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C44-A

Harmonization of Glycohemoglobin Measurements; Approved Guideline

This document describes an established program to harmonize glycohemoglobin (GHB) testing results among laboratories to a common, outcomes-based reference system and includes recommendations for the clinical application of harmonized GHB testing results.

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

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Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: 610.688.0100
F: 610.688.0700
www.clsi.org
standard@clsi.org

NOTE: This document is no longer being reviewed as part of the CLSI consensus process. However, because of its usefulness to segments of the health care community, it is available for its informational content.

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Harmonization of Glycohemoglobin Measurements; Approved Guideline

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David E. Goldstein, M.D., Chairholder
V. Michelle Chenault, Ph.D., M.T.(ASCP)
W. Jeff Durban
John H. Eckfeldt, M.D., Ph.D.
J. Gilbert Hill, M.D., Ph.D.
Lowry J. Messenger, Ph.D.
Gary L. Myers, Ph.D.
Ewald Vorberg, Ph.D.

Abstract

Clinical and Laboratory Standards Institute document C44-A—*Harmonization of Glycohemoglobin Measurements; Approved Guideline* provides a scheme for harmonization of glycohemoglobin testing results among laboratories. The document approach describes an established program, the National Glycohemoglobin Standardization Program (NGSP). The guideline is intended for manufacturers of glycohemoglobin testing products, laboratorians, clinicians, and others interested in glycohemoglobin testing. It includes information on the rationale for harmonization of glycohemoglobin testing results, the process (including the administrative structure of the NGSP), and the clinical application of harmonized glycohemoglobin measurements in the management of patients with diabetes mellitus. The appendix contains an outline of the NGSP website which includes the current NGSP protocol and sample data collection forms for manufacturers of glycohemoglobin assay methods, as well as for clinical laboratories for certification testing.

While this document will serve as a useful resource for a wider audience, it is intended for use primarily in the United States.

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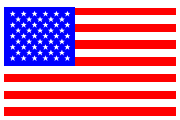

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Lowry J. Messenger, Ph.D.	LXN Corporation San Diego, California
Gary L. Myers, Ph.D.	Centers for Disease Control and Prevention Atlanta, Georgia
Ewald Vorberg, Ph.D.	Roche Diagnostics Germany

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Nina M. Chace, M.S.	Food and Drug Administration Center for Devices/Rad. Health Rockville, Maryland
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Contents

Abstract v

Committee Membership v

Active Membership vii

Foreword xv

The Quality System Approach xix

1 Introduction 1

2 Scope 1

3 Definitions 1

4 Rationale for Harmonization of Glycohemoglobin Measurements 3

5 Description of the Harmonization Scheme 5

5.1 Overview of the NGSP 5
5.2 Steering Committee 5
5.3 Laboratory Network 5
5.4 Implementation of the Harmonization Program 6

6 Clinical Application 7

6.1 Rationale for Using an NGSP-Certified Method 7
6.2 Consideration for Selecting a GHB Test Method 8
6.3 Proficiency Testing 9
6.4 Clinical Interpretation 10

7 Summary 11

References 12

Appendix. The NGSP Protocol 17

Summary of Comments and Subcommittee Responses 18

Summary of Delegate Comments and Subcommittee Responses 19

Related NCCLS Publications 23

Foreword

Background

Diabetes mellitus is a major public health problem worldwide, affecting more than 100 million people.[1] Recent National Health and Nutrition Examination Survey (NHANES) data show that in the U.S. alone, the prevalence of diabetes is estimated at 5.1% of the population, or 10.2 million people.[2] In addition, the prevalence is increasing dramatically: the prevalence of diabetes in people 40 to 74 years of age increased from 8.9% in the years 1976 to 1980 to 12.3% in the years 1988 to 1994. Complications from the disease are serious, accounting for a large share of vision loss, kidney failure, nontraumatic limb amputation, and cardiovascular disease. The disease is also economically devastating, accounting for more than 100 billion U.S. dollars in actual expenditures in 1992[3]; it is estimated that one in every seven healthcare dollars in the U.S. is spent on diabetes, with the majority of the expense for treating the chronic complications of diabetes rather than for primary prevention.[4]

The cause of diabetes complications, and in particular, the relationship between the level of glycemia and complications, had been debated vigorously for more than 50 years, until 1993 when the results of the landmark Diabetes Control and Complications Trial (DCCT) were published.[5] The DCCT was a nine-year clinical trial in patients with Type 1 diabetes. Study volunteers were randomly assigned to either intensive therapy, designed to bring blood glucose levels as close as possible to those in people without diabetes, or to standard therapy, designed to approximate conventional diabetes therapy. Study results showed dramatic reductions in the development and progression of microvascular and neuropathic complications with intensive therapy compared to standard therapy. Risks were directly related to the level of glycemic control, regardless of treatment group. Glycemic control was assessed by serial glycohemoglobin (GHB) determinations performed in a central laboratory.

Based on the DCCT results, the National Institutes of Health (NIH), the American Diabetes Association (ADA), and other expert groups recommended that all patients with diabetes be treated to bring blood glucose levels as close to normal as possible to decrease risks of complications.[6,7] For the first time, there was a firm scientific basis for recommending specific glycemic goals, and these were based on DCCT GHB values. For example, the ADA recommended that most patients with diabetes should aim for GHB levels of 7% or less (nondiabetic reference range of 4 to 6%); levels of 8% or greater were considered to require "additional action."[8]

Unfortunately, DCCT GHB numbers were not readily available to patients and their healthcare providers. The state of GHB testing was, in fact, in considerable disarray.[9] GHB testing was first performed in routine clinical laboratories in the late 1970s. By the time the DCCT results were published in 1993, there were many different types of GHB assay methods, and no harmonization of test results among laboratories. Thus, two different assay methods would likely give very different numerical results for the same blood specimen.[10] Data from the College of American Pathologists proficiency testing program (CAP Survey) for GHB demonstrated that even among similar assay methods, GHB results varied considerably, and interlaboratory coefficients of variation for proficiency testing specimens were large.[11]

A number of previous studies in both the U.S. and Europe had demonstrated the feasibility of harmonizing GHB test results against a common reference, but no organized approach to actually harmonize test results had been developed.[12-15] Thus, in 1993, even before the DCCT results were announced, the American Association for Clinical Chemistry (AACC) authorized formation of a Subcommittee on Glycohemoglobin Standardization.[16,17] In this document, the term "standardization," as it applies to GHB testing, is synonymous with the term "harmonization," the process by which GHB test results among laboratories are made comparable to a common reference.)

Foreword (Continued)

The subcommittee's charge was to develop a glycohemoglobin harmonization program. Although the subcommittee's first priority was to develop a harmonization program for U.S. laboratories, the importance of international harmonization of GHB testing was recognized; the subcommittee included members from Europe who had extensive experience in GHB harmonization and proficiency testing.

The AACC subcommittee first determined that a suitable definitive/reference method for GHB determinations and purified GHB reference standards were not available, but ultimately would be important components of a universal harmonization program. The subcommittee recommended that while investigations proceeded to develop purified reference standards and definitive/reference methods, a harmonization program similar in design to the Cholesterol Reference Method Laboratory Network could be initiated relatively quickly using the DCCT reference laboratories already in place, as interim anchors for harmonization.[18] Thus, routine clinical laboratories using harmonized GHB assay methods would be able to report GHB test results that were comparable to DCCT values; this would give patients with diabetes and their healthcare providers a laboratory test result that quantified both mean glycemia and complication risks.[10]

When the DCCT ended in 1993, it was succeeded by another long-term study called the Epidemiology of Diabetes Interventions and Complications (EDIC).[19] The EDIC required serial measurements of GHB in the former DCCT study volunteers for up to ten years. Thus, the DCCT reference laboratories remained operational when the DCCT ended to provide glycohemoglobin measurements for the EDIC.

The DCCT reference system consisted of two laboratories—one at the University of Missouri and the other at the University of Minnesota. The Missouri laboratory had a modular ion-exchange high performance liquid chromatography (HPLC) system, a designated comparison method that served as the reference anchor for the DCCT.[20,21] The Minnesota laboratory had an automated ion-exchange HPLC system dedicated to GHB determinations and was the site where routine study specimens were analyzed.[5]

The AACC subcommittee thus developed a harmonization protocol around the DCCT/EDIC reference laboratories, which was approved in 1995 after a consensus conference with U.S. manufacturers. In 1996, the AACC subcommittee was disbanded and replaced by the National Glycohemoglobin Standardization Program (NGSP), which began operation in July 1996.[22,23] The primary focus of the NGSP was to assist manufacturers in establishing proper calibration and then to document comparability of their assay results to the DCCT database. An important adjunct to the NGSP program was a new CAP GHB proficiency testing program, initiated in May 1996, which used fresh blood specimens.[24] By December 1996, the first group of GHB assay methods had been formally tested and certified as having results comparable to those obtained with the DCCT reference method. In 1997, the ADA endorsed the NGSP.[25]

In 1998 the results of the UK Prospective Diabetes Study (UKPDS) were published.[26] This ten-year study in patients with Type 2 diabetes replicated the findings in the DCCT with respect to reduction in complication risk associated with a reduction in GHB. The laboratory that performed GHB determinations for the UKPDS used an NGSP-certified assay method and, in addition, participated in careful comparison procedures with the NGSP reference network to assure comparability of test results between the DCCT and UKPDS.[27] Thus, GHB values in both the DCCT and UKPDS could be used in patients with either Type 1 or Type 2 diabetes to estimate a person's risk of developing complications.[28]

Foreword (Continued)

The Role of the IFCC Reference Method in the Harmonization Process

During the same time period that the AACC was forming its strategy to harmonize GHB results in the U.S., the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) formed a Working Group on HbA_{1c} Standardization (IFCC-WG) in 1995 to achieve uniform international standardization of HbA_{1c} measurements. Two candidate reference methods and reference material were developed and validated to serve as the analytical base for global harmonization. In the first step hemoglobin is cleaved into peptides by a proteolytic enzyme, and thereafter the specific glycated and nonglycated N-terminal peptides of the B-chains are measured by HPLC and either mass spectrometry or capillary electrophoresis. The IFCC-WG created an international network of reference laboratories incorporating these two reference methods.[29-31] These reference methods could potentially provide a better analytical anchor for the NGSP than the current designated comparison method. However, studies show that the IFCC reference methods give different results for the same blood samples compared to the current NGSP anchor. Consequently the IFCC results are numerically different from the clinically validated DCCT-, EDIC- and UKPDS-based results. Studies are currently underway to 1) evaluate the stability of the IFCC reference methods over time, and 2) establish the relationships between the IFCC reference methods and the current NGSP anchor. At such time as the IFCC method is fully validated, the NGSP and other structured harmonization schemes can use it as the reference method to provide a stable anchor for harmonization.

Current evidence-based medical practice in several countries is based on the DCCT-derived numerical values.[26-28] In these countries, adoption of the IFCC reference method as harmonization anchor will require development of a statistically robust algorithm to define the numeric relationship to the DCCT-based results. Alternatively, the clinical interpretive guidelines can be modified to the IFCC numeric values with appropriate clinical trial validation.

The Role of NCCLS and C44 in the Harmonization Process

One of NCCLS's overriding organizational goals is the achievement of worldwide harmonization in its standards and guidelines wherever possible. NCCLS defines harmonization as a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity; and recognizes that harmonization is an evolutionary and educational process that begins with new projects and revisions of existing documents.

Because current international studies indicate that the IFCC reference methods for glycohemoglobin measurements are better analytical anchors for NGSP than the current designated comparison method, NCCLS and its Area Committee on Clinical Chemistry and Toxicology and the Subcommittee on Glycohemoglobin Measurements is committed to revising the C44 guideline when the IFCC methodology studies are complete and the NGSB anchor has been changed.

A Note on Terminology

NCCLS recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in NCCLS, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, NCCLS recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention.

In keeping with NCCLS's commitment to align terminology with that of ISO, the following terms are used in C44:

The term “trueness” is used when referring to the closeness of the agreement between the average value from a large series of measurements and to an accepted reference value. The term “accuracy,” in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, thus comprising both random and systematic effects.

NCCLS consensus documents are developed through an open process that ensures wide review and broad application. This unique approach leads to standards and guidelines for medical testing and healthcare services that address identified needs of both its global and national constituents. Most NCCLS consensus documents are intended for global application. Under certain circumstances, however, an NCCLS standard or guideline may be intended for primary use in a specific country or region.

NCCLS document C44-A—*Harmonization of Glycohemoglobin Measurements; Approved Guideline* is one such consensus document. While this document will serve as a useful resource for a wider audience, it is intended for use primarily in the United States.

The imprint of the flag and the unique tagline on the cover call attention to its national focus, and differentiate C44-A from our global consensus documents.

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 comprehensive 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. 1996;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 document M29—*Protection of Laboratory Workers from Occupationally Acquired Infections.*

Key Words

Diabetes mellitus, glycohemoglobin, harmonization, hemoglobin A_{1c}, proficiency testing

The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1—*A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Service & Satisfaction
Personnel	Process Control	Assessment	Facilities & Safety

C44-A addresses the following quality system essentials (QSEs):

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
								X			

Adapted from NCCLS document HS1— *A Quality System Model for Health Care*.

Harmonization of Glycohemoglobin Measurements; Approved Guideline

1 Introduction

Harmonization of glycohemoglobin (GHB) testing results is essential to maximize the clinical utility of GHB testing. This guideline describes an established program, the National Glycohemoglobin Standardization Program (NGSP), the purpose of which is to harmonize GHB test results among laboratories to a common, outcome-based reference system. This guideline has two main sections. The first describes the administrative/organizational structure and procedures employed by the NGSP, with an emphasis on the harmonization process rather than on specific NGSP protocol details (an outline of the NGSP website is included in the appendix). The second section provides information on the clinical application of GHB testing, including recommendations for the clinical application of harmonized GHB testing results.

2 Scope

This document presents information on the rationale for harmonization of glycohemoglobin testing among clinical laboratories. The process is described by which the NGSP has established, on a large scale, comparability of GHB test results among laboratories to a common reference. The reference values are, in turn, indexed to clinical outcomes data. The document also includes information about the structure of the laboratory network which is the backbone of the harmonization program, as well as procedures for monitoring the network, for testing and certifying manufacturers' assay methods and laboratories, and for monitoring the effectiveness of the program by proficiency testing of routine clinical laboratories. The information is designed to facilitate participation in the NGSP by manufacturers of GHB testing methods and materials, as well as routine clinical laboratories. This document also includes information on clinical application of GHB testing results and should be useful to both laboratorians and healthcare providers involved in the care of patients with diabetes mellitus, as well as to individuals and organizations involved in quality assurance programs for patients with diabetes mellitus. In addition, this document is a starting point for discussion regarding development of a universal harmonization program for GHB.

While C44-A may serve as a useful resource for a wider audience, it is intended for use primarily in the United States.

3 Definitions[a]

The definitions of method type used in this document conform to the National Reference System for the Clinical Laboratory (NRSCL) guidelines. (See NCCLS document NRSCL13—*The Reference System for the Clinical Laboratory: Criteria for Development and Credentialing of Methods and Materials for Harmonization of Results.*)

Accuracy - Closeness of the agreement between the result of a measurement and an accepted reference value of the measurand/analyte; **NOTE**: See *Note on Terminology* in the Foreword.

Bias - 1) The systematic, signed deviation of the test results from the accepted reference value; **NOTES:** a) Defined in ***(ISO3534-1/93-3.13)*** as "the difference between the expectation of the test results and an accepted reference value"; b) In general, the deviation/difference is based on replicate measurement using

[a] 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.

