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C37-A

Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline

This guideline details procedures for the manufacture and evaluation of human serum pools for cholesterol measurement.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline

Abstract

Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline (C37-A) outlines procedures for selecting, processing, and combining donor units to prepare frozen serum pools which are commutable among multiple methods for serum cholesterol measurement. The guideline also addresses issues related to the evaluation of the pooled materials. The manufacture and evaluation of two levels of serum cholesterol pools prepared according to this guideline are described. The appendix includes a summary of the results from the pilot study conducted to evaluate the scientific basis of this guideline.

This guideline will provide information to develop reference materials which can be useful to manufacturers of *in vitro* diagnostic (IVD) reagents, systems, and quality control products in establishment of calibration (or assigned values) for their products. Additionally, these reference materials can be beneficial to proficiency testing agencies, as well as end users in the clinical laboratory as tools to independently assess performance (and trueness) of procedures for the routine measurement of serum cholesterol.

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Contents

Foreword

Numerous epidemiological and clinical investigations across the world have documented that elevated levels of blood cholesterol are a major risk factor for coronary heart disease (CHD) and that lowering blood cholesterol levels decreases morbidity and mortality from CHD.[1-5] Reduction in the prevalence of elevated blood cholesterol has been a primary objective of the National Cholesterol Education Program (NCEP), established in 1985 by the National Heart, Lung and Blood Institute.[6,7] The efforts of NCEP and other similar international cholesterol education programs to reduce high blood cholesterol are based on the need for reliable blood cholesterol measurements for proper patient risk classification.[8] An important milestone in the NCEP effort was the establishment of the National Reference System for Cholesterol (NRS/CHOL) by NCCLS, which provides the accuracy target for cholesterol measurement.[9] The NCEP's Laboratory Standardization Panel recommended that all cholesterol measurements be standardized and traceable to the NRS/CHOL.[8] It is extremely important that manufacturers of clinical instruments, reagents, and calibrator materials, as well as clinical laboratories, have available to them reference materials that will establish traceability to the NRS/CHOL and assure true and precise results on human subjects, in all field methods being used worldwide. In order to achieve this goal, reference materials with long-term stability and appropriate analyte concentrations are required.

An additional very important requirement is commutability, termed "transmutability" by some investigators. Even though often prepared from human sources, processed reference materials in the past have often taken on properties, loosely termed "matrix effects," that make them behave differently from patient specimens in some reagent/instrument systems.[10] Matrix effects differ from more typical analytical interferences in that the latter are effects of exogenous (e.g., drug) or endogenous (e.g., bilirubin) substances that have similar effects on both patient and manufactured control and calibrator materials. In contrast, matrix effects are properties that are unique to the processed reference materials (and control materials). Since matrix effects lead to underrecovery, or less commonly overrecovery, of the analyte of interest in some field methods, knowing very true and precise analyte concentrations on a reference material which demonstrates matrix effects with certain field methods does little to transfer trueness to those methods.

The currently accepted approach to document traceability to the NRS/CHOL for many field methods is via a split-sample comparison with the reference method using fresh human serum specimens.[11] The presence or absence of matrix-effect interferences with field methods in a given sample can be confirmed by direct comparison of field method measurements with measurements from a reference method which is not subject to matrix effects. Protocols have been developed which can identify matrix effects in particular materials.[12] However, the use of commutable reference materials is the preferred approach and, therefore, a need exists to develop reference materials for cholesterol measurement procedures that do not demonstrate matrix effects. The few materials-formulation guidelines that exist are of a generic nature, not specifically addressing the problem of modern cholesterol methods and the newer, high-throughput, microsampling analytical equipment.[13-15] It is therefore clear that there is a significant gap in the NRS/CHOL and that an immediate need exists for agreement on material standards applicable to the establishment of the calibration and trueness of serum cholesterol measurement systems.

Key Words

Cholesterol, commutable, matrix effects, NRS/CHOL, reference materials, serum pools, traceability

Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline

1 Introduction

This guideline describes the procedures for preparing frozen human serum pools of high quality suitable for cholesterol measurement. Although prepared for cholesterol, the concepts described in this written guideline may be applied to the preparation of frozen human serum pools for other analytes.

2 Scope

These specifications are designed to enable laboratory scientists, *in vitro* diagnostic (IVD) manufacturers, proficiency testing providers, and suppliers of clinical laboratory reference materials[a] to prepare frozen human serum pools which demonstrate minimal matrix effects, are commutable across different cholesterol measurement procedures, and, as such, are suitable for assessing the trueness of these procedures. These serum pools, when assigned target values by the definitive method and/or reference method of the National Reference System for Cholesterol (NRS/CHOL), may be used to properly calibrate and/or assess trueness of field methods for serum cholesterol measurement, and provide an alternative method to split-sample comparisons with human specimens for establishing traceability of calibration of field methods to the NRS/CHOL. This document provides guidance for collecting and processing raw materials to manufacture frozen serum pools and for performing quality assurance of the final product. As part of the guideline development, two frozen human serum pools using a large number of selected individual donor units of "off-the-clot" serum were prepared and characterized. The performance of the pools was assessed in terms of the degree of commutability (observed response versus predicted response) relative to the individual sera which comprised the pools.

3 Standard Precautions

Because it is often impossible to know what might be infectious, all human blood specimens are to be treated as infectious and handled according to "standard precautions." Standard precautions are new guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of any pathogen and thus are more compre-hensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard precaution and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (Guideline for Isolation Precautions in Hospitals, Infection Control and Hospital Epidemiology, CDC, Vol 17;1:53-80.), [MMWR 1987;36(suppl 2S):2S-18S] and (MMWR 1988;37:377-382, 387-388). For specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure, refer to NCCLS docu-ment M29—*Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue*.

4 Definitions[b]

Accuracy, *n* - Closeness of the agreement between the result of a measurement and a true value of the measurand. **NOTE:** The concept of accuracy of measurement is described by trueness of measurement and precision of measurement. Thus, accuracy is not a synonym for trueness or for precision (VIM: 1993, 3.5[16]).

Aseptic, *adj* - Environmental conditions which minimize microbial contamination.

[a] Examples of suppliers of reference materials in the U.S are the National Institute of Standards and Technology, the College of American Pathologists, and the Centers for Disease Control and Prevention.

[b] Some of these definitions are found in NCCLS document NRSCL8—*Terminology and Definitions for Use in NCCLS Documents*. For complete definitions and detailed source information, please refer to the most current edition of that document.