relative response due to mean beta radiation energy	0,8 MeV	Indicated value maximal 10 % of $H_p(0{,}07)$ dose equivalent	11.5.2
11	As in lines 9 and 10 but new reference direction opposite to that one used	See lines 9 and 10, if no statement by the manufacturer	See lines 9 and 10, if no statement by the manufacturer	8.4 f)
12	Radiation incidence from the side of the dosemeter	Radiation incidence from 60° to 120°	Indication less than 1,5 times of indication due to irradiation free in air from the front	11.8
13	Response to mixed irradiations	Irradiation with different radiation qualities	Response within ranges of radiation qualities under test	12

But also some robustness testing

14	Total effect due to environmental performance requirements	Temperature, light, time; for details, see Table 13	See Table 13	13
15	Deviation due to electromagnetic performance requirements	See Table 14	See Table 14	14
16	Deviation due to mechanical performance requirements	Drop; for details, see Table 15	$\pm$ 0,7$\cdot H_{\mathrm{low}}$ at a dose of H = 7 H_{low}	15
NOTE The non-symmetrical borders of relative responses r are derived from symmetrical borders of correction factors (1/r), for example: $\pm$ 40 % for 1/$r \in$ [0,6 .. 1,4] ➔ $r \in$ [1/1,4 .. 1/0,6] = [0,71 .. 1,67]				



Validation Planning

Validation of external monitoring/IMS, using TLD batches, or similar devices can be done by:

- Calibration of the readers and dosimeters by irradiating at a Secondary Standard Dosimetry Laboratory
- Laboratory intercomparison exercises
- Performance or Type Testing
- Comparison of results achieved with other methods
- Systematic assessment of the factors influencing the results/ the uncertainty of the results based on scientific understanding of the theoretical principles of the method and practical experience.

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Validation Planning (2)

- Start with method selection
- Define acceptable performance criteria
- Plan irradiations to cover the performance criteria
- Do the irradiations
- Evaluate the dosimeters/data
- Assess the performance criteria
- Issue validation statement

Validation Planning (3)

Need for one “validation report “ ?

- You have to demonstrate the quality of the performance indicators for the method you are going to use.
- This can be done using various files of experimental work, control charts, records, etc.
- It is sufficient if you have a reference file such as Excel where to find evidence on accuracy, repeatability etc. so that things are easy retrievable.

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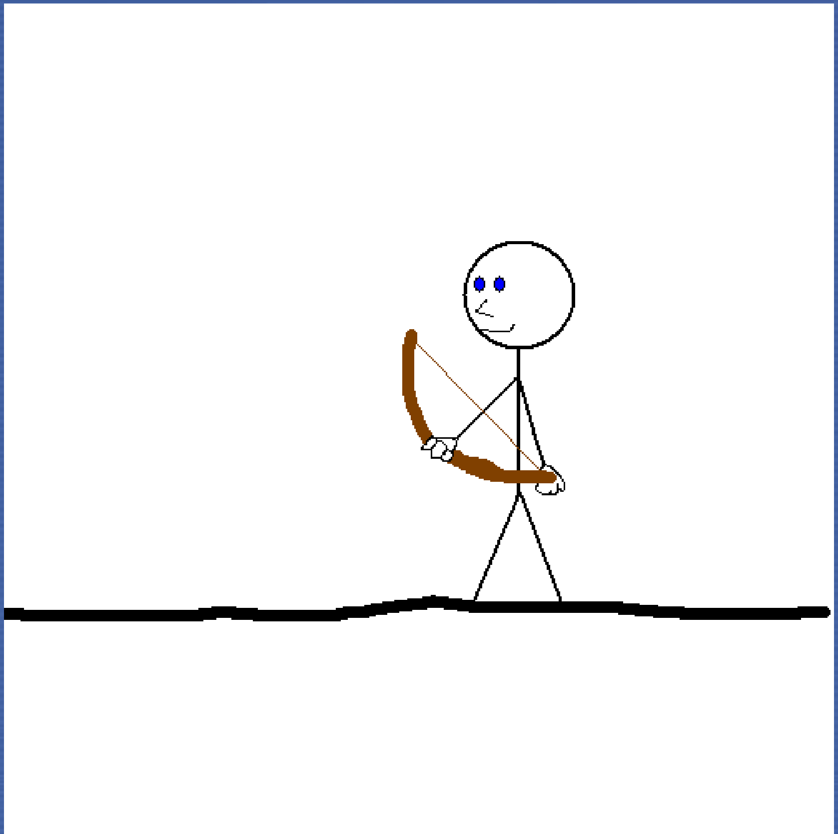
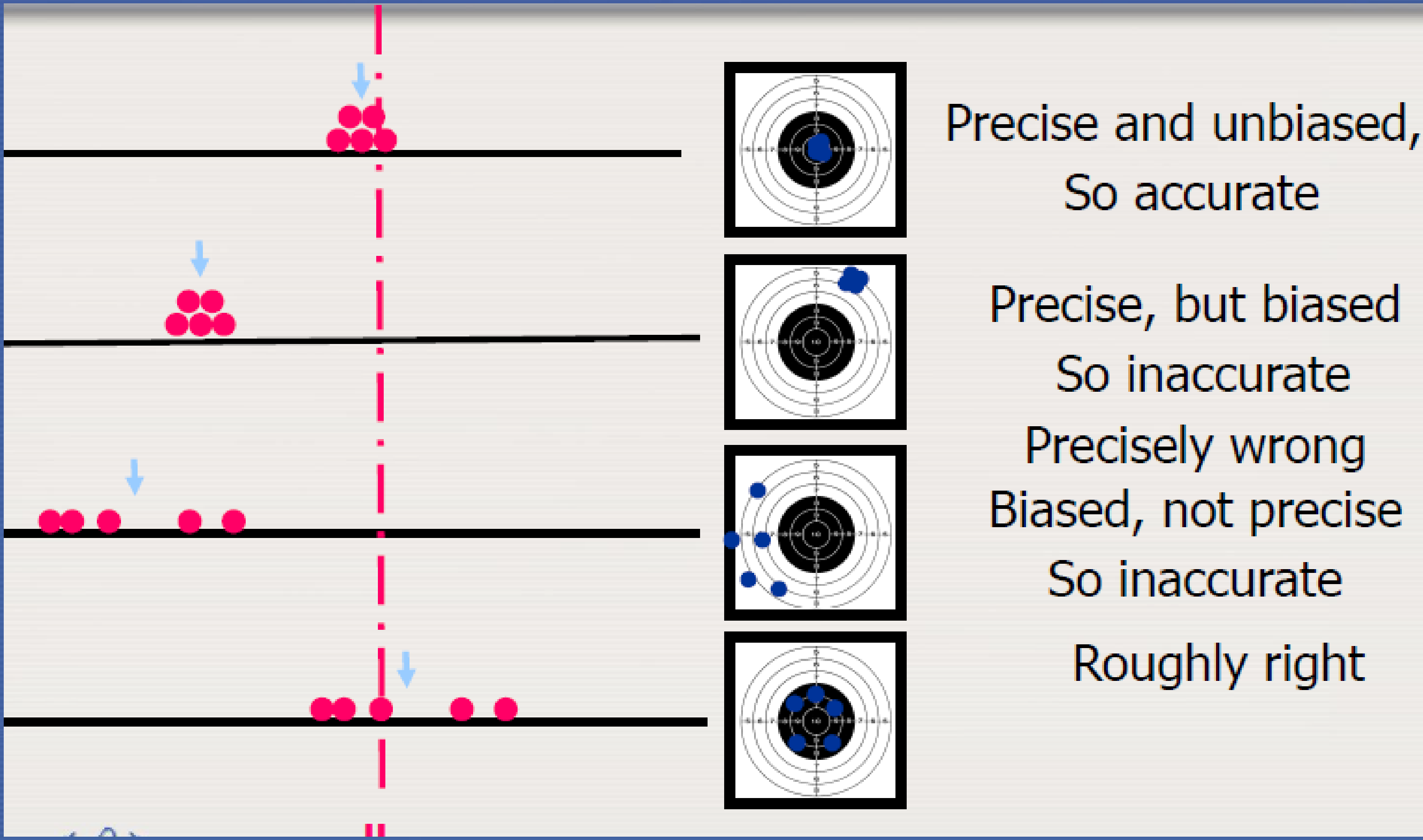
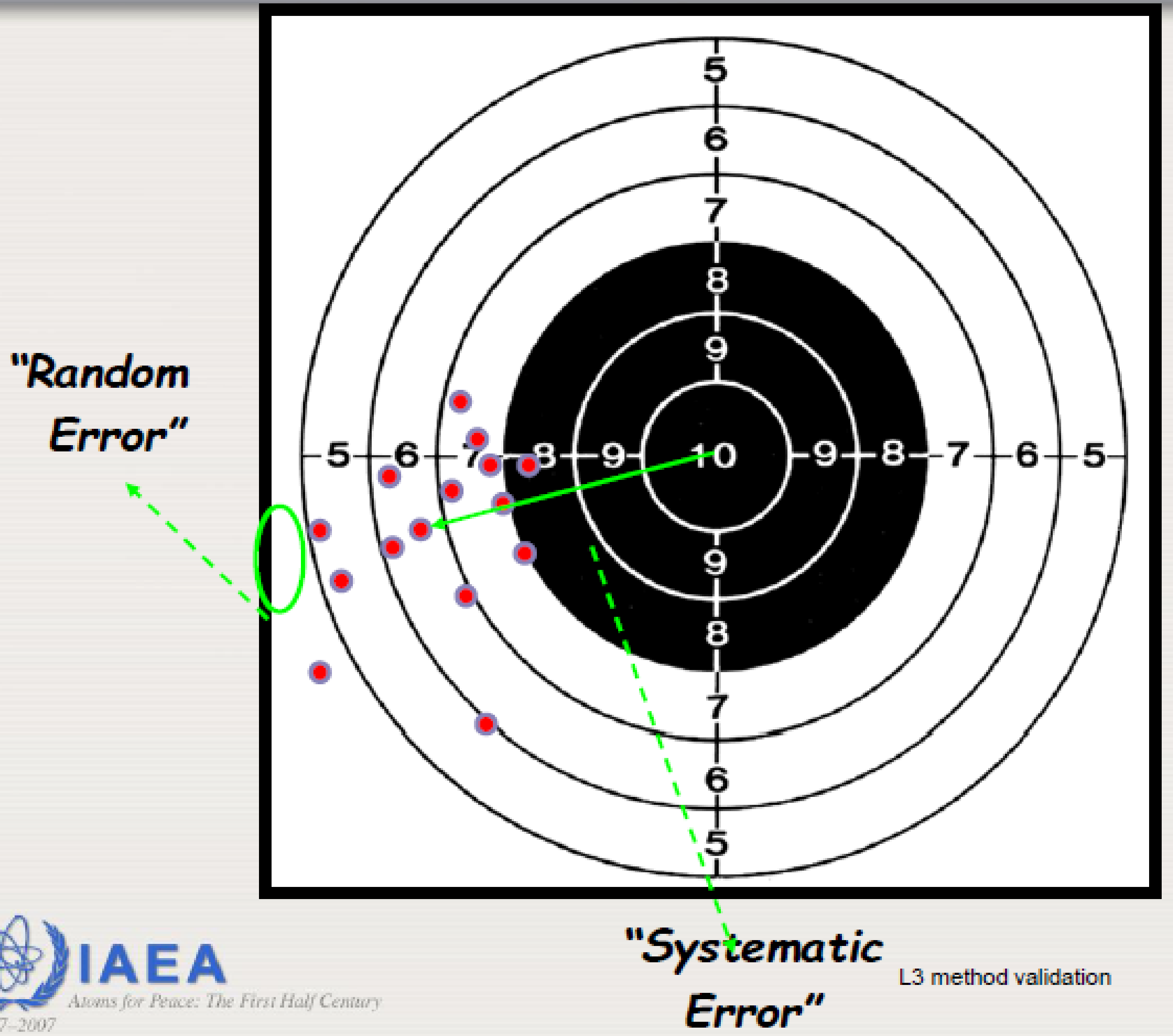
Precision and accuracy



Accuracy and precision





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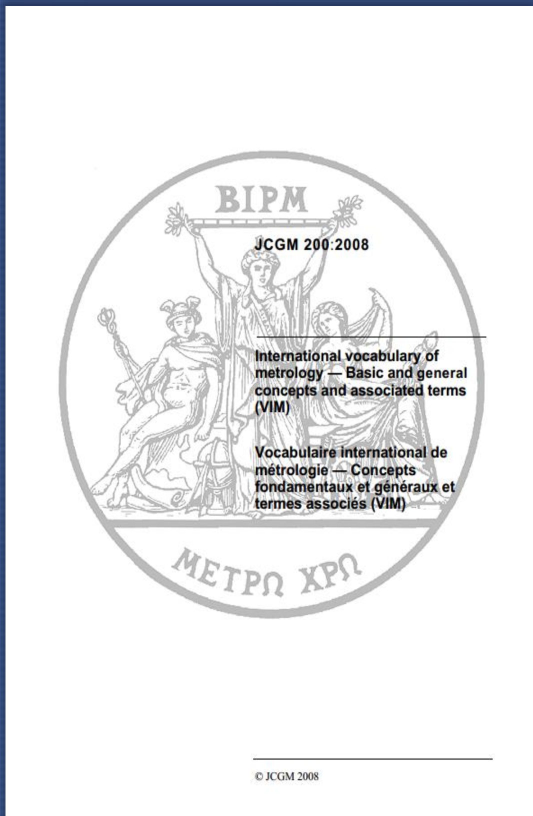
Atoms for Peace: The First Half Century
1957–2007

Definitions


BIPM

JCGM 200:2008

International vocabulary of metrology — Basic and general concepts and associated terms (VIM)

Vocabulaire international de métrologie — Concepts fondamentaux et généraux et termes associés (VIM)

ΜΕΤΡΩ ΧΡΩ

Accuracy [VIM 2.13]

– **Classical (Error) approach:**
  Δ = measured quantity value - true quantity value

– **Uncertainty approach:**
  no numerical value, a **measurement** is said to be more accurate when it offers a smaller **measurement error**

Trueness [VIM 2.14]

closeness of agreement between the average of an infinite number of replicate **measured quantity values** and a **reference quantity value**

Bias [VIM 2.18]

estimate of a **systematic measurement error**

Precision [VIM 2.15]

closeness of agreement between **indications** or **measured quantity values** obtained by replicate **measurements** on the same or similar objects under specified conditions

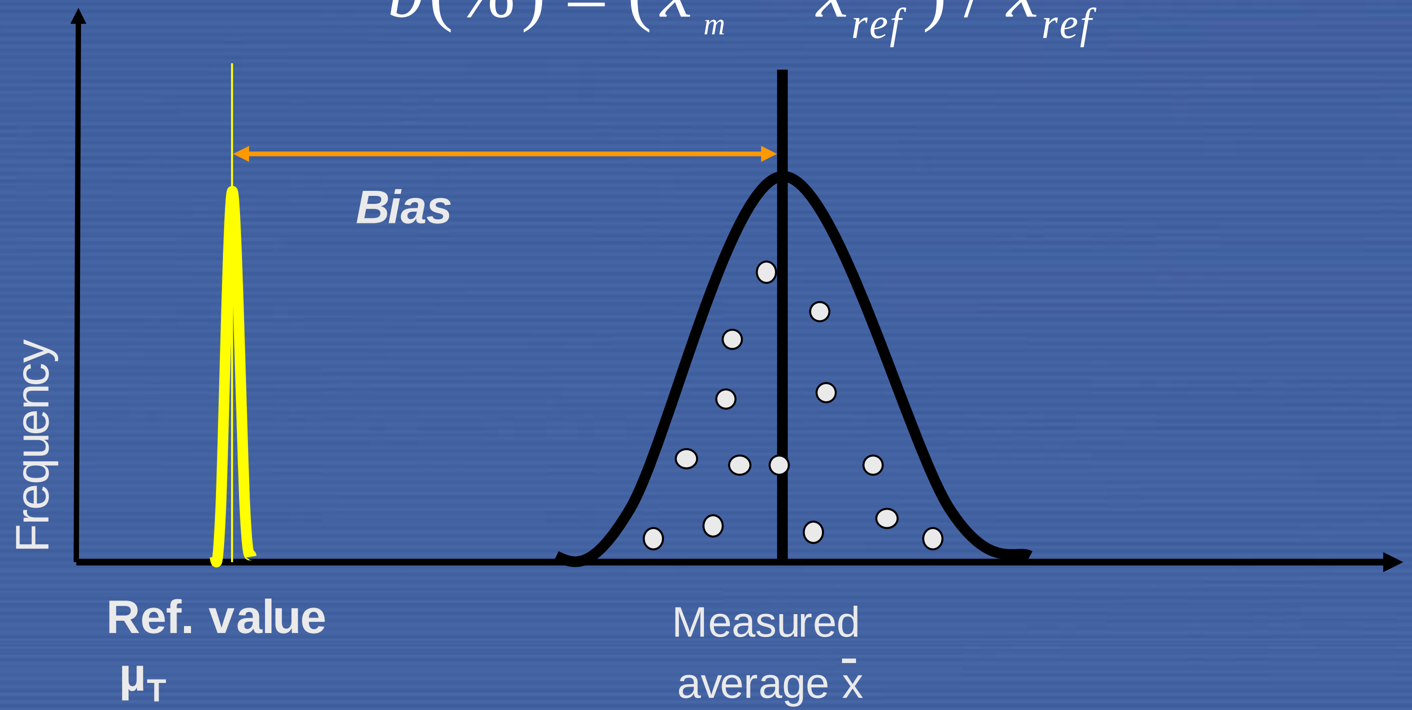
Error [VIM 2.16]

Δ = measured quantity value – reference quantity value

Trueness is estimated using the bias or a relative quotient

$$b = \bar{x}_m - x_{ref}$$

$$b(\%) = (\bar{x}_m - x_{ref}) / x_{ref}$$



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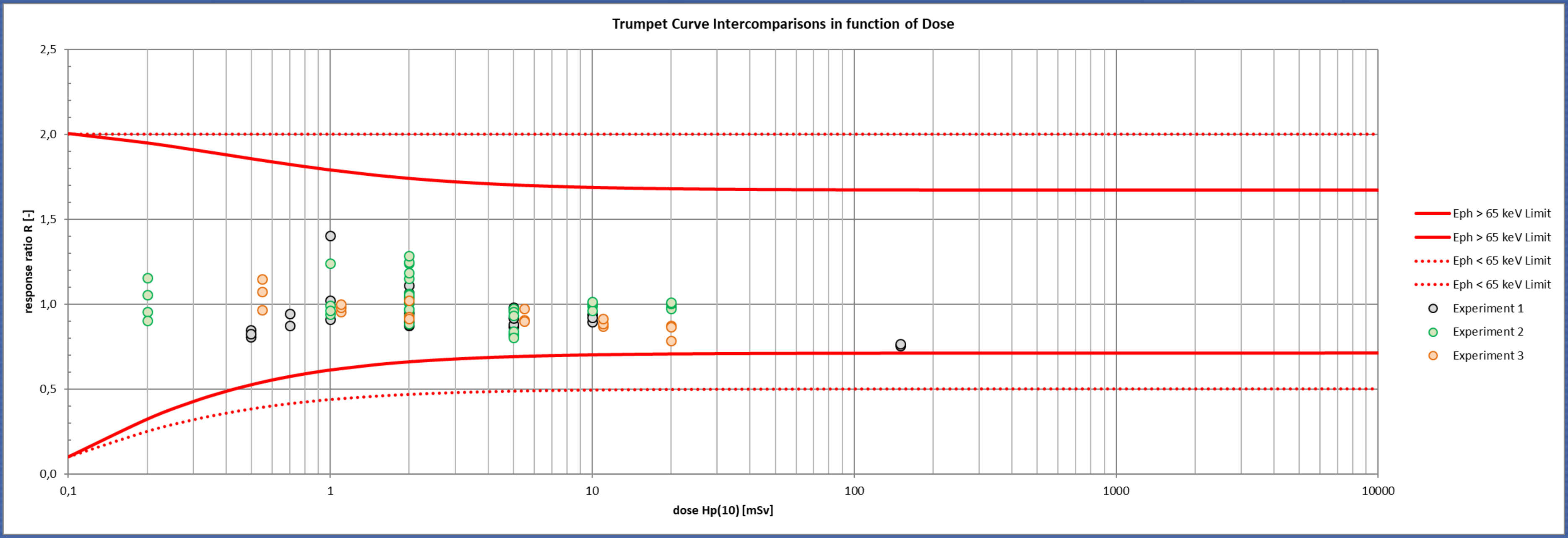
Trueness in function of dose - example of IMS

Expressed as quotient R of the measured dose and the conventional reference value $R = G/H_{ref}$



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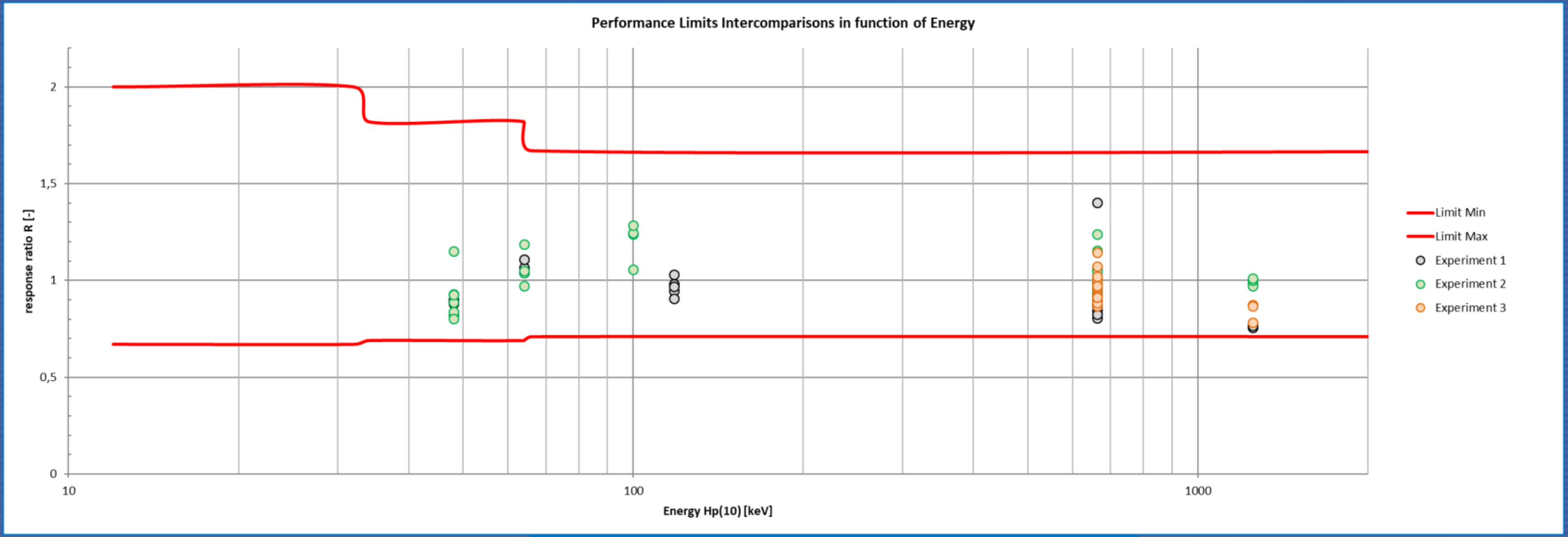
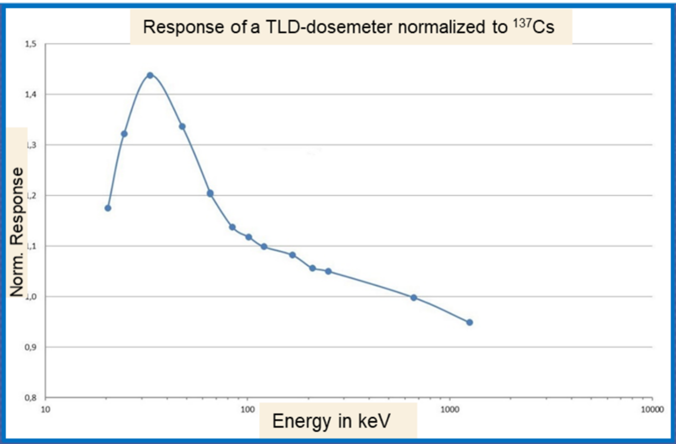
Trueness: Energy response - example of IMS

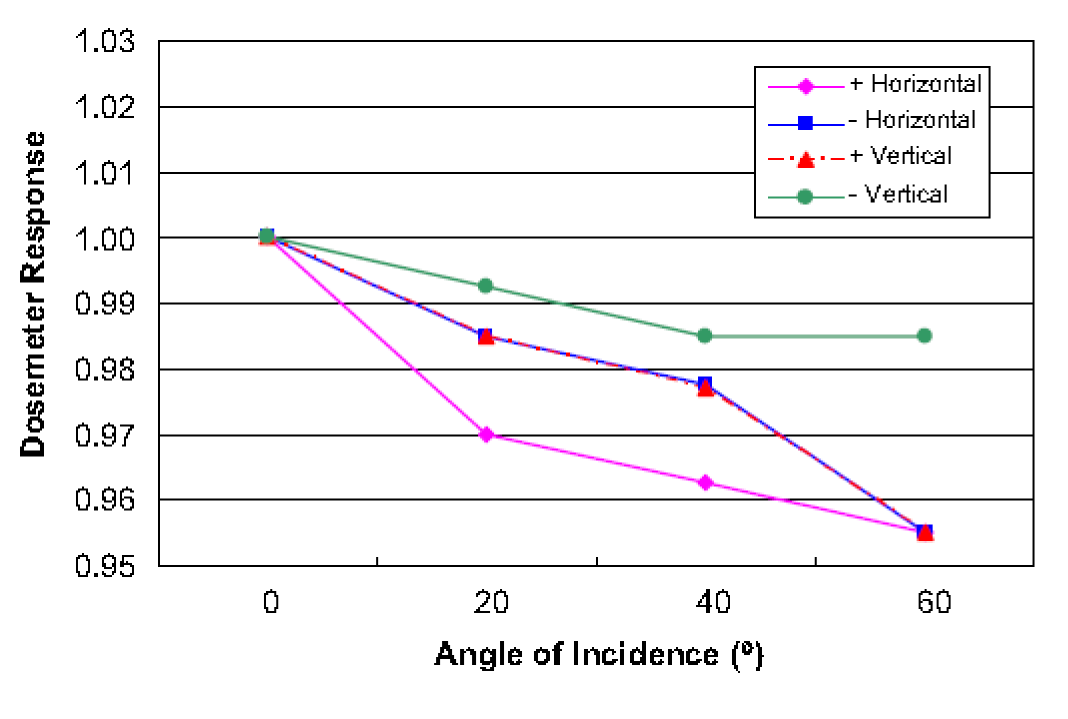
Method: several dosimeters irradiated at a SSDL with different radiation qualities. Plot relative response measured/reference – should be within IEC 62387 criteria





Trueness: Angular dependence - example of IMS

When irradiated at different angles of incidence e.g. 20º, 40º and 60º (SSDL) shall not differ from the corresponding response for normal incidence by more than e.g. 10%



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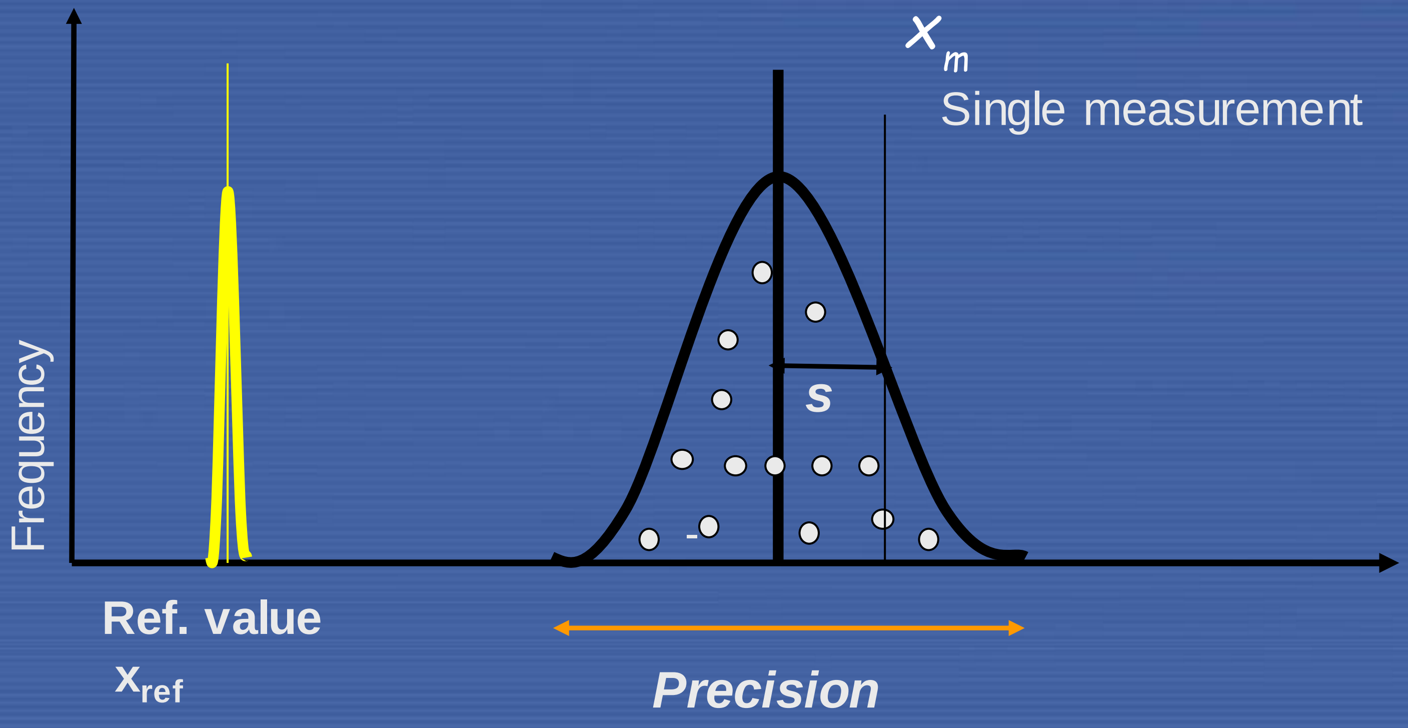
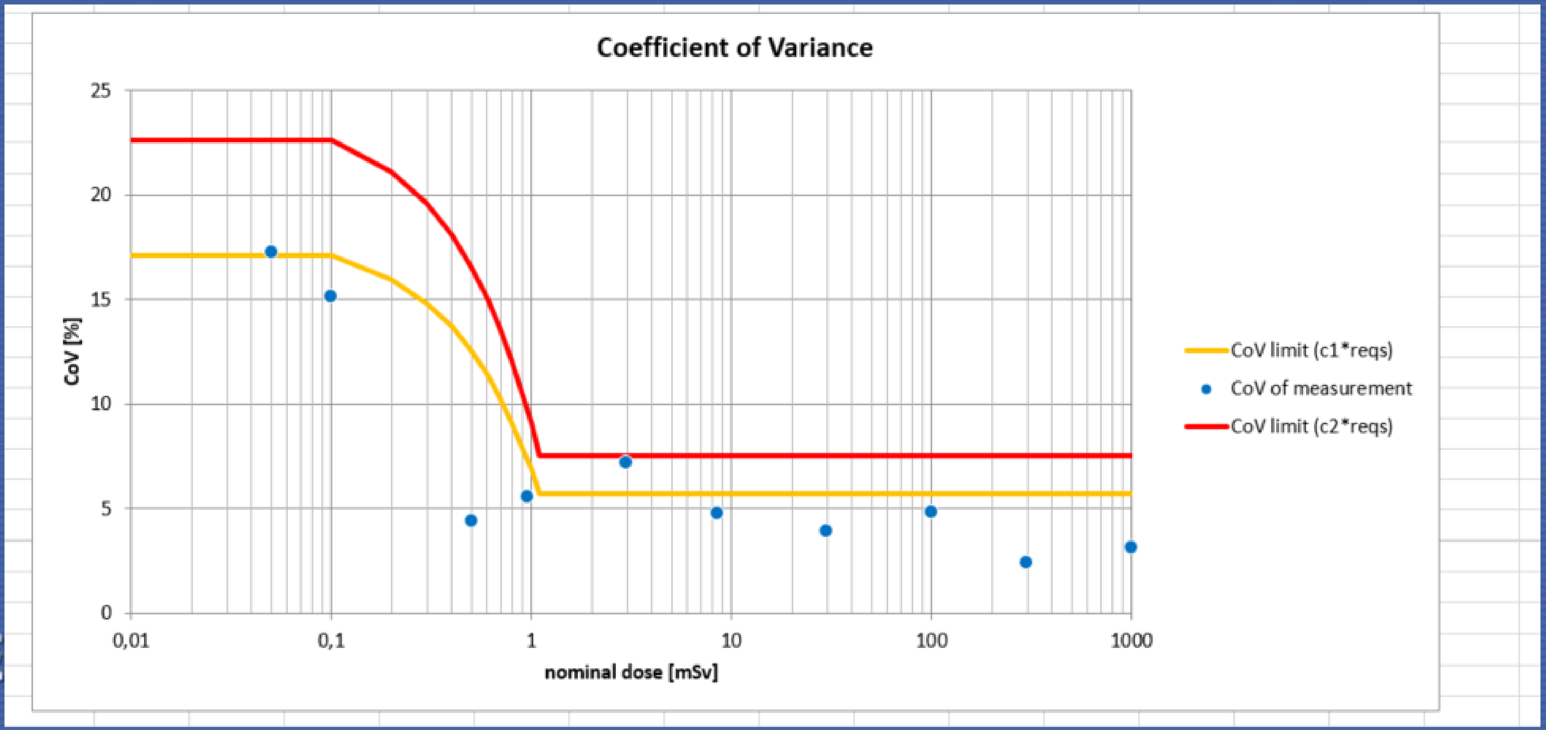
Precision is expressed as a SD (standard deviation, absolute) or as coefficient of variance (CoV or RSD, relative)

$$CV(\%)(=RSD(\%)) = \frac{s_m}{\bar{x}_m}$$



Precision: CoV- example of IMS

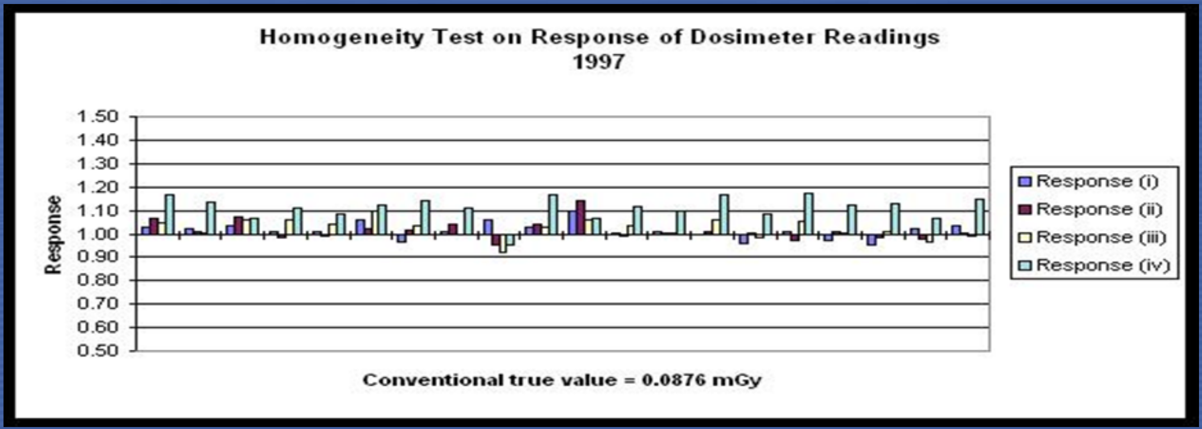
- The CoV coefficient of variation (standard deviation divided by the mean) of the evaluated value shall not exceed a prefixed % (e.g. 7.5% for doses well above the detection limit – see IEC 62387)
- Anneal ten dosemeters - irradiate to x mSv for several doses per decade and read out. Calculate standard deviation (e.g. by MS Excel)



Precision: Batch homogeneity – example of TLD

- The evaluated value for any one dosimeter in a batch shall not differ from the evaluated value for any other dosimeter in the batch by e.g. more than 30% for a dose equal to 10 times the required detection threshold limit.

- Make histogram an look for values > 30 %



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Repeatability

- **Condition of measurement - repeatability condition:** *condition of* ***measurement,*** *out of a set of conditions that includes the same* ***measurement procedure,*** *same operators, same* ***measuring system,*** *same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time*
  - NOTE 1 A condition of measurement is a repeatability condition only with respect to a specified set of repeatability conditions.
  - NOTE 2 In chemistry, the term “intra-serial precision condition of measurement” is sometimes used to designate this concept.

- **Measurement repeatability – repeatability: measurement precision** under a set of **repeatability conditions of measurement**

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In reality # factors have an influence

- Differences in T and humidity
- Operators with several years of experience, order, respect for the procedures,…
- Equipment with several characterizations or drift and aging of the apparatus
- Differences in calibration,…

- For this reason a distinction is made between repeatability and other conditions of precision

Intermediate precision

- **Intermediate precision condition of measurement - intermediate precision condition:** *condition of **measurement,** out of a set of conditions that includes the same **measurement procedure,** same location, and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions involving changes*
  - NOTE 1 The changes can include new **calibrations, calibrators, operators**, and **measuring systems.**
  - NOTE 2 A specification for the conditions should contain the conditions changed and unchanged, to the extent practical.
  - NOTE 3 In chemistry, the term “inter-serial precision condition of measurement” is sometimes used to designate this concept.
- **Intermediate measurement precision intermediate precision**: ***measurement precision** under a set of **intermediate precision conditions of measurement***

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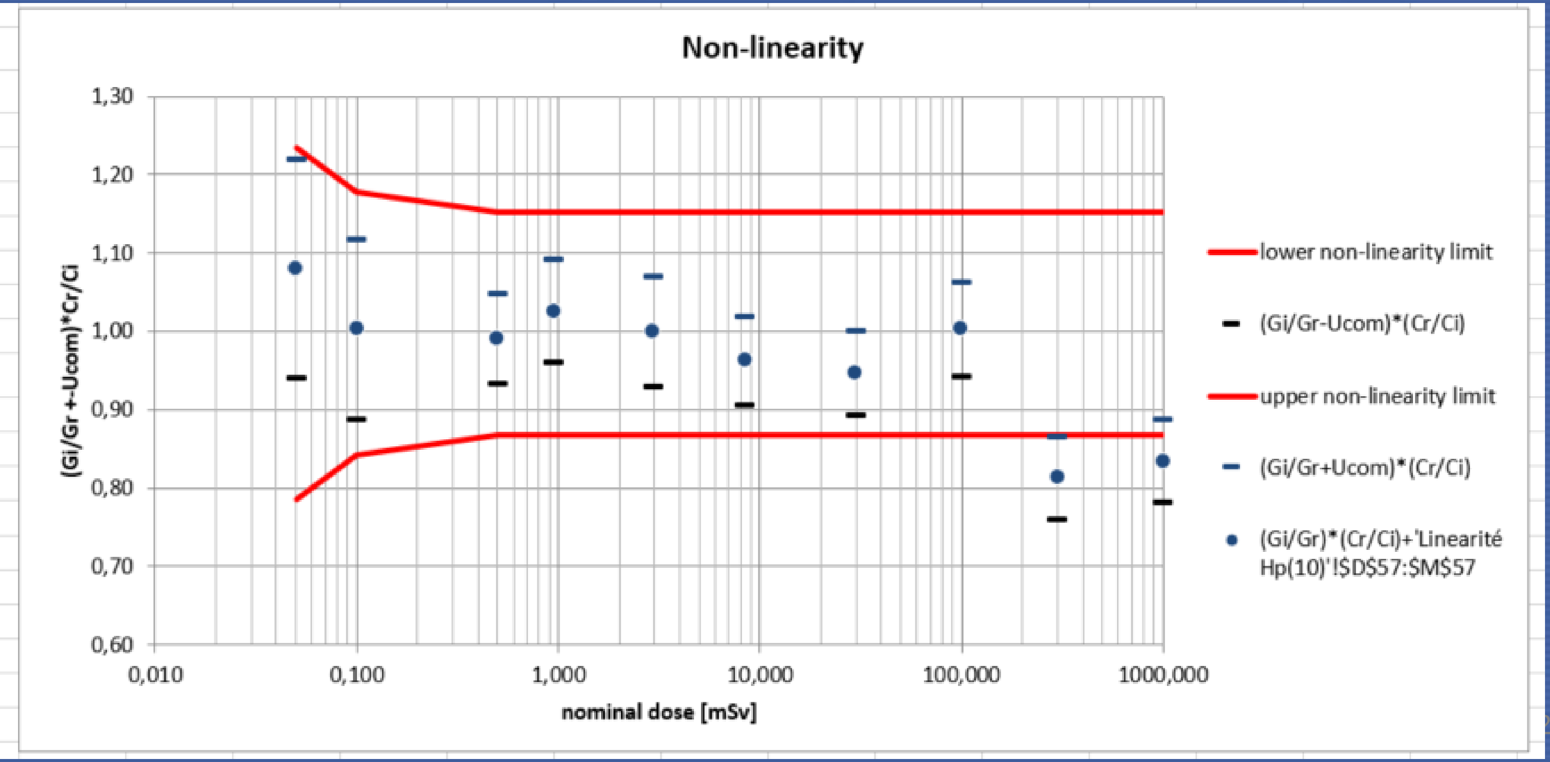
Reproducibility

- **Reproducibility condition of measurement - reproducibility condition**: *condition of **measurement,** out of a set of conditions that includes different locations, operators, **measuring systems,** and replicate measurements on the same or similar objects*
  - NOTE 1 The different measuring systems may use different **measurement procedures.**
  - NOTE 2 A specification should give the conditions changed and unchanged, to the extent practical.

- **Measurement reproducibility – reproducibility: measurement precision** under **reproducibility conditions of measurement**
  - NOTE Relevant statistical terms are given in ISO 5725-1 and ISO 5725-2

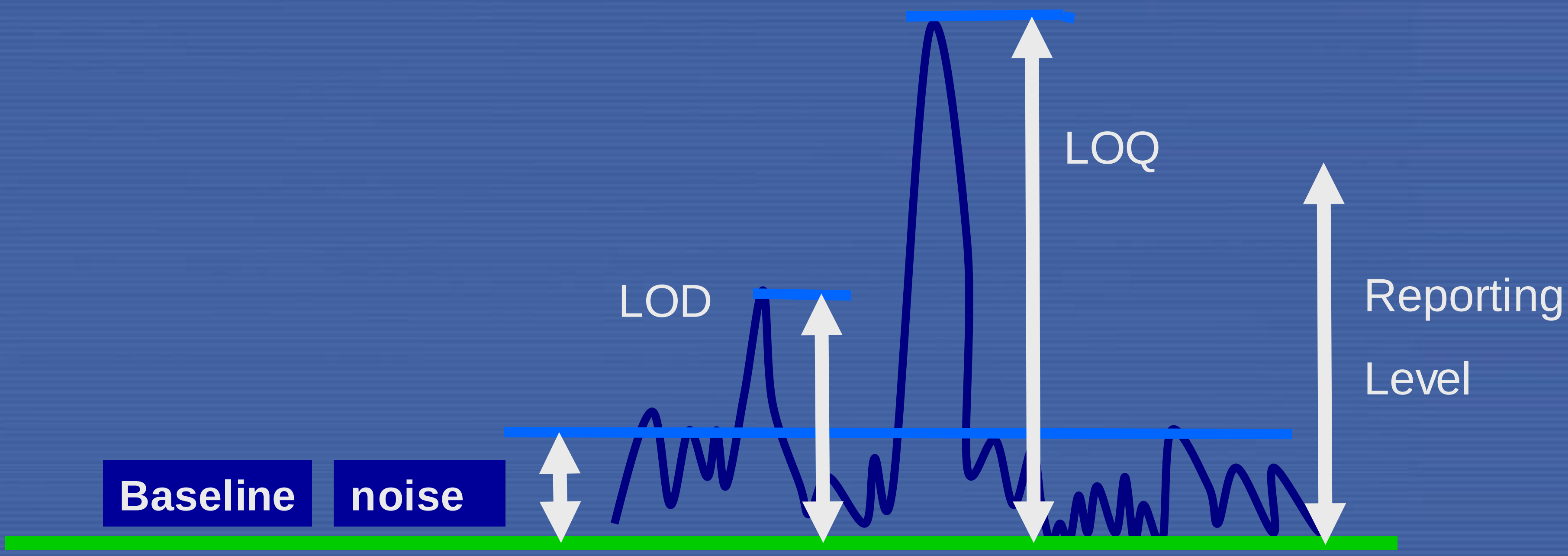
Linearity - example of IMS

- What is the range over which acceptable accuracy and precision are obtained"? Linearity is the ability of the method when used with a given matrix to give results that are in proportion to the amount present in the sample. The response Measured/Reference should be stable over the doserange versus the reference dose provided by SSDL. Again several dosemeters per energy and per decade



Limit of Detection

- There is difference between a Limit of Detection, a Limit of Quantification and a Reporting limit

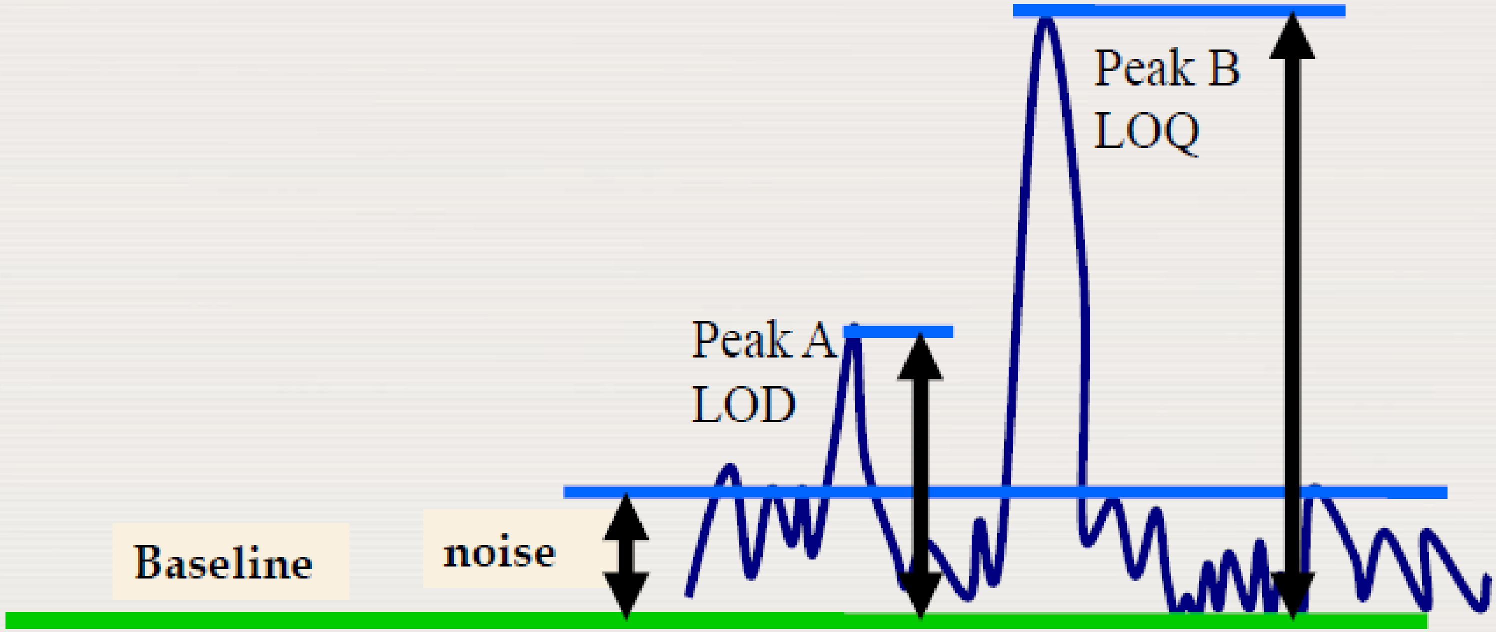


LOD VS LOQ

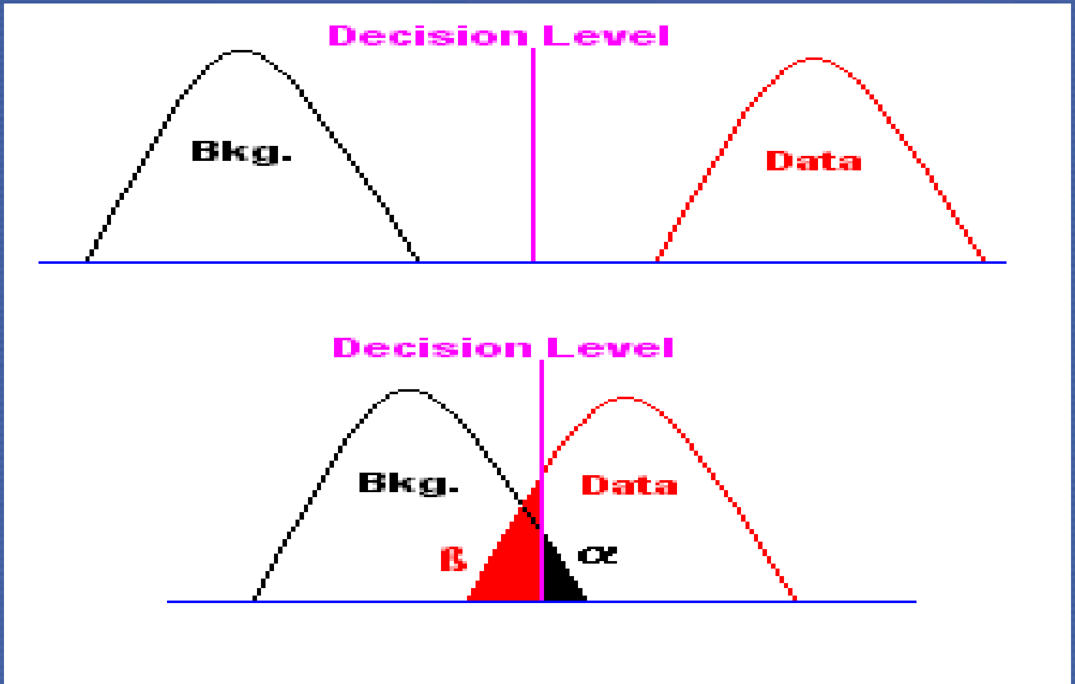
Limit of Quantification

Limit of Detection

Reporting limit



What is the lowest amount that can be detected at a level of 95 % confidence given the background in the sample?”



- α: false positive: wrongly declaring a substance to be present
- β: false negative: wrongly declaring a substance to be absent

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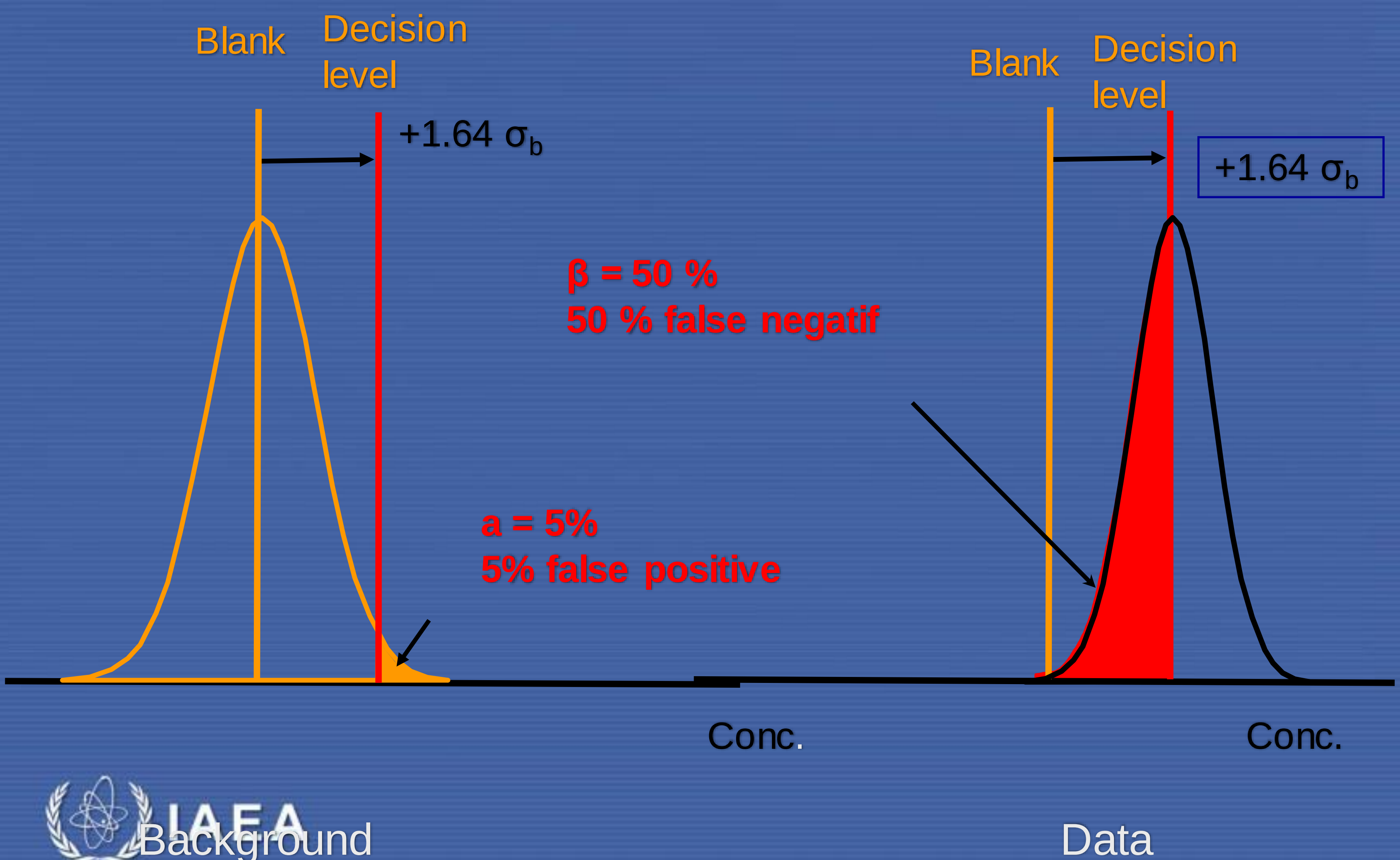
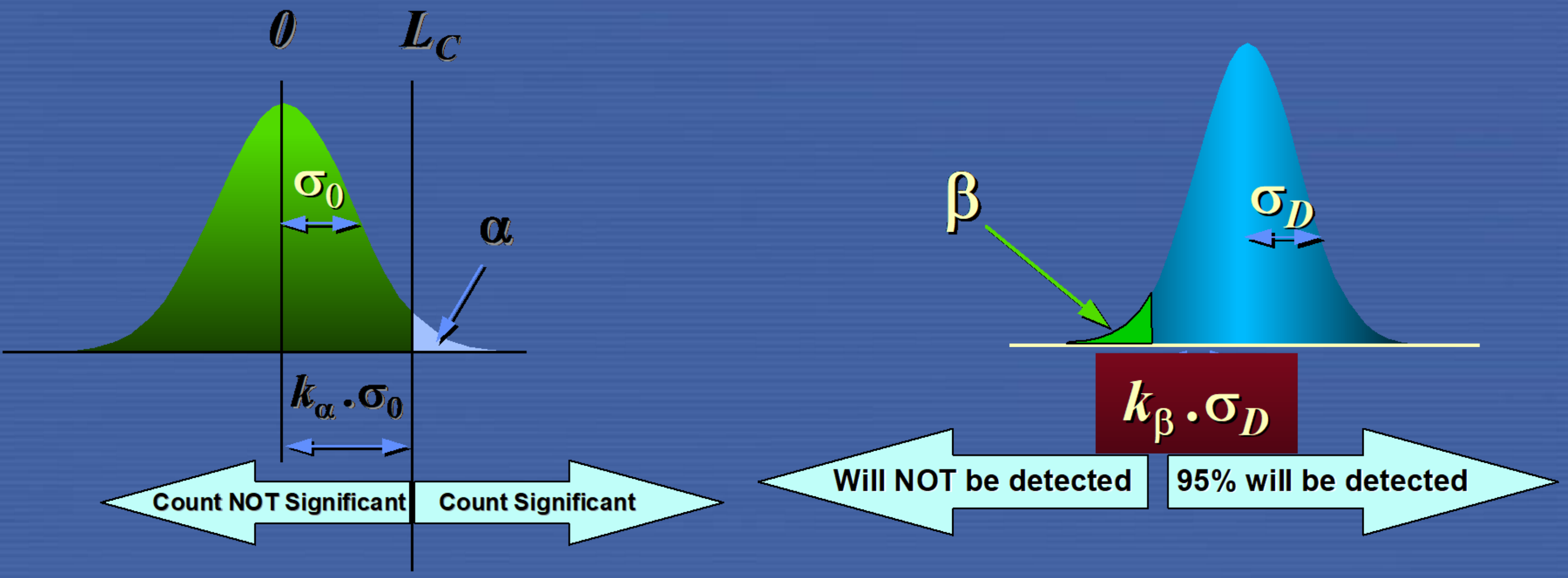
α and β-errors



Detection Limit: "what is the lowest amount I can be 95 % confident of detecting given the peak background in the sample?"



$$L_d = k_a . \sigma_0 + k_ß \bullet \sigma_D \quad \text{or} \sim 3,3\ \sigma_b$$

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Detection threshold - example of IMS

Method

- Prepare a large set of dosimeters, left under the same conditions (not exposed) during fixed period and read out.
- Calculate for all dosimeters standard deviation sb
- Detection limit = LD = 3.3 u(0) (standard combined uncertainty extrapolated at zero dose) or very much simplified ≈ 3.3 $s_{background}$
- Detection limit should be lower than the doserange you promise to your customer

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