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The Selection & Utility of Potency Standards for Biotechnology Products

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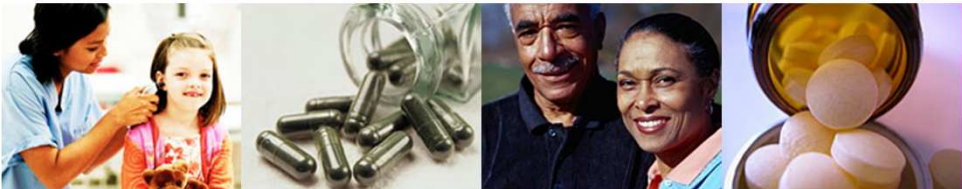
IABS Conference
September 20-21, 2011
NIH Campus, Bethesda, Maryland



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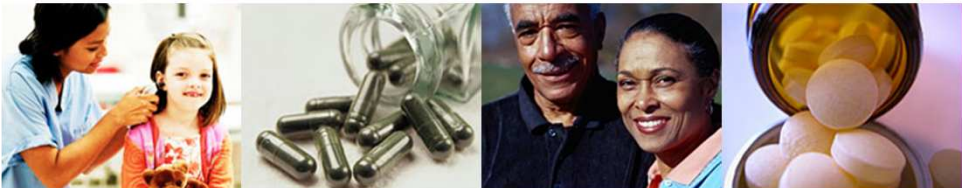
OUTLINE

- Introduction
- Definition of biological activity & potency
- Procedures used to measure biological activity
- Role of a reference standard in a bioassay
- Key attributes of a reference standard used in a bioassay
- Types of reference standards used in bioassays
- Concluding remarks



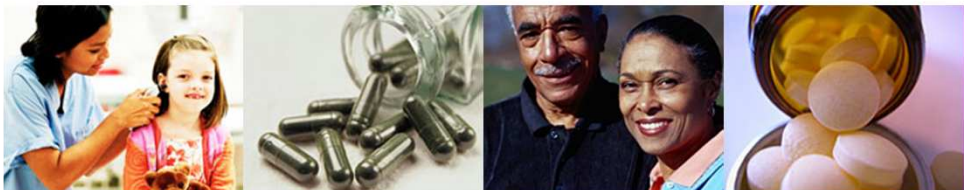
Biologics and Genetic Therapies Directorate:

- Health Canada's BGTD is the Canadian federal authority responsible for the regulation of biological drugs and radiopharmaceuticals for human use.
- Products regulated by BGTD include:
 - biotherapeutics (cytokines, hormones, enzymes & monoclonal antibodies)
 - radiopharmaceuticals
 - cell and genetic therapies
 - viral, bacterial and combination vaccines
 - blood and blood products
 - cells, tissues and organs for transplantation



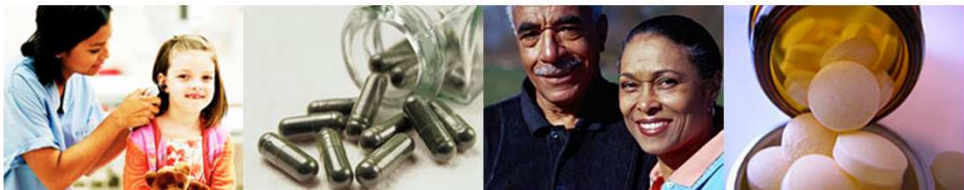
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Guideline Q6B):

- Biological activity is the specific ability or capacity of the product to achieve a defined biological effect.
- Potency is the quantitative measure of the biological activity using a suitably quantitative biological assay (also called potency bioassay), based on the attribute of the product which is linked to the relevant biological properties.
- A relevant, validated potency assay should be part of the specifications for a biotechnological or biological drug substance and/or drug product.



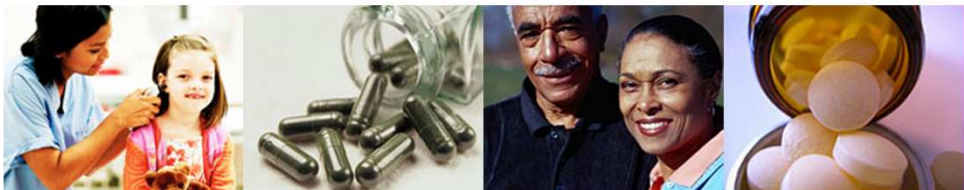
ICH Guideline Q6B:

- Examples of procedures used to measure biological activity:
 - Animal-based biological assays, which measure an organism's biological response to the product.
 - Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level.
 - Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.



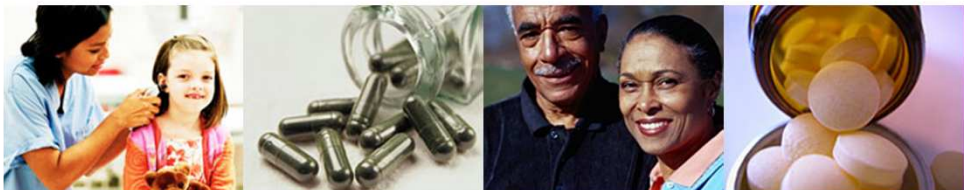
ICH Guideline Q6B:

- Other procedures such as ligand and receptor binding assays, may be acceptable.
- A biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where:
 - sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
 - there exists a well-established manufacturing history.

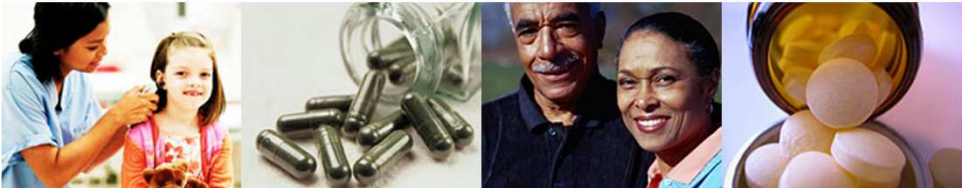
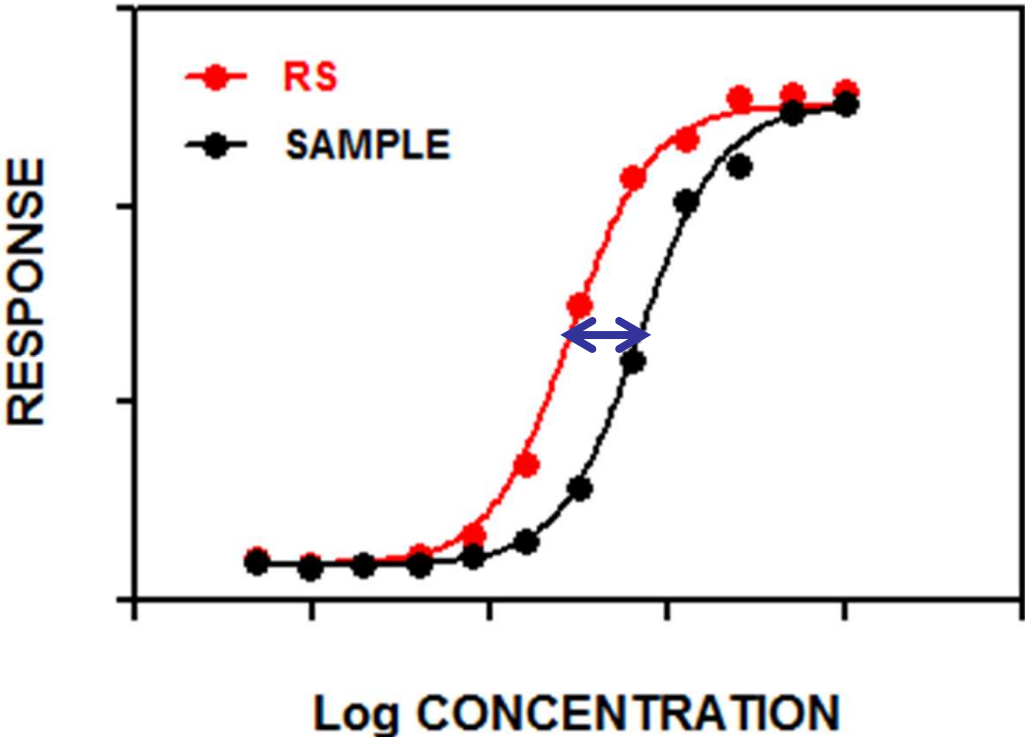


Bioassays are indirect (i.e. comparative) quantitative procedures:

- Bioassays are complex test systems that are susceptible to many variables.
- The performance of bioassays (and hence their biological readouts) can vary from day to day and especially from laboratory to laboratory.
- The response of a bioassay system to a test material can not be used by itself to assign an absolute potency value.
- The biological response of a test material is measured relative to that of a reference preparation.

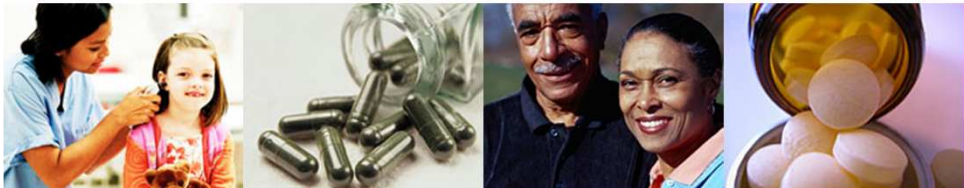


Relative potency assessment:

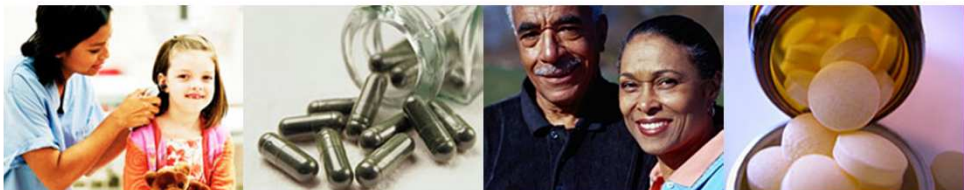
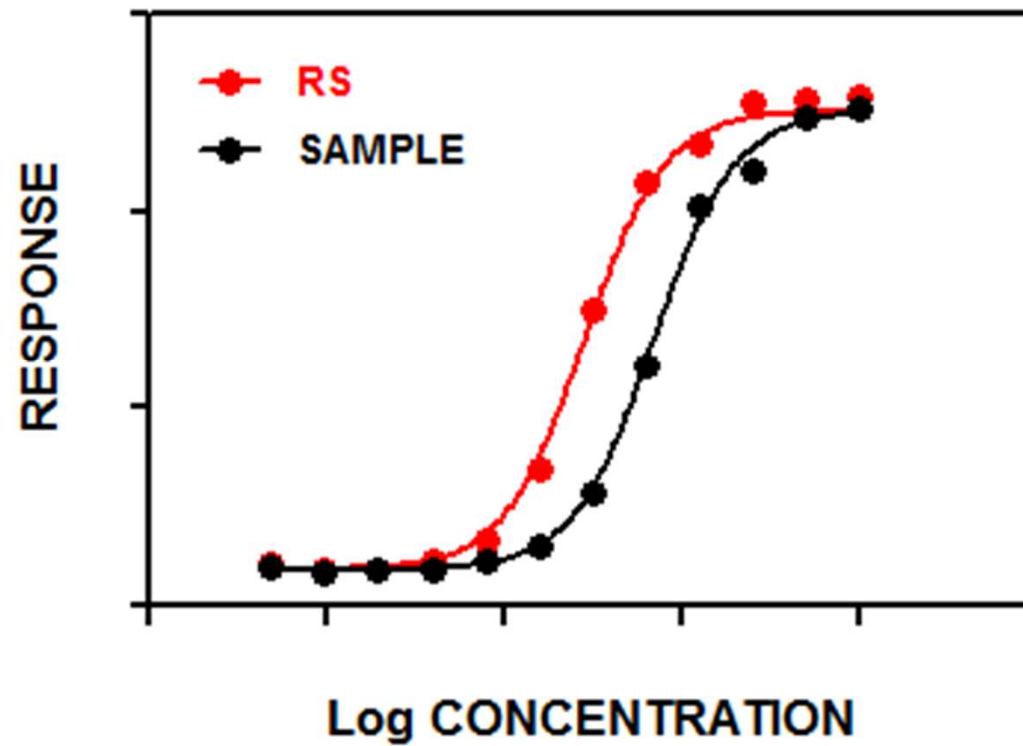


System suitability criteria for bioassays:

- Adequacy of model used to fit dose-response data.
- Replicate variability.
- Potency of control sample(s).
- Parameter(s) of the reference standard response.
- Similarity (parallelism).

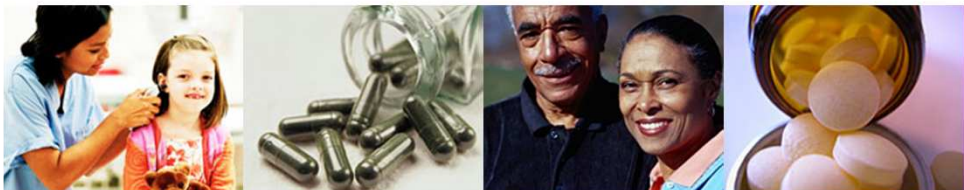


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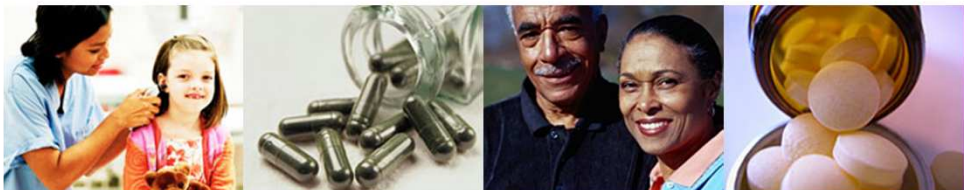
Similarity (parallelism):

- Different statistical approaches may be used to assess parallelism.
- The absence of parallelism shows functional dissimilarity between two preparations.
- Molecular changes to the biological material may result in nonparallel responses.
- Formulation differences between reference standard and test sample may also result in nonparallel responses.



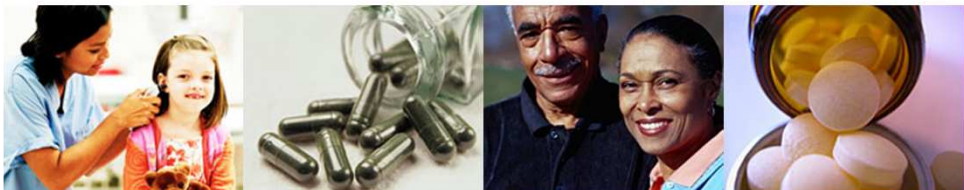
Validation of Analytical Procedures (ICH Guideline Q2[R1]):

- Accuracy
- Precision
 - Repeatability
 - Intermediate precision
 - Reproducibility
- Specificity
- Linearity
- Range
- Robustness



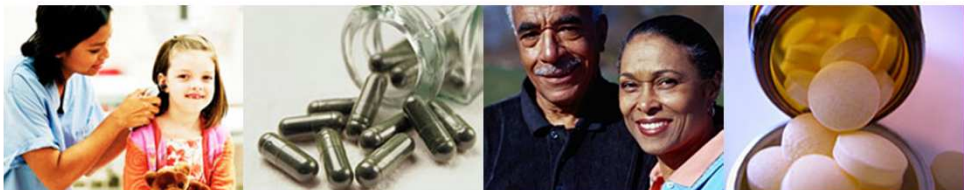
Key attributes of a reference standard used in a bioassay:

- Within a particular bioassay, the reference standard must have a biological activity that is identical to the biological activity of the test sample.
- Characterized.
- Stable.
- Free from substances that may interfere with the assay.
- Homogeneous preparation (i.e. minimal vial-to-vial variation).
- Available in sufficient quantities.



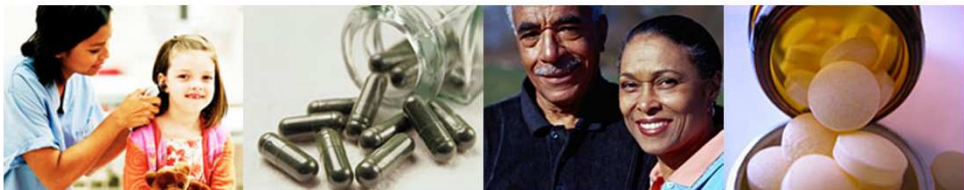
ICH Guideline Q6B:

- The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized.
- Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.

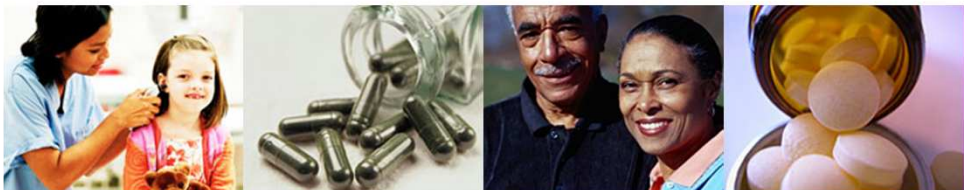
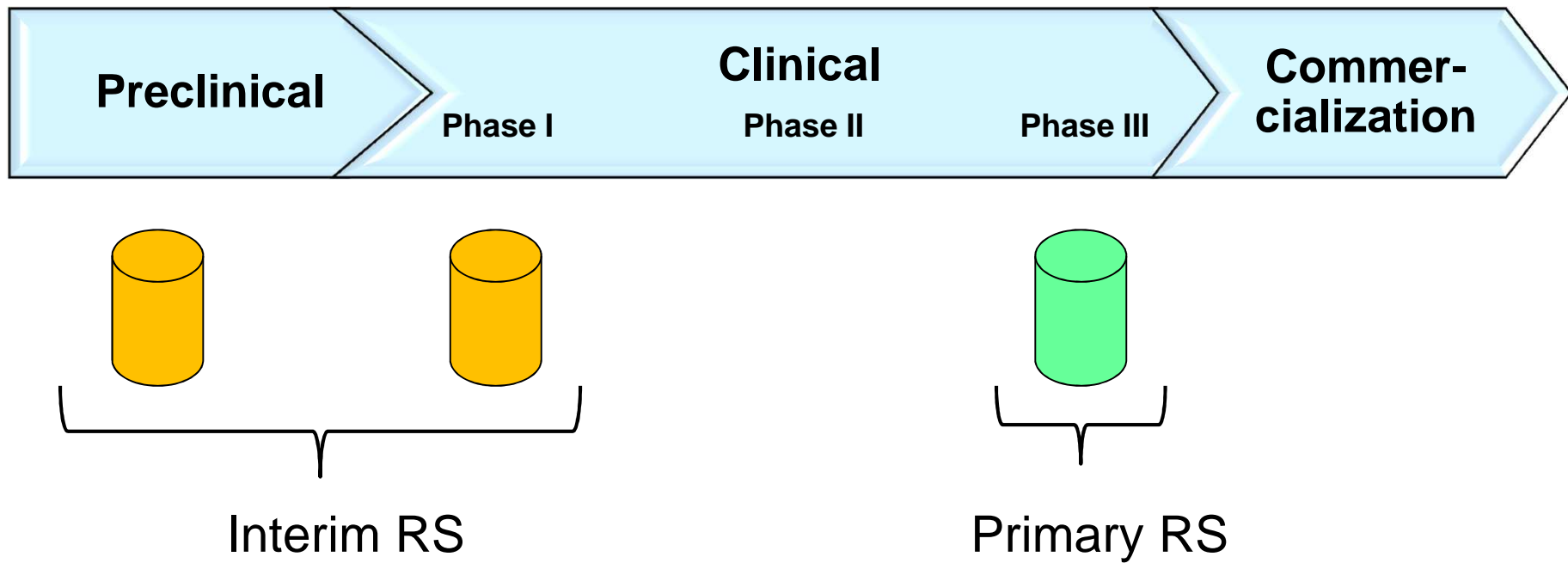


ICH Guideline Q6B:

- **In-house Primary Reference Material:** An appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

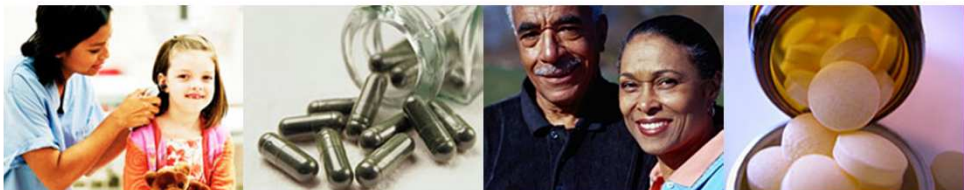


Establishment of a primary reference standard during drug development :



SOP for the qualification of a new Reference Standard provides instructions and acceptance criteria to be used in:

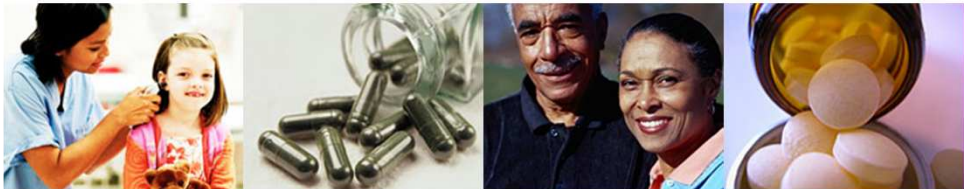
- Selection
- Qualification
- Storage
- Re-qualification
- Replacement





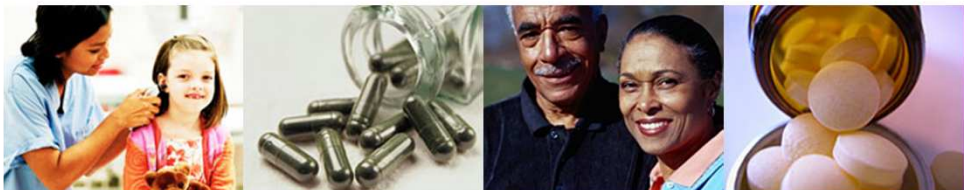
ICH Guideline Q6B:

- **In-house Working Reference Material:** A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.



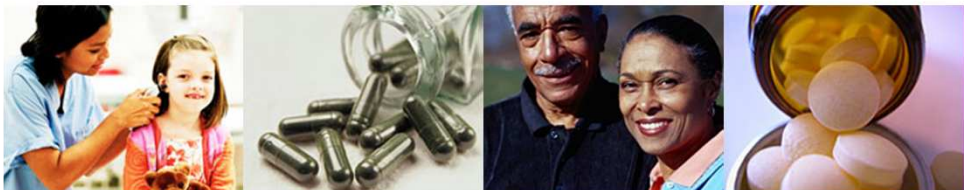
Potency calibration of an in-house working reference standard:

- Statistical evaluation.
- Accuracy with which a reference material has to be calibrated is related to the accuracy of the test in which the reference standard is used.
- The error of the calibration must always be insignificant compared with the error of a single estimate by the method in question.



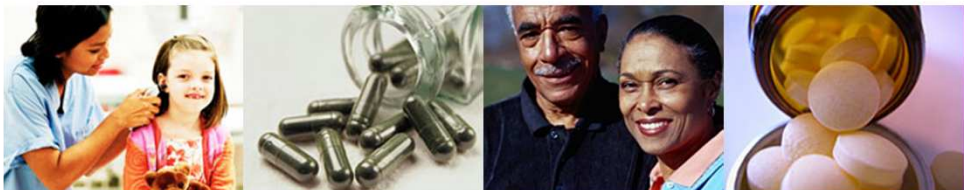
International standards: WHO Reference Preparations

- The WHO Reference Preparations are established through a standard operating procedure under which representative materials (often one of several candidates donated to WHO for the purpose) are tested by participating laboratories using their own methodologies.
- The successful material is one where consistent results are obtained across the methods in use.
- Upon establishment of the Reference Preparation by the WHO Expert Committee on Biological Standardization (ECBS), the material is assigned a unitage, often in International Units.



WHO Reference Preparations

- The choice of what unitage to use for any material is part of the collaborative study process, but is essentially an arbitrary unitage, defined solely by the WHO standard.
- WHO international biological reference preparations are often in limited supply.
- WHO preparations are generally intended for use in the characterization of the activity of secondary reference preparations (regional, national or in-house working standards).



Conclusion:

- The reference standard is a critical reagent in a bioassay.
- Intended use includes quality control testing, assay validation, assay verification, and calibration.
- The selection and assessment of suitability of the reference standard must be well documented.

