GUIDANCE MANUAL
for
"Quality Control of Blood Glucose Test Strips"

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FOREWORD

India is ranked second in the world in diabetes prevalence, just behind China. According to the International Diabetes Federation, 61.3 million people in India had diabetes in 2011 and that figure is projected to rise to 101.2 million by 2030. India aims to combat rising diabetes healthcare costs trough the diabetes screening program; the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS), that was approved in 2010 by the Cabinet Committee of Economic Affairs for 100 districts across 15 states and Union Territories. The program plans to screen 150 million people across the country. A national project to screen school children was also rolled out in March 2011 to identify diabetes prevalence in school. In these programs Glucometers +Blood Glucose Test Strips will be the preferred tool since they can be widely used in hospitals, outpatient clinics, emergency rooms, ambulatory medical care and home self- monitoring. So predictably the Glucometers (Self Blood Glucose Monitoring) industry has already grown to over Rs 150 crore, with a growth rate of 15- 18 percent in the recent years.

Glucometers are utilized by a diverse population of patients, representing all ages and acuteness of medical conditions. Both patients and doctors need reliability in the results of glucometers. In keeping with the trend with all medical devices, the Glucometers also have limitations. Establishing the accuracy of glucometers is challenging. Glucometers can only analyze whole blood, and glucose is unstable in whole blood. Serum cannot be analyzed by glucometers. Concensus standards recommend comparing whole blood analysis on a glucometer against plasma / serum centrifuged from a capillary specimen and analyzed by a clinical laboratory comparative method. Yet capillary samples may not provide sufficient volume to test by both methods, and venous samples may be used as an alternative when differences between venous and capillary blood are considered. Thus there are multiple complexities involved in ascertaining the accuracy of glucometer values which eventually contribute to clinical agreement of the glucometer with a serum/ plasma laboratory result.

There are a number of opinions about 'Technical Accuracy' when comparing glucometers against a laboratory method. The American Diabetes Association (ADA) has recommended that glucometers agree to within $\pm$15% of the laboratory method at all concentrations, with a future performance goal of +5% agreement at glucose concentration. Since glucometer performance can change across the range of the glucose concentrations, some performance criteria differ between the hypoglycemic range and the hyperglycemic range. The International Standards Organization (ISO) and the United States Food and Drug Administration (USFDA) has set accuracy criteria to $\pm$20mg/dl for levels <100mg/dl or $\pm$20% for glucose levels > 100mg/dl for at least 95% of the results. There is thus no single standard to assess the accuracy of a glucometer, so the determination of accuracy will vary by country and recommendation utilized for the judgment.

References

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ABBREVIATIONS USED

ADA	American Diabetes Association
ADC(I)	Additional Drugs Controller of India
CDSCO	Central Drugs Standards Control Organization
CDRH	Center for Devices and Radiological Health
CLSI	Clinical Laboratory Standards Institute
CMC	Comprehensive Maintenance Contract
CV	Coefficient of Variation
DCG(I)	Drugs Controller General of India
ICMR	Indian Council of Medical Research
IPC	Indian Pharmacopoeia Commission
ISO	International Standards Organization
LL	Lower Limit
NIB	National Institute of Biologicals
NIST	National Institute of Standards and Technology
NPCDCS	National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke
QA	Quality Assurance
QC	Quality Control
SD	Standard Deviation
SOP	Standard Operating Procedure
SR&RDU	Sample Receipt & Report Dispatch Unit
UL	Upper Limit
USFDA	United States Food and Drugs Administration
WHO	World Health Organization

CONTRIBUTORS

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The encouragement provided by Dr. Surinder Singh- Director (i/c) to prepare this document is deeply acknowledged. I hope the Guidance Manual on Quality Control of Blood Glucose Test Strips will serve as a Reference Document, not only for the prospective Manufacturer's of such products but also for the Clinical Laboratories for putting a Quality System in place.

Dr G R Soni,
Scientist Grade I and Head,
Biochemical Kits Laboratory

CONTENTS

PURPOSE

The purpose of this guidance manual is to explain to the prospective manufacturers/ importers of Glucometers + Blood glucose test strips in our country; the quality parameters, testing requirements, and also the procedures adopted for testing the various quality parameters at NIB. It may also help the institutions or laboratories who are currently engaged in the Government programs for screening the population for diabetes cases, in understanding and correlating the quality of these medical devices to their performance. The quality specifications and the maximum and minimum limits for the 'Acceptance criteria' may help the end user to select a relatively better product from a milieu of similar products. The manual may also serve to sensitize the interested reader to the concepts of quality control in the area of Biochemical Kits/ Devices; an area which is new and regarded to be in an evolutionary phase.

SCOPE

This guidance manual provides general information on procedures and practices in the area of quality control of Clinical chemistry investigations and may be useful to the prospective manufacturers of related products in developing and administering a QA program. Clinical Laboratories may also follow these guidelines for standardizing and validating their test procedures. The methodologies enumerated in this manual are applicable to all the clinical chemistry investigations though the specifications/ acceptance criteria may vary with the analyte. However, referring to the specifications/ limits of quality parameters laid out for various analytes from a registered repertoire that is available in the public domain, the discussed methodologies can be fruitfully used for any/ all clinical biochemistry investigations.

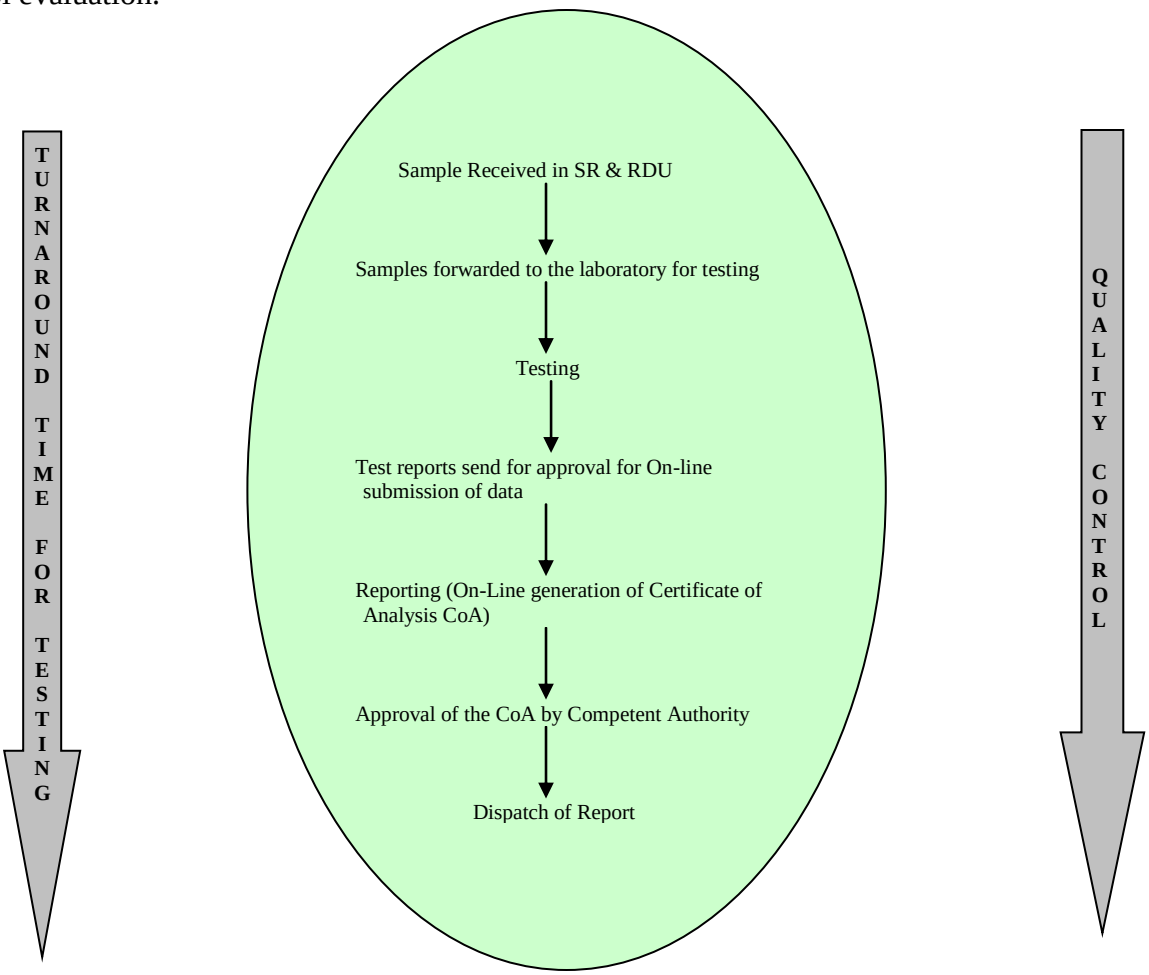
INTRODUCTION

National Institute of Biologicals is an autonomous institute under the Ministry of Health & Family Welfare set up for the quality assessment of biological products are manufactured indigenously or imported in the country. It works in coordination with the Regulatory Authorities such as the Drugs Controller General of India DCG (I) and the Indian Pharmacopoeia Commission. The Biochemical Kits Laboratory was set up in July 2009 keeping in view the need for the evaluation of the intrinsic quality of Biochemical Kits in terms of accuracy/specificity and of related devices such as Glucometers in order to establish a system of quality control in this area. The course envisages bringing about harmonization of clinical laboratory test results in the country; thus improving the diagnostic accuracy. The process will also help/ guide manufacturers in judging whether their routine test system is (*a*) sufficiently specific and performs accurately enough for its intended application; (*b*) needs recalibration or (*c*) needs general improvement of the intrinsic quality.

Clinical Laboratory Standards Institute (CLSI) guidelines and the International Standards Organization (ISO) guidelines were referred for development of the experimental design, data collection and statistical analysis for evaluation of the recommended QC parameters; precision, accuracy, linearity, and range. The particulars of testing and the 'Acceptance criteria' based upon calculation of 'Allowable Total Error' limits were presented before and vetted by an experts group that was represented by members of the CDSCO, members coordinating the program related to systemic disorders and health care in the ICMR, members who are experts in the field, members from WHO, IPC and members from the industry who are engaged in the manufacture/ import and marketing of biochemical Kits and Devices; during a meeting held at NIB on the 9th of December 2010. The ISO15197 based modified procedure for evaluating batches of Blood Glucose Test Strips was also presented during this meeting. The office of the DCG (I) was informed and a request was made for receiving samples of the said kind. The laboratory has been receiving a steady supply of such samples for evaluation since then and has evaluated about 87 batches of Blood Glucose Test Strips/ Kits up till now.

SAMPLE RECEIVING

Samples of Blood Glucose Test Strips are sent by the various offices of the DCG (I)/ ADC (I)/ Drug Inspectors. They are received by Sample Receipt and Report Dispatch Unit (SR & RDU) at NIB. The samples are then sent to the Biochemical Kits Laboratory for Quality Control evaluation.



A. PROCEDURE FOR RECEIVING THE SAMPLE IN THE LABORATORY

1. It is noted whether the cold chain has been maintained wherever it is required for a sample.
2. The samples are physically examined and the following details are documented in the 'Sample receipt register' of the laboratory.

- Date of receiving in the laboratory
- Name /type of the sample
- Lot/ Batch No. and expiry of the Blood Glucose Test Strips
- Pack size
- No. of Test Strips submitted
- No. of Glucometers submitted and whether they are in working condition

- Details of manufacturer's 'Controls' preparation
- Whether sample submission complete with respect to requirements for testing

3. Any deficiencies noted regarding 'sample submission' is intimated to the SR & RDU with the request to have the requirement fulfilled so as to enable the laboratory to initiate testing.

B. STORAGE BEFORE TESTING

1. Blood Glucose Test Strips and the Manufacturer's Control solution received from SR & RDU are stored at recommended temperature.
2. Only those samples which are under testing/ planned for testing are stored in the laboratory.

C. STORAGE AFTER TESTING

1. Leftover strips of a batch of Blood Glucose test Strip are stored under stipulated storage conditions in the 'Store Room'.
2. Leftover manufacturer's Controls if any are stored in the designated place in the laboratory.

D. CRITERIA FOR ACCEPTANCE OF SAMPLES

1. Type of Sample: Blood Glucose Test Strips designed for use with specific Glucometers as a closed system that reports the human blood glucose values in mg/dL units.
2. Condition of Packing: Blood Glucose Test Strips should be packed in properly labeled sealed containers that give the details of the manufacturer and/ or the importer and the Range of values reported by the strips for the 'Normal (Level I)' and the 'Pathological (Level II)' Control preparations.
3. Number of Samples Essential: 2400 Test Strips (1200 for the Laboratory and 1200 as retained samples with the Sample Receipt unit) for testing one Batch by the Laboratory
4. Accessories Required: 10 Glucometers designated for use with the Blood Glucose Test Strips as a closed system.
5. 3ml each of the manufacturer's Normal/ Level I and Pathological/ Level II Glucose control Solution for testing one batch of Blood Glucose Test Strips.
6. Documents Required: Documents to be submitted as per check list at Annexure-A.

QUALITY ASSURANCE OF BLOOD GLUCOSE TEST STRIPS

A. POLICY ON TESTING

1. 1200 Blood Glucose test strips shall be used by the laboratory for the testing of various parameters (details as per Annexure C).
2. 1200 Blood Glucose test strips shall be kept by the Sample Receipt Unit as retained sample.

B. QUALITY CONTROL TESTING

1. Quality Control evaluation shall be based upon testing of various parameters, their acceptance criteria and interpretation is as mentioned in Annexure- B.
2. Validation of Tests: Records of validation of individual tests shall be maintained in the laboratory.
3. Calibration of Equipment: Calibrated pipettes and Weighing Balance shall be used. Other equipments as the Biochemical Analyzer, Biosafety cabinet, Walk-in cold room shall be maintained at their optimum functional status through CMC with respective manufacturer.
4. Verification of Reports and Signature: The worksheets shall be verified by Lab. in-charge (Supervisor). Test report of each parameter shall be signed by the Analyst and the Head of the Laboratory.
5. Presentation of Results: The Certificate of Analysis shall mention the values obtained for each test parameter and depending whether they meet with the respective 'acceptance criteria', the results shall be designated as 'Complies' or 'Does not Comply'.
6. Approval of the Certificate of Analysis: Certificate of Analysis shall be signed by Analyst and the Head of Division. Approval of the same shall be done by the Director, NIB.
7. Turn around Time for testing a batch of Blood Glucose Test Strips shall be 20 working days from the date of receipt of sample in the laboratory.
8. Retention of samples and Report: 1200 strips will be retained by the Sample Receipt department as retained sample. One copy of Test Report will be retained by Sample Receipt and Dispatch Unit in archives.
9. Administrative Review: The Reports shall be submitted for Administrative Review as per SOP of QA department.
10. Disposal of Samples and retention of Reports: Samples shall be retained under specified condition by the Sample Receipt and Dispatch Unit up to one year after the date of expiry after which they will be disposed as per the procedures of the 'Waste Disposal Committee'. Reports/ documents shall be retained in Archives as per SOP of QA department.

C. PROCEDURE FOR INTERMEDIATE PRECISION EVALUATION

1. The manufacturer's instructions are read for using the Glucometer Strip together with its specific glucometer.
2. The range of the values for the normal and the pathological Control solutions provided by the manufacturer together with the Lot# and the Expiry date for each preparation is noted together with the details of the Glucometer Strip Lot# and Expiry date and the Device Serial Nos. on the Data recording format.
3. The Control Solutions are loaded on the 'Glucometer strip + glucometer' test system to see whether it reproduces a value that is within the range claimed by the manufacturer for each of the Control preparations.

4. If values obtained found to be within range, then using 10 glucometers and a Control preparation, the values of each Control preparation are recorded in replicates of 10 each day; for a period of 10 days.
5. The values obtained each day with each Control preparations are recorded in respective Data recording formats as follows.

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INTERMEDIATE PRECISION EVALUATION EXPERIMENT DATA

GLUCOMETER STRIP DETAILS: …name of strip..., Lot#....., Expiry:……..

PERIOD OF TESTING: ……

CONTROL SOLUTION USED: …name of Normal Control Solution…., Lot#....., Expiry, …….

GLUCOSE CONCENTRATION: INTERVAL (….to….mg/dL)

Sno.	Name and Device Serial No.	READINGS									
		DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DAY7	DAY8	DAY9	DAY10
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Test Done by: Verified by

Approved by:……. Head, BK Laboratory

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INTERMEDIATE PRECISION EVALUATION EXPERIMENT DATA

GLUCOMETER STRIP DETAILS: …name of strip..., Lot#....., Expiry:……..

PERIOD OF TESTING: ……

CONTROL SOLUTION USED: …name of Pathological Control Solution…., Lot#....., Expiry, …….

GLUCOSE CONCENTRATION: INTERVAL (….to….mg/dL)

Sno.	Name and Device Serial No.	READINGS									
		DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DAY7	DAY8	DAY9	DAY10
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Test Done by: Verified by:

Approved by:……
Head, BK Laboratory

6. At the end of 10 days, the mean value, standard deviation and coefficient of variation for each meter is calculated from the ten measurements.
7. The grand mean, the pooled standard deviation and the pooled CV is calculated.
8. Interpretation of Result
    - The % Coefficient of Variation (%CV) is calculated using the following equation-

$$\%CV = \frac{\text{pooled SD}}{\text{Grand mean of value for each control material}} \times 100$$

    - The %CV is a measure of **Imprecision** of 'Glucometer strip + Glucometer' test system at that particular concentration of the analyte Glucose.
    - To qualify for intended use, the value of %CV obtained is required to fall between $\leq$ 3.0-7.1 which is the limit prescribed in WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002.

REFERENCES

1. International Standards ISO; 15197: In vitro diagnostic test systems- Requirements for blood- glucose monitoring systems for self- testing in managing diabetes mellitus.
2. Manufacturer's instructions for use of Glucometer+ Strip together with the Control Preparations as applicable.

D PROCEDURE FOR REPEATABILITY PRECISION EVALUATION

1. Sample used is human venous blood samples collected in tubes containing anticoagulant and preservative (fluoride) and hematocrit adjusted to 36% (700µl plasma + 400µl of packed cells).
2. At least 1ml volume of three such samples, each having glucose concentrations falling between 51- 110mg/dL, 111- 150mg/dL and 151- 250mg/dL respectively is used.
3. The manufacturer's instructions are read for using the Glucometer Strip together with its specific glucometer.
4. At a time only one sample is used. The sample loaded on a 'Glucometer strip + glucometer' test system and the reading noted down. This is repeated with 9 other meters.
5. The step at 4 is repeated nine more times to collect the set of 100 observations per sample
6. The values for each sample are recorded in respective Data recording formats as follows.

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REPEATABILITY EVALUATION EXPERIMENT DATA

GLUCOMETER STRIP DETAILS: …name of strip..., Lot#....., Expiry:……..
DATE OF TESTING :……
SAMPLE DETAILS: Human venous blood sample
GLUCOSE CONCENTRATION: INTERVAL II (51- 110mg/dL)

S.no.	Name and Device Serial No.	READINGS 1	2	3	4	5	6	7	8	9	10
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Test Done by: Verified by:……(Analyst)
Signature:

Approved by:……(Head, BK Laboratory)

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REPEATABILITY EVALUATION EXPERIMENT DATA

GLUCOMETER STRIP DETAILS: …name of strip..., Lot#....., Expiry:……..
DATE OF TESTING :……
SAMPLE DETAILS: Human venous blood sample
GLUCOSE CONCENTRATION: INTERVAL II (111- 150mg/dL)

S.no.	Name and Device Serial No.	READINGS 1	2	3	4	5	6	7	8	9	10
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Test Done by: Verified by:……(Analyst)
Signature:

Approved by:……(Head, BK aboratory)

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REPEATABILITY EVALUATION EXPERIMENT DATA

GLUCOMETER STRIP DETAILS: …name of strip..., Lot#....., Expiry:……..
DATE OF TESTING :……
SAMPLE DETAILS: Human venous blood sample
GLUCOSE CONCENTRATION: INTERVAL II (151- 250mg/dL)

S.no.	Name and Device Serial No.	READINGS 1	2	3	4	5	6	7	8	9	10
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											

Test Done by: Verified by:……(Analyst)
Signature:

Approved by:……(Head, BKLab)

7. For the set of 100 values obtained for each sample, the mean value, standard deviation and coefficient of variation for each meter is calculated from the ten measurements.
8. The grand mean, the pooled standard deviation and the pooled %CV calculated.
9. Interpretation of Result
    - The % Coefficient of Variation (%CV) calculated using the following equation-

$$\%CV = \frac{\text{pooled SD}}{\text{Grand mean of value for each sample}} \times 100$$

    - The %CV is a measure of **Repeatability** of 'Glucometer strip + Glucometer' test system at that particular concentration of the analyte Glucose.
10. To qualify for intended use, the value of %CV obtained is required to fall between $\leq$ 3.0-7.1 which is the limit prescribed in WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002.

REFERENCES

1. International Standards ISO; 15197: In vitro diagnostic test systems- Requirements for blood- glucose monitoring systems for self- testing in managing diabetes mellitus.
2. Manufacturer's instructions for use of Glucometer+ Strip together with the Control Preparations as applicable.

E PROCEDURE FOR ACCURACY EVALUATION

Principle

Individual glucose measurements in human blood samples by the blood glucose monitoring system (Glucose test strips + Glucometer) are collected within two hours of analysis of the same set of samples using the laboratory Reference method. Following the fulfillment of the basic requirement i.e.; the laboratory Reference method is in proper quality control throughout the evaluation period, data generated using both the blood glucose monitoring system and the laboratory Reference methods for a set of samples covering the required range of analyte- glucose concentrations is statistically analyzed to compute the bias/ expected difference between two methods at the 'clinical decision level' of 100mg/dL for analyte glucose. The data is also analyzed to compute the system accuracy findings as per the method and criteria specified in the ISO guideline 15197.

1. Leftover human venous blood samples containing anticoagulant and preservative (fluoride) are used and the hematocrit is adjusted to suit the requirements of the Glucometer.
2. 150 samples collected to suffice the numbers in the recommended 'Range' of glucose concentration as per table below

3. **Table : Glucose concentrations of samples for system accuracy evaluation**

Percentage of samples (%)	Glucose concentration (mg/dL)
5	<50
15	50 to 80
20	80 to 120
30	120 to 200
15	201 to 300
10	301 to 400
5	> 400

4. 20 human venous samples are analyzed on the Laboratory Reference method (Analyzer based Method).
5. The manufacturer's instructions are read and followed for using the glucose test strips with the specific Glucometer for estimation of glucose in the samples.
6. Within two hours of estimation using the Reference method, the same samples are analyzed on the glucose test strips + Glucometer test system, in duplicate, after reconstitution as per step 1.
7. The values are recorded in the data recording sheets as below:

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SYSTEM ACCURACY EVALUATION EXPERIMENT DATA															
PERIOD/ DATE OF TESTING:															
GLUCOMETER STRIP DETAILS															
Sno.	Sample Code	Glmtr/Sno.		Glmtr/Sno.		Glmtr/Sno.		Glmtr/Sno.		Glmtr/Sno.		Glmtr/Sno.		Glmtr/Sno.	
		Result 1	Result 2	Result 1	Result 2	Result 1	Result 2	Result 1	Result 2	Result 1	Result 2	Result 1	Result 2	Result 1	Result 2
1															
2															
3															

8. In this way approximately 150 samples are analyzed over 7-8 working days.

F DATA ANALYSIS FOR SYSTEM ACCURACY ESTIMATION

1. The samples are categorized into two groups viz., $\leq$75mg/dL and $\geq$75mg/dL with respect to their values obtained from the laboratory reference method.
2. The values obtained using the laboratory Reference method and the Blood glucose monitoring system (Glucometer+Strips) for these two categories of samples are tabulated and analyzed separately as shown in table below.

SYSTEM ACCURACY EVALUATION EXPERIMENT DATA TABULATION FOR SAMPLES WITH>80mg% GLUCOSE															
Sno.	Code	Glmtr Result1	Glmtr Result2	analyzr Result1	analyzr Result2	Diff Y-X (mg%)	Diff Y-X (mg%)	5% analyzr Val	5% analyzr Val	10% analyzr Val	10% analyzr Val	15% analyzr Val	15% analyzr Val	20% analyzr Val	20% analyzr Val
1	G129	134	133	139.7	141.6	-5.7	-8.6	6.985	7.08	13.97	14.16	20.96	21.24	27.94	28.32
2	G129	129	134	132.4	132.9	-3.4	1.1	6.62	6.645	13.24	13.29	19.86	19.94	26.48	26.58
3	G129	92	91	86.2	85.2	5.8	5.8	4.31	4.26	8.62	8.52	12.93	12.78	17.24	17.04

SYSTEM ACCURACY EVALUATION EXPERIMENT DATA TABULATION FOR SAMPLES WITH < 80mg% GLUCOSE CONCENTRATION																	
Sno.	Code	Glmtr Result1	Glmtr Result2	analyzr Result1	analyzr Result2	minus 5mg analyzr val	minus 5mg analyzr val	plus 5mg analyzr val	plus 5mg analyzr Val	minus 10mg analyzr val	minus 10mg analyzr val	plus 10mg Anlzr Val	plus 10mg Anlzr Val	minus 15mg analyzr val	minus 15mg analyzr val	plus 15mg analyzr val	plus 15mg analyzr val
1	G139	87	88	78.1	77.4	73.1	72.4	83.1	82.4	68.1	67.4	88.1	87.4	63.1	62.4	93.1	92.4
2	G144	69	69	78.2	76.3	73.2	71.3	83.2	81.3	68.2	66.3	88.2	86.3	63.2	61.3	93.2	91.3
3	G146	46	47	48.7	48.2	43.7	43.2	53.7	53.2	38.7	38.2	58.7	58.2	33.7	33.2	63.7	63.2
4	G146	14	17	10.6	10.7	5.6	5.7	15.6	15.7	0.6	0.7	20.6	20.7	-4.4	-4.3	25.6	25.7

3. In the $\geq$ 75mg/dL category, the number of results which show a difference of $\leq$ 5%, $\leq$10%, $\leq$15% and $\leq$20% from the Reference method values are counted separately.
4. In the $\leq$ 75mg/dL category, the number of results which show a difference of $\leq$ 5 mg/dL $\leq$10 mg/dL , and $\leq$15 mg/dL from the Reference method values are counted separately.
5. The percentage of results that fall in the group 'within 20% of the reference method value' for samples in the >80mg/dL category is calculated.
6. The percentage of results that fall in the group 'within 15mg/dL of the reference method value' for samples in the <80mg/dL category calculated.

G DATA ANALYSIS FOR BIAS ESTIMATION

1. The Reference Method is designated - (X) and the Test Method (Blood Glucose Monitoring System) - (Y), and the data is tabulated as shown in the table below and the mean is compute at the bottom of each column.

		Test Method(Y)		Ref. Method(X)				Test(Y)	Ref.(X)
Sno.	Sample ID	Rep1	Rep2	Rep1	Rep2	Mean(Y)	Mean(X)	Rep1-Rep2 [DYi]	Rep1-Rep2 [DXi]
1	G1	114.2	114	117.6	125.2	114.1	121.4	0.2	-7.6
2	G2	107.1	108.5	111.2	111.8	107.8	111.5	-1.4	-0.6
3	G3	145.8	146.8	153.5	154.7	146.3	154.1	-1	-1.2
						Mean	**Mean**	**Mean(DY)**	**Mean(DX)**

2. For detecting outliers the mean DX and DY values are multiplied by 4 (Range). Any data point whose individual DX_i or DY_i value is more than this value is eliminated.
3. Further analysis is continued by extending the computation of data as per the following table:

MeanY-MeanX	Aver of MeanX&Y	DXi'	DYi'	Ei1	Ei2	Ei1'	Ei2'	Ei1'plus Ei2'
-7.3	117.75	-0.0626	0.001753	-3.4	-11.2	-0.02891	-0.08946	-0.11837
-3.7	109.65	-0.00538	-0.01299	-4.1	-3.3	-0.03687	-0.02952	-0.06639
-4.75	126.175	0.010113	0	-5.4	-4.1	-0.0418	-0.03206	-0.07385
-7.3	117.75	-0.0626	0.001753	-3.4	-11.2	-0.02891	-0.08946	-0.11837
		Mean	**Mean**					**Sum/2N**

Where,
DXi' and DYi' are relative absolute difference of methods obtained by dividing the Difference by the Mean;
Ei1 & Ei2 are absolute difference between methods obtained from the difference between
rep1 of X&Y, rep2 of X&Y and
Ei1' & Ei2' are relative absolute difference between methods obtained by dividing Ei1 by the value of rep1 of X and Ei2 by the value of rep2 of X .

4. More outliers are detected by multiplying the mean DX' and DY' values obtained by 4 (Relative Range). Any data point whose individual DXi' or DYi' value is more than this value is eliminated.
5. Further analysis is continued by extending the computation of data as per the following table:

Ei1plus Ei2	Xij-meanX	Yij-meanY	square of Xij-meanX	square of Yij-meanY	(Xij-meanX) (Yij-meanY)	Yij	Xij	b into Xij
-14.6	-22.09	-22.29	487.9681	496.8441	492.3861	114.2	117.6	118.3056
-7.4	-28.49	-29.39	811.6801	863.7721	837.3211	107.1	111.2	111.8672
-9.5	-10.49	-12.69	110.0401	161.0361	133.1181	123.8	129.2	129.9752
Sum/2N			**Sum (1)**	**Sum(2)**	**Sum (3)**			

6. The sums of Ei1' plus Ei2' and Ei1plus Ei2 are divided by 2N respectively and multiplied by 4 to get the test limits (TL). Any data point whose individual Ei1' plus Ei2' or Ei1plus Ei2 exceed these limits is eliminate.
7. Only 2.5% of the data is principally eliminated as outliers. If more data qualifies for elimination then the complete data set is rejected and a new set of data is generated.
8. Adequate range of X is calculated by the formula-

$$\text{correlation coefficient } r, \quad = \frac{(3)}{\sqrt{(1)} \times \sqrt{(2)}}$$

For acceptability r should be > 0.975

9. The data is further analyzed to calculate the 'Predicted value', 'Residual' and the 'Squared Residual' as follows:

Predicted value	Residual	Squared Residual
114.1876	0.0124	0.000154
107.7492	-0.6492	0.421461
125.8572	-2.0572	4.232072
		Sum (4)

10. Slope b is calculated = (3)
(1)

b should be ~ 1 for linear relationship
Intercept a is calculated as-
a = mean y – b * mean x

Where, y = overall mean of method Y and x = overall mean of method X
Predicted value $\hat{Y}$ is obtained by, $a + b * x_{ij}$

Residual is obtained by subtracting the predicted value from y_{ij}

11. The Standard error of estimate calculated as below-

$$\text{Standard error of estimate } (S_{y.x}) = \sqrt{\frac{(4)}{2N-2}}$$

12. The estimate of predicted bias, B_c at a given Medical Decision level, X_c (100 for analyte Glucose) is calculated as-

$$B_c = a + b.\ X_c$$

13. The 95% confidence interval for true bias is calculated as-

$$B_c \text{ (at } X_c) = Bc \pm 2S_{y.x} \sqrt{\frac{1}{2N}} + \frac{(Xc\text{-mean } x)^2}{(1)}$$

H INTERPRETATION OF RESULT

For System Accuracy

System Accuracy requirement: 95% of the individual Glucometer results shall fall within ± 15mg/dL of the results of the 'Reference Method' at glucose concentrations <75mg/dL and within ±20% at glucose concentrations ≥75mg/dL (ISO guideline 15197)

For Bias

Maximum allowable deviation should be less than 15% (Who: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002)

REFERENCES

1. International Standards ISO; 15197: In vitro diagnostic test systems- Requirements for blood- glucose monitoring systems for self- testing in managing diabetes mellitus.
2. Clinical Laboratory Standards Institute; EP9-A2, Vol. 22, No. 19: Method comparison and Bias estimation using patient samples; Approved Guidelines – Second Edition.
3. Manufacturer's instructions for using the Glucometer Strips and the Laboratory Reference Method.

I PROCEDURE FOR REPORTING

1. The results of Precision parameters for the Glucose Test Strips sample is reported in the following format:

NATIONAL INSTITUTE OF BIOLOGICALS **(BIOCHEMICAL KITS LABORATORY)** REPORT FOR PRECISION PERFORMANCE EVALUATION	
Title: Evaluation of Precision of Glucometer Strips	
Proforma No.: PRO/GLMTRSTRP/PREC	**Page** 1 of 1
Revision No.: 0	**Department:** Biochemical Kits Laboratory

		Reference
Name of the Product	----------	NA
Lot No.	Lot#----------	NA
Expiry	----------	NA
Period of Testing: Repeatability Intermediate Precision	 From ---------- to---------- From---------- to ----------	NA
Details of Controls used	Repeatability: Human venous blood samples Intermediate Precision: Manufacturer's Control Solution, Lot#---------, Expiry, ----------	NA
Experimental design (Intermediate Precision)	• Normal Control and Pathological Control preparations (supplied by the manufacturer/ in-house) tested in replicates of 10 using 10 Glucometer Devices+ strips over 10 days. • Statistical analysis of data to compute 'Precision Standard Deviation' and % Coefficient of Variation (CV).	ISO15197
Experimental design (Repeatability)	• Human venous samples with Glucose concentrations falling in the concentration intervals- 51- 100mg/dL, 111- 150mg/dL, 151- 250mg/dL tested in replicates of 10 using each of the 10 Glucometer Devices+ strips • Statistical analysis of data to compute 'Precision Standard Deviation' and % Coefficient of Variation (CV).	ISO15197
Criteria for acceptance	Value of %CV obtained between ≤ 3.0-7.1	WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002
% CV obtained for **Intermediate Precision** at	Low concentration - -------- Pathological concentration - ---------	'Annexure' Pg (---to---)
% CV obtained for **Repeatability** at Glucose conc.	51- 100mg/dL - -------- 111- 150mg/dL - -------- 151- 250mg/dL - -------	'Annexure' Pg(--- to---)

Test done by:……..
(Name & Signature)

Verified by…….
(Signature)

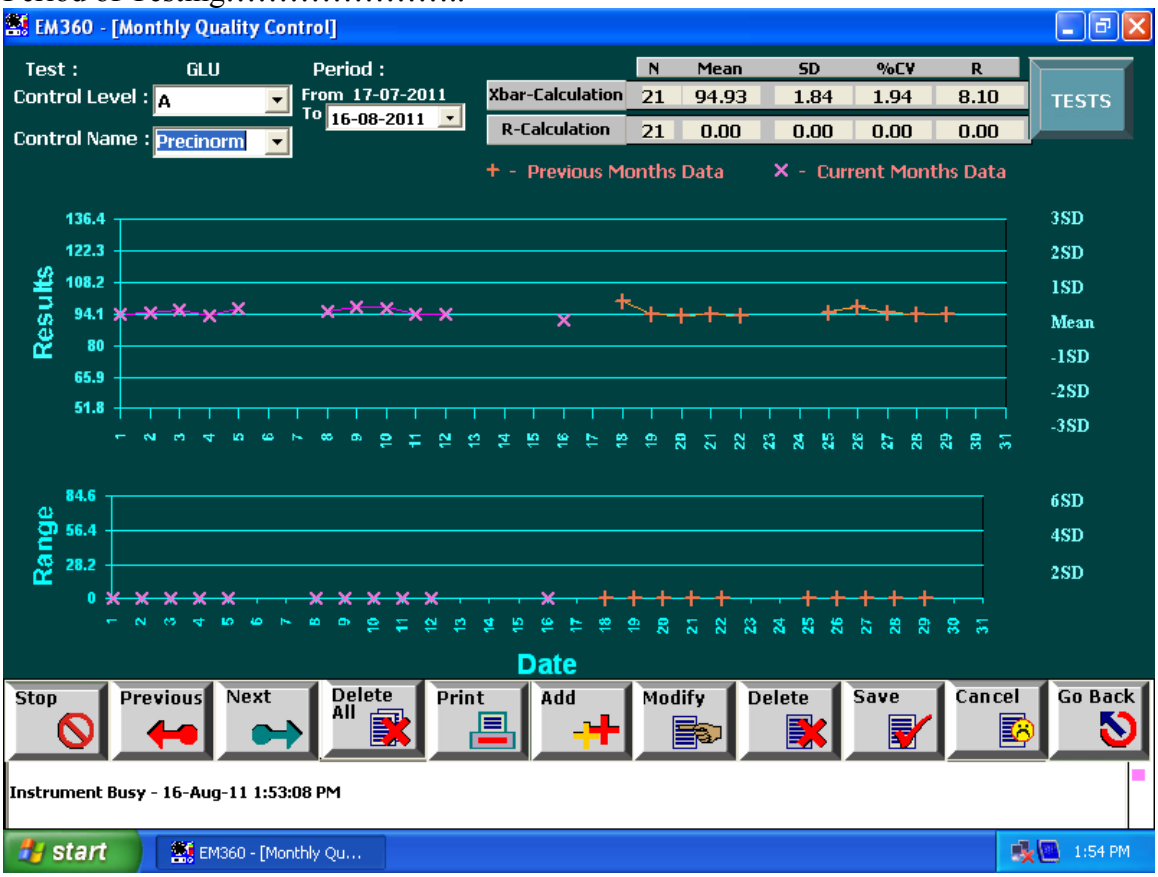
Approved by……..
(Signature)

2. The daily Quality Control Chart during the period of testing for the laboratory 'Reference Method' at both the Normal and the Pathological Control Levels is documented in the following format-

A. Monthly QC Chart for Reference Method at Normal Control Level
Glucose Reagent name….. Lot#/ Expiry……

Name of the Control Preparation……, Lot#/ Expiry…….

Period of Testing……..



Test done by:…….. Verified by…….
(Name & Signature) (Signature)

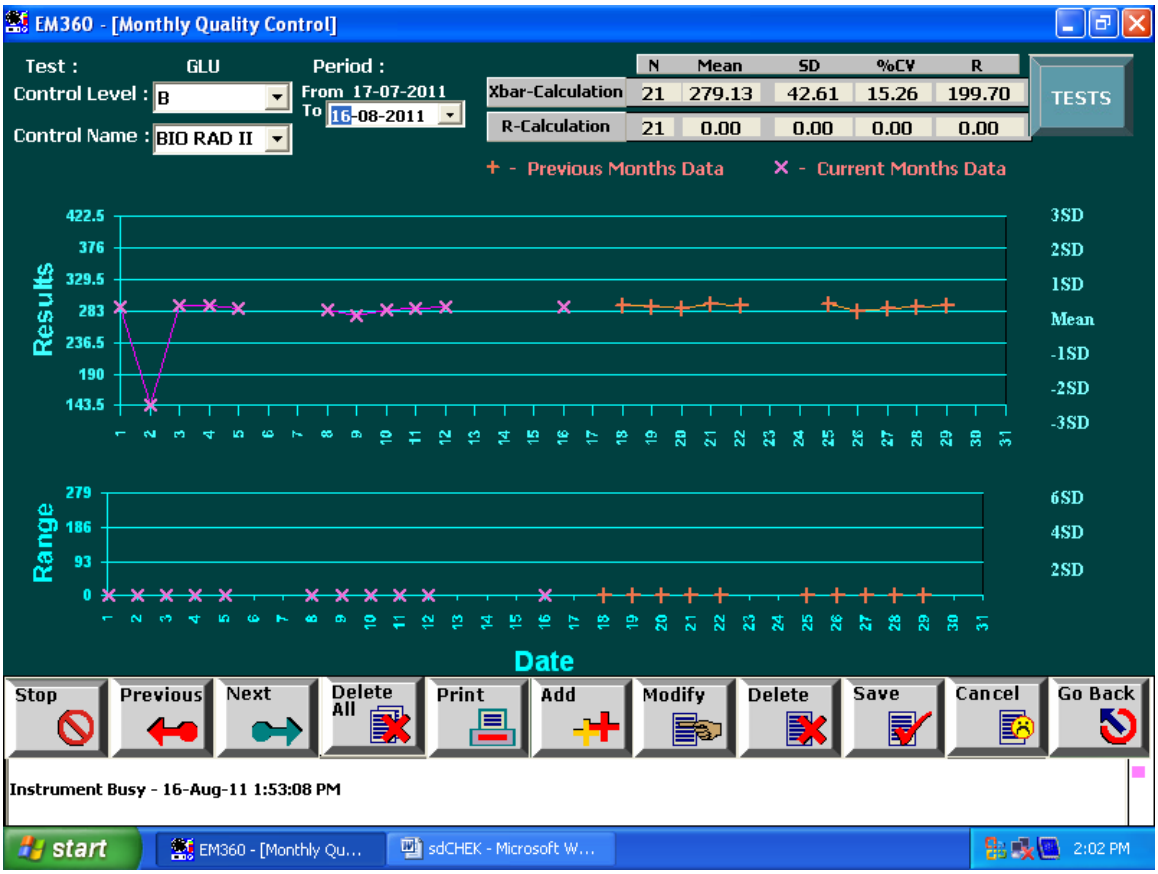
Approved by……..
(Signature)

B. Monthly QC Chart for Reference Method at Pathological Control Level

Glucose Reagent name….. Lot#/ Expiry……

Name of the Control Preparation……, Lot#/ Expiry…….

Period of Testing……..

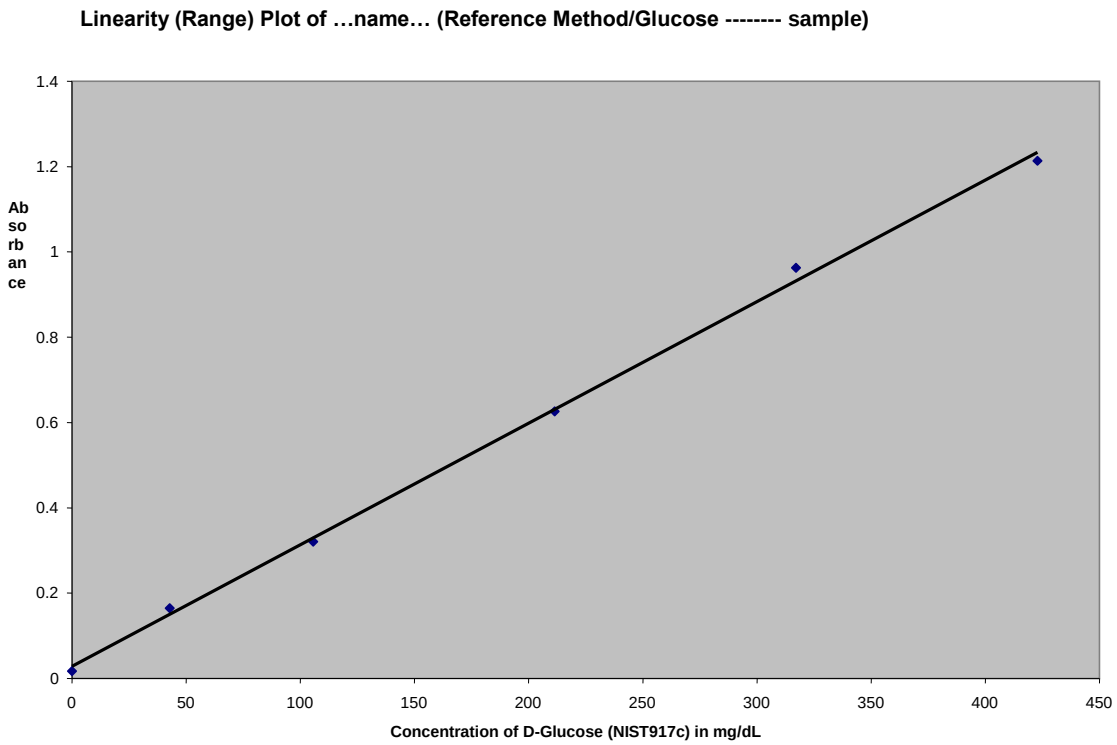


Test done by:……..
(Name & Signature)

Verified by…….
(Signature)

Approved by……..
(Signature)

3. The Linearity and Range for the laboratory reference method obtained using the International Reference Preparation' NIST 917c is documented in the following format:



Test done by:……..
(Name & Signature)

Verified by……
(Signature)

Approved by……..
(Signature)

4. Reference Method 'Process In- control' during the 'Period of Testing' at normal and pathological glucose concentration levels is documented by the 'Data Analysis Sheets' for precision estimates of the reference method at these 'Control Levels'.

5. The Accuracy of the laboratory Reference Method is documented by the Recovery assay data generated using the International Reference Preparation' NIST 917c in the following format:

CALIBRATION RESULT AND DATA ANALYSIS OF ….name……(Reference Method)

Date …….

Spiking done using 25µl of Stock I Glucose solution in 475µl of human sample.

(Stock I Glucose: 27.7mg NIST - D-Glucose [917c] per 1.25ml saline,equivalent to 2216mg/dL)

S No	Sample ID	Value	S No	Sample ID	Value
1	NIB03(6/12)	57.9	21	spkdNIB03 (6/12)	170.1
2	NIB03(6/12)	56.7	22	spkdNIB03 (6/12)	168.1
3	NIB03(6/12)	57.3	23	spkdNIB03 (6/12)	168.8
4	NIB03(6/12)	56.4	24	spkdNIB03 (6/12)	166.6
5	NIB03(6/12)	58.6	25	spkdNIB03 (6/12)	171.7
6	NIB03(6/12)	59	26	spkdNIB03 (6/12)	170.3
7	NIB03(6/12)	59.1	27	spkdNIB03 (6/12)	170.8
8	NIB03(6/12)	59.5	28	spkdNIB03 (6/12)	171.7
9	NIB03(6/12)	60.3	29	spkdNIB03 (6/12)	172.1
10	NIB03(6/12)	58.4	30	spkdNIB03 (6/12)	170.1
11	NIB03(6/12)	60	31	spkdNIB03 (6/12)	171.7

(for 20 observations)

Average	58.63	169.845
Std Dev	1.180589	1.550713
% CV	2.013625	0.913017
Difference	111.215	
%Recovery(110.8)	100.3745	

Test done by:…….. Verified by…….

(Name & Signature) (Signature)

Approved by……..

(Signature)

6. The results of Bias estimation experiment for the Glucose Test Strip sample is reported in the following format-

NATIONAL INSTITUTE OF BIOLOGICALS **(BIOCHEMICAL KITS LABORATORY)** REPORT FOR ESTIMATION OF BIAS	
Title: Bias estimation of Glucometer Strips	
Proforma No.: PRO/ GLMTRSTRP /BIAS	**Page** 1 of 1
Revision No.: 0	**Department:** Biochemical Kits Laboratory

		Reference
Name of the Product	----------	NA
Lot No.	Lot#----------	NA
Expiry	----------	NA
Period of Testing	---------- TO ----------	NA
Reference Method	Erba System Pack Glucose, Lot No.:----------, Expry: ----------	NA
Details of Equipment used	Erba XL300, Sr. No. 30153	NA
Reference method performance characteristics	• Daily QC plot for the normal and pathological control preparations are within limits of ± 1SD • **Precision** %CV at normal concentration= --------- %CV at pathological concentration=---------- • **Accuracy** % Recovery of NIST917c= ---------- • **Linearity & Range**= Linear (between ---------to---------mg/dL)	'Annexure' Pgs (--- to---)
Details of clinical samples used	Human venous Blood Samples (IDs as shown in column 'Code' of Data sheets)	NA
Experimental design	• At least 150 patient samples covering the entire physiologic range, tested in duplicate using 2 Glucometer Devices+ strips and the 'Reference method' through at least 5 working days. • The difference between individual results from the Glucometers and the mean of the reference values is calculated and the magnitude of the difference analysed as per system accuracy requirement. • Statistical analysis of data to compute 'True Bias' at the Clinical decision level and '% Inaccuracy' at 95% confidence interval	ISO15197 ISO15197 CLSI EP9-A2
Criteria for acceptance	• System Accuracy requirement: 95% of the individual Glucometer results shall fall within ± 15mg/dL of the results of the 'Reference Method' at glucose concentrations <75mg/dL and within ±20% at glucose concentrations ≥75mg/dL • Maximum allowable deviation should be less than 15%	ISO15197 Who: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002
System Accuracy Results obtained	• --------% of individual glucometer results are within ±15mg/dL of the results of the 'Reference Method' at glucose concentrations <75mg/dL • ---------% of individual glucometer results are within ±20% of the results of the 'Reference Method' at glucose concentrations ≥75mg/dL	Annexure Pgs(--- to---)
% Inaccuracy obtained	------% (Lower limit at 95% confidence interval) ------% (Upper limit at 95% confidence interval)	'Annexure' Pgs (---to---)

Test done by:…….. Verified by…….

(Name & Signature) (Signature)

Approved by……..

(Signature)

7. The final report for onward transmission is submitted in the following format-

File No.: N.9----/2011-SRRD/BCL
NATIONAL INSTITUTE OF BIOLOGICALS, NOIDA
BIOCHEMICAL KITS LABORATORY

CERTIFICATE OF ANALYSIS

Dated the ----------

Analytical Report No. : NIB/BK/2011/REP/ GLMTR-STRP/---
Name of Product and dosage Form : ---------- Test Strips , (2X25 Strips per pack)
Lot No. : Lot#----------
Expiry Date : Expiry:----------
Name of the Manufacturer : M/s----------
Importer : M/s ----------.

S.No	Test	Specifications/ limits	Results
1	PRECISION EVALUATION	Value of %CV obtained between ≤ 3.0-7.1 (WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002)	Intermediate precision – %CV= ------- (with Low Control) %CV= ------- (with Pathological/ High Control) Repeatability – %CV= ---- (at 51-100mg/dL glucose) %CV= ---- (at 111-150mg/dL glucose) %CV= ---- (at 151-250mg/dL glucose)
2	SYSTEM ACCURACY AND BIAS EVALUATION	• System Accuracy requirement: 95% of the individual Glucometer results shall fall within ±15mg/dL of the results of the 'Reference method' at glucose concentrations <75mg/dL and within ±20% at glucose concentrations ≥75mg/dL (ISO15197) • Maximum allowable deviation should be ≤ 15% (WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002)	• -----% of individual glucometer results are within ±15mg/dL of the results of the 'Reference Method' at glucose concentrations <75mg/dL • -----% of individual glucometer results are within ±20% of the results of the 'Reference Method' at glucose concentrations ≥75mg/dL % Inaccuracy obtained – -----% (LL at 95% confidence interval) -----% (UL at 95% confidence interval)

CONCLUSION: Based upon the findings of the test parameters, the above mentioned product complies/ ~~does not comply~~ to the requirements as mentioned in the guidelines; ISO15197 and WHO: Laboratory Diagnosis and Monitoring of Diabetes Mellitus, 2002 and its performance with respect to Precision and System Accuracy and Bias is acceptable/ not acceptable.

Signature of the Analyst
Scientist- III
Date: ----------

Signature……
Head, Biochemical Kits Lab
Date: ----------

ANNEXURE A

CHECK LIST OF DOCUMENTS

Documents required to be submitted along with batch of sample for Quality Control evaluation-

1. Forwarding letter from the Authorized official(s) of CDSCO/ Zonal, Sub zonal and Port offices etc.

2. Quality Control Protocols specific for the product.

3. Batch specific Certificate of Analysis and Quality Control Test Results.

4. Batch Release Certificate from the country of origin of product.

5. Copy of Import License/ test license/ manufacturing license issued by the DCG (I) / Drug Licensing Authority.

ANNEXURE B

QUALITY CONTROL TESTS, ACCEPTANCE CRITERIA AND RESULT

S No.	Test(s) conducted	Acceptance criteria	Results
1.	**Intermediate Precision** Normal Control and Pathological Control preparations (supplied by the manufacturer) tested in replicates of 10 using 10 Glucometer Devices and the Blood Glucose Strip sample over 10 days. Statistical analysis of data to compute 'Precision Standard Deviation' and % Coefficient of Variation (CV).	Value of %CV obtained should be $\leq$ 3.0-7.1	Complies
2.	**Repeatability** Human venous samples with Glucose concentrations falling in the concentration intervals- 51- 100mg/dL, 111- 150mg/dL, 151- 250mg/dL tested in replicates of 10 using each of the 10 Glucometer Devices and the Blood Glucose Strip sample. Statistical analysis of data to compute 'Precision Standard Deviation' and % Coefficient of Variation (CV).	Value of %CV obtained should be $\leq$ 3.0-7.1	Complies
3.	**System Accuracy** At least 150 patient samples covering the entire physiologic range, tested in duplicate using 2 Glucometer Devices + the blood glucose test strip sample and the 'Reference method' through at least 5 working days. The difference between individual results from the Glucometers and the mean of the reference values is calculated and the magnitude of the difference analyzed as per system accuracy requirement. Statistical analysis of data to compute 'True Bias' at the Clinical decision level and '% Inaccuracy' at 95% confidence interval.	System Accuracy requirement: 95% of the individual Glucometer results shall fall within $\pm$ 15mg/dL of the results of the 'Reference Method' at glucose concentrations <75mg/dL and within $\pm$20% at glucose concentrations $\geq$75mg/dL. --- % Inaccuracy or Maximum allowable deviation (Bias) should be less than 15%	Complies

ANNEXURE C

Requirement of blood glucose test strips for performing the Quality Control Tests

S No.	QC Test	No. of Test Strips Required	
		Test	Retained
1	Standardization/ Method Familiarization	100 Test Strips	Equal number retained by the SR&RD at NIB
2	Intermediate Precision at Normal and Pathological Control Levels	200 Test Strips	
3	Repeatability at Glucose concentration levels- 51- 100mg/dL, 111- 150mg/dL, 151- 250mg/dL	300 Test Strips	
4	System Accuracy test with ~ 150 human samples	300 Test Strips	
5	Overcoming problem of erroneous results shown by most 'Glucometer + Blood Glucose Test' test system	200 Test Strips	
6	Unprecedented situations that might demand some repetitions	100 Test Strips	
GRAND TOTAL		1200 Test Strips	1200 Test Strips