This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR 14 1996

Dear Interested Party:

The Division of Clinical Laboratory Devices within FDA's Office of Device Evaluation has many initiatives underway directed toward achieving consistency of premarket notification (510k) review of in vitro diagnostic devices (IVDs).

The enclosed copy of our "Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices" provides quidance for calibration recommendations and labeling in support of 510k submissions.

We invite your comments to assist us in addressing general or specific areas of the document that need improvement, clarifications or further definition.

The document will also be available for distribution through Division of Small Manufacturers' Assistance (DSMA), 800-638-2041, or their electronic docket, 800-252-1366.

Please forward any comments you may have before May 30, 1996 to:

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
9200 Corporate Boulevard HFZ-440
Rockville, MD 20850

If you have any questions regarding this document, contact me or Clara A. Sliva via phone 301-594-3084 or fax 301-594-5940.

Sincerely,

Steven Gutman

Steve I. Gutman, M.D., M.B.A.

February 1, 1996 DRAFT

Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices

OBJECTIVES OF THIS DOCUMENT

This draft document provides FDA's guidance for calibration and quality control (QC) recommendations and labeling in support of premarket notification 510(k) in vitro diagnostic (IVD) device submissions. The intent is to provide both manufacturers and Division of Clinical Laboratory Device (DCLD) reviewers with a basis for improved review consistency. Review criteria for individual submissions for calibration or quality control materials are not included in the scope of this document.

BACKGROUND

Calibration and quality control are key requirements of FDA review, as noted in the labeling regulations for in vitro devices [(21 CFR 809.10(b)(8)(v and vi)]. As a result FDA routinely reviews details of calibration and the kinds of quality control procedures and materials required as part of its product review.

The other major regulatory program that affects laboratories is the Clinical Laboratory Improvement Act of 1988 (CLIA 88) which currently mandates that all clinical laboratories follow quality control procedures as published in regulations (CFR Part 493, Subpart K).

FDA's LABELING REGULATION

FDA's labeling regulations contain provisions to deal with both device accuracy and precision.

CFR 809.10(b)(8)(v) reads: "Details of calibration: Identify reference material. Describe preparation of reference samples(s), use of blanks, preparation of the standard curve, etc. The description of the range of calibration should include the highest and lowest values measurable by the procedure."

FDA currently requires information on calibration procedures performed both to support data collection as part of the submission and to provide users with information on the appropriate routine operation of the device. Whenever possible we encourage traceability of device performance to a reference

method or material. Recommended calibration frequencies should be included as part of each submission with appropriate supporting data.

CFR 809.10(b)(8)(vi) reads: "Details of kinds of quality control procedures and materials required. If there is need for both positive and negative controls, this should be stated. State what are considered satisfactory limits of performance."

FDA currently requires that the package inserts of all devices contain information on the quality control materials appropriate for a test system. In addition any internal, electronic, reagent, or process control which is an integral component of the device must be clearly described and the nature of the information provided by its use explained. Recommended QC specific rules including run frequencies to be followed for assessing quality are left to the discretion of the individual laboratory.

The intent of the above review is to ensure that users clearly understand the operating characteristics of QC systems so that they can make informed choices about minimal QC requirements for a particular system and setting.

CALIBRATION PROCEDURES

Calibration procedures refer to the methods used to translate a device response measurement into a concentration, activity, or other outcome measurement. Calibration usually involves measurement of the device response in relation to special samples of known values called calibrators. Proper calibration and maintenance of calibration impacts on both the accuracy and precision of test results.

CALIBRATION CATEGORIES

Calibration is most commonly performed using calibrators specifically prepared to set up a standard curve or cut-off point for an assay. In some instances calibration may be based on a rigid determination of the operating characteristics of a system and its known performance parameters (e.g. enzymes) and in some instances selected patient samples or other samples are used to correlate accuracy between a reference method to a working method.

REQUIREMENTS FOR METHOD CALIBRATION

Requirements for method calibration are outlined in 21 CFR 809.10(b)(8)(v) and include:

1. identification of reference material

2. a description of the preparation of reference sample(s)

3. a description of preparation of the standard curve (if applicable)

4. a description of the range of calibration

QUALITY CONTROL PROCEDURES

Quality control procedures are the set of laboratory materials and analytical processes used to:

a. monitor the performance of laboratory analytical systems (reagents, instruments, and/or operators).

b. monitor the precision and accuracy of a test procedure.

c. ensure that proper testing conditions and instructions have been met.

All in vitro devices which result in generation of test results must include information on quality control to comply with the labeling requirements noted above.

QUALITY CONTROL CATEGORIES

Quality control of in vitro devices may be composed of two different components:

A. **External quality control samples:** These are external samples which are run in parallel with patient samples to assess the analytical reliability of the total analytical test system. Ideally these are handled in exactly the same manner as the patient samples and are in an identical matrix. Results generated through use of QC samples optimally could be used to evaluate all components of the analytical system from specimen preparation through generation of test results.

B. **Device quality control components (so-called procedural controls):** These are device components which can complement or augment external quality control samples. Quality control components include a wide variety of methods or mechanisms internal to a device which can be used to evaluate parts of the system including (but not limited to) the following examples:

1. the operating integrity of the instrument system (internal electronic calibration or system checks)

2. the integrity of reagents and sample (internal components used to check for volume flow, integrity of antibody/antigen, or the activity of important reaction ingredients) and/or

3. proper procedures (internal design components to monitor that reagents have been added in the proper order.)

Appropriate control limits can be established for both external quality control samples and device quality control components and these mechanisms can be used together to monitor and assess devices and components involved and to predict analytical failure.

REQUIREMENTS FOR QUALITY CONTROL

External samples for use in QC

External samples for use in QC evaluation of a device may be included as part of a diagnostic test system or may be purchased as an accessory. If the QC material is included as a part of the device under review, performance information and labeling should follow that of the FDA Points to Consider for Quality Control Materials. Whatever the recommended source for QC materials, package inserts should include information on what types of QC material should be obtained, where they may be obtained, and why they must be used in support of device performance.

At a minimum, labeling should indicate the types of QC samples recommended including appropriate levels and matrices to be used. QC recommendations should be chosen to adequately assess ongoing test performance at key performance intervals or medical decision points. For qualitative tests it is recommended that positive and negative cut-offs be carefully identified and that controls be provided which adequately challenge performance at these levels.

Device quality control components (procedural controls)

All device quality control components which contribute to evaluation of testing should be clearly identified and the actions and limitations of each of these components should be addressed. For example, devices which include a color control line as part of a visual read-out should clearly indicate what development of the colored line means; does it assess for proper fluid uptake alone; does it test reactivity of antibody; does it evaluate addition of reagents in a proper order, etc? The procedural instructions for the assay should specify the acceptability of: temperature and time variation, instrument maintenance, and functionality. Well established ranges for these areas of the procedure reflect on the adequacy of the assay's QC.

In most instances the frequency of quality control testing will depend on a variety of laboratory specific factors including testing volume, testing frequency, and the nature of the laboratory's operational quality control and quality assurance programs. In some instances minimal quality control specifications may be required by FDA. These are directed at control of the medical device alone and are not intended to establish parameters for laboratory practice or accreditation. Consequently, these recommendations should be accompanied by a clear disclaimer indicating that quality control requirements should be performed in conformance with local, state, and/or federal regulations or accreditation requirements.

Written - K. Aziz - 7/95
Revised - S. Gutman 8/2/95
Revised - S. Gutman with input from DCLD staff - 10/5/95
Revised - S. Gutman with input from chemistry - 11/2/95
Corrected - S. Gutman - 11/6/95
Corrected with input from CDC - 12/26/95
Corrected with input from S. Alpert and branch chiefs - 1/28/96
Corrected with input from branch chiefs - 1/31/96