A. Purpose: Products that are non-compendial, OTC, or pharmacy-compounded do not require an NDA or ANDA to be marketed. Nevertheless, ORA labs can be called upon to test these products. Instances also exist where "Standard Methods" (Compendial or NDA/ANDA methods) are not applicable to a certain product, require equipment not available in the laboratory, are outdated or not readily available, or are not the most efficient use of a laboratory's resources. This document provides uniform guidance to ORA laboratories on minimum requirements for validation of drug analytical methods developed for this purpose.

Validation, in simplest terms, is defined as the demonstration that an analytical method is suitable for its intended purpose. It is important to recognize that, especially in drug analysis, different types of methods exist for different purposes. These methods can be grouped into categories, each category requiring a different set of validation parameters. Categories of methods are discussed below.

The ORA Laboratory Manual directs that validation is required when a new method is developed, when an existing validated method is significantly modified, or when an existing validated method is applied to a sample matrix significantly different from that for which the method was developed.

Verification (sometimes also referred to as "method transfer") is defined as an assurance that a laboratory other than the originator of a Standard Method or other previously-validated method can obtain comparable results, using its equipment and personnel, as the originator of the method; in other words, that the method is suitable under actual conditions of use in a particular laboratory.

Presented here are the ***minimum*** requirements for validation of drug methods within ORA. This is primarily designed to address methods for single-occurrence or internal use: for a single sample or a small group of similar samples. Validation of methods intended for use by multiple labs, for publication in a scientific journal, or for establishment as a future "Standard Method" require additional validation; this is addressed in Notes (c) and (d), below. In any case, labs may in certain circumstances justifiably find the need to perform additional validation steps. However, the value of additional information gained by such work must be weighed against the resources expended in the process.

Also presented are acceptance criteria for each validation parameter. These must be considered carefully. These acceptance criteria apply to "conventional" dosage forms (tablets, capsules, solutions, aqueous injections, etc.) where matrix interference is usually minimal. For more complex matrices (creams, suppositories, etc.), meeting these criteria may be impossible. Other considerations, such as reduction of spiking levels due to limited standard availability, may also cause difficulties in meeting the criteria. Such situations must be evaluated, approved, and documented on a case-by-case basis (see note a).

References:

International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: Text on Validation of Analytical Procedures (Q2A)

International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: Validation of Analytical Procedures: Methodology (Q2B)

United States Pharmacopeia (USP) section <1225>: Validation of Compendial Methods

B. Validation Parameters: The following validation parameters (referred to as "Analytical Performance Characteristics" in USP and ICH documents), are to be applied based on the category of method being validated, according to the chart below. Definitions are as are commonly accepted by the scientific community, and expressed in the USP and ICH documents referenced above.

1. **Accuracy**: Prepare 3 preparations of composited sample, containing a known quantity of added analyte ("matrix spike"), so that the expected concentrations are as follows:
   a. Assay: range at least 80%-120% of expected content
   b. Content Uniformity: range at least 70%-130% of expected content (note: if Assay and Content Uniformity methods are the same, accuracy determination ranging 70%-130% of expected content will satisfy requirements for both methods.)
   c. Dissolution/release rate determinative step: range at least 20% less than lower dissolution limit to 20% greater than higher dissolution limit

   Acceptance Criteria: 97.0% - 103.0% recovery for each spike level for APIs; 95.0% - 105.0% for finished dosage forms. (see note a.)
2. **Precision (repeatability):** Perform 5 replicate injections of standard solution of analyte at 100% of expected concentration, unless otherwise specified.
   Acceptance Criteria: RSD less than or equal to 2.0%, unless otherwise specified
3. **Linearity:** Prepare a set of a minimum of 5 concentrations of analyte standard, with minimum range as defined for Content Uniformity solutions under "Accuracy," above. Perform the determination, and generate a standard curve.
   Acceptance Criteria: Linear Regression Coefficient of Determination r(2) greater than or equal to .995 (see note e.).
4. **Specificity:** Assessment of specificity depends on the technique being used. Certain techniques (i.e. titrations) are non-specific by nature; a combination of two or more analytical procedures is necessary to achieve the required level of discrimination. Techniques such as HPLC-UV or UV spectrophotometry are somewhat more specific in nature: visual comparison of standard and sample spectra or chromatograms should be performed; no interferences should be apparent. Peak-purity technology should be used when possible to assist in this evaluation. Techniques such as IR spectrophotometry or mass spectrometry are highly specific: sample and standard maxima or bands should occur at the same wavelengths or masses.
   When impurity or degradant standards are available, specificity can be additionally assessed by addition of these compounds to the primary analyte, to assure that interferences do not occur.
5. **Limit of Detection:** For chromatographic or spectrophotometric methods, determine the minimum level at which a compound can be detected, using analyte solutions of decreasing concentration. L.O.D. is generally defined as 3 times the noise level. Other scientifically-sound approaches may also be used. For other types of methods, estimate through visual evaluation the minimum level at which a compound can be detected, using analyte solutions of decreasing concentration.
6. **Limit of Quantitation:** For chromatographic or spectrophotometric methods, determine the minimum level at which a compound can be quantitated, using analyte solutions of decreasing concentration. L.O.Q. is generally defined as 10 times the noise level. Other scientifically-sound approaches may also be used.
   For other types of methods, estimate through visual evaluation the minimum level at which a compound can be quantitated, using analyte solutions of decreasing concentration.

Notes:

a. If acceptance criteria are not met, due to situations described in this paragraph, the occurrence should be evaluated in the form of a discussion between analyst(s), lab managers, and QA managers, with the purpose of the analysis and the requirements of the customer being taken into account. The specified acceptance criteria can then be modified, if sufficiently justified.

b. the validation parameter "Range" is often discussed separately. For most purposes, the quantitative or qualitative range of a method will be appropriately established through determination of linearity, accuracy, and LOD/LOQ, as described above.

c. the validation parameters "Ruggedness" and "Robustness" are also frequently discussed. When the method being validated is for single-occurrence use or internal use, these determinations may not be necessary. For a more complete validation, as in cases where the method is intended for publication or establishment as a future "Standard Method", ruggedness and robustness should be assessed through use of differing equipment, by a different analyst or laboratory, over several time intervals, or a combination of the above.

d. ICH and other guidelines recommend, for Accuracy determination, an assessment using a minimum of 3 replicates at each of 3 concentrations, thereby equating to a minimum of 9 determinations. This should be done when the method is intended for publication or establishment as a future "Standard Method." For routine regulatory analytical purposes, 17025 requirements will be considered met if each of the three single preparations evaluated under "Accuracy" meet the Acceptance Criteria. If one or more preparations fails to meet these criteria, the laboratory should conduct a failure investigation, to include an examination of possible causes for this failure

e. For certain types of methods, i.e. Atomic Emission Spectroscopy, a non-linear standard curve may be expected, and can be used. Linear Regression analysis would not apply to such situations.

C. Categories of Methods; Validation Parameter Requirements

1. **Category I: Quantitative Assessment of Major Components:** (i.e. Assay, Content Uniformity, determinative step for Dissolution/Release Rate). Required parameters: Accuracy, Precision, Linearity, Specificity
2. **Category IIa: Quantitative Assessment of Minor Components:** (i.e. Impurity and Degradant quantitative determinations). Required parameters: Accuracy, Precision, Linearity, Specificity, Limit of Quantitation
3. **Category IIb: Qualitative Assessment of Minor Components:** (i.e. Impurity and Degradant Limit Tests). Required parameters: Specificity, Limit of Detection
4. **Category III: Qualitative Assessment of Major Components:** (i.e. Identification). Required parameter: Specificity

D. Verification of Methods: As is mentioned above, a laboratory must verify that any validated method (including USP or other "Standard Methods") can be performed acceptably under actual conditions of use. Method Verification should be performed upon the first use of a method by a particular analyst on a particular instrument to document that the **method performance criteria** can be met. After this, **instrument performance criteria** (for example, system suitability parameters, criteria specified in the method, etc.) should be met as directed by the method or per batch of similar samples.
Verification should include, as a minimum:

1. Full system suitability testing, as defined in the compendial method, with acceptance criteria as defined in the compendium. If this is not applicable, system precision for chromatographic procedures should be assessed using six replicate injections (RSD $\leq$ 2.0); specificity should be assessed using either a chromatographic resolution factor (>1.3) or a visual examination of chromatograms or spectra for freedom from interference.
2. Accuracy determination through analysis of a matrix spike (acceptance criteria: 97.0%-103.0% recovery for APIs, 95.0%-105.0% for finished dosage forms; see note a. above).