Control Testing of Batches of 'Blood Glucose Test Strips'- made for use with Glucometers as closed system; at the National Institute of Biologicals, NOIDA, INDIA: An overview of the procedure, profile of samples tested and the findings

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Abstract : *A wide variety of Self-Monitoring of Blood Glucose (SMBG) test systems enter the Indian market from various parts of the world. Blood Glucose Test Strip form the key component of an SMBG test system. The batches of Blood Glucose Test Strips that are repeatedly and periodically imported in India for use with these devices often come without any certified account of their performance aspects as 'precision' and 'accuracy'; from source. Even though they look like insignificant bits of plastic, their performance plays a very important role in monitoring the glucose control of patients with Diabetes. Hence, there is a need for monitoring and regulating the quality of these products. The Biochemical Kit Laboratory (BKL) of National Institute of Biologicals (NIB) that functions under the Ministry of Health & Family Welfare (MOHFW)-Government of India; is the only central drug testing laboratory where control testing of batches of Blood glucose test strips is being carried out in India since 2010. About 567 batches of Blood glucose test strips have been tested and reported with respect to the parameters; 'Precision' and 'Accuracy' using protocols and test specifications based upon ISO15197: 2003 and World Health Organization (WHO) reference document.*
Keywords: *Accuracy, Glucometer quality, Precision, SMBG performance*

I. Introduction

Diabetes, even though a Non- Communicable Disease; is gaining epidemic proportions in India. India ranks among the top three nations of the world with highest numbers of diabetic individuals. Strategically, for serving the objectives; 'Risk reduction for prevention of Non- Communicable Diseases' and 'Early diagnosis and appropriate management of CVD and Stroke', the Government of India has been in the process of implementing the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) for interventions up to district level under the 'National Health Mission' since 2008. Consequently, there has been an increased awareness about Diabetes and the associated use of Glucometers and the Glucometer market in India has boomed since then. The Central Drugs Standard Control Organization (CDSCO) that functions under the Ministry of Health and Family Welfare is the regulatory authority responsible for regulating the quality of Biologicals that are imported into India. It forwards the biological product batches to the National Institute of Biologicals for control testing. Batches of Blood glucose test strips thus received are being evaluated at the Biochemical Kit Laboratory.

The laboratory had referred the applicable International Guideline, ISO 15197: 2003, In vitro diagnostic test systems- Requirements for blood- glucose monitoring systems for self- testing in managing diabetes mellitus [1], in the year of its inception, for test protocols for the analytical performance parameters; 'Intermediate Precision', 'Repeatability Precision', 'System Accuracy' and 'Bias'. In keeping with the trend as seen with all the rapid diagnostic medical devices, evaluating the performance of the Glucometers+ Blood glucose test strips by a regulatory testing laboratory poses several challenges that have not been addressed in the said guideline. Glucometers can only analyze whole blood, and glucose is unstable in whole blood. Serum cannot be analyzed by glucometers. Consensus standard recommend comparing the results of capillary blood analysis on a glucometer against plasma / serum prepared from the same capillary specimen and analyzed by a laboratory analyzer based 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. Hence, on the 9th of December 2010, a modified and validated ISO 15197: 2003 based protocol for 'Intermediate Precision', 'Repeatability Precision' and 'System Accuracy' evaluation, was presented before a

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national expert committee that had representatives from the CDSCO, Indian Pharmacopoeia Commission (IPC), WHO, academia and industry; and consensus was obtained for using the same for the control testing of this product. This national expert committee also approved the specifications and limits of acceptance for the results of these test parameters that were set according to the ISO15197:2003 criteria and the WHO Reference document [2]. They were later vetted by the National Expert Committees subsequently constituted by the CDSCO.

II. Material Method

2.1 Sample Receiving The BKL receives batches of 'Blood glucose test strip' sample from the Sample Receiving & Report Dispatch Unit (SRRDU) of NIB following approved procedure [2]. SRRDU receives the required quantity of glucose test strips per batch together with 10 Glucometers displaying glucose concentration values in mg/dL unit and compatible for use with the test strips. The manufacturer's Glucose Control solutions at Normal and Pathological glucose concentrations are also received as accessories for testing. As a regulatory prerequisite the blood glucose test strip sample is officially forwarded by the CDSCO office or State Drug Control office or the Zonal or Sub zonal and Port offices of the CDSCO to NIB for testing. Other supporting documents that are required to be submitted for completing the sample submission requirements are the Manufacturer's in- house Quality Control Protocols specific for the product, Batch specific Certificate of Analysis and Quality Control Test Results from source, Batch Release Certificate from the country of origin of product, copy of Import License/ Test License/ manufacturing license issued by the Licensing Authority. The Requirement of blood glucose test strips for performing the Quality Control Tests is 100 Tests for Standardization/ Method Familiarization, 200 Tests for Intermediate Precision at Normal and Pathological Control Levels, 300 Tests for Repeatability Precision at Glucose concentration levels 51- 100mg/dL,111- 150mg/dL, and 151- 250mg/dL, 300 Tests for System Accuracy, 200 Tests for overcoming problem of erroneous results shown by most 'Glucometer test systems and 100 Tests for unprecedented situations that might demand some repetitions; thus a total of 1200 test strips.

2.2 Intermediate Precision Intermediate Precision (IP) protocol is performed as per approved laboratory procedure [3] using Manufacturer's Control solutions at the 'Normal' and 'Pathological' glucose concentrations and 10 Glucometers; following the manufacturer's instructions for using the Glucometer Strip together with its specific glucometer. 10 readings are recorded over 10 Glucometers each day; for a period of 10 days. The % Coefficient of Variance (CV) which is a measure of the Precision (Intermediate) of 'Glucometer strip + Glucometer' test system at a particular concentration of the analyte Glucose is calculated from the 100 data values thus generated. To qualify for intended use, the value of % CV obtained is required to be ≤ 7.1 which has been considered to be good for a SMBG test system [4].

2.3 Repeatability Precision Repeatability Precision (RP) test is performed as per approved laboratory procedure [5] using three different human venous plasma samples having glucose concentrations that fall within the intervals; 51- 110mg/dL (Interval II) , 111- 150mg/dL (Interval III) and 151- 250mg/dL (Interval IV) respectively. 100 data values are generated consecutively using 10 Glucometers for each samples at a time. The %CV which is a measure of the Precision (Repeatability) of 'Glucometer strip + Glucometer' test system over the three concentration intervals of the analyte Glucose is calculated from each of the 100 data values thus generated. To qualify for intended use, the value of % CV obtained is required to be ≤ 7.1.

2.4 System Accuracy and Bias The approved protocol for System Accuracy [6] is based on the design of a method comparison experiment using split patient samples and data analysis. Freshly collected human venous blood samples are used under an ethical clearance from the Institutional Human Ethics Committee (IHEC) vide Protocol No. NIB/ IHEC/2010/05. Two glucose measurement values of the blood sample are generated using the Glucose test strips on two Glucometer devices. Within two hours, analysis of the same sample is done on the automated analyzer based laboratory Reference method for Glucose estimation. Keeping in view the requirement for a sufficient sample volume, human venous samples containing Sodium fluoride and EDTA are used in this protocol. Continuous validation of the laboratory Reference method for Glucose estimation is done by demonstrating 'Process In- control'; using a calibrator preparation that comes with a certificate of traceability and Uncertainty of measurement and periodic use of the Standard Reference Material, NIST 917c for the Recovery assay. In this way about 100 human samples are analyzed to generate two data sets using the two test systems. Sample inclusion criteria in the data set ensures that the Glucose concentration in 5% of these samples is <50 mg/dL, in 15% of these samples is between 50- 80 mg/dL, in 20% of these samples is between 80- 120 mg/dL, in 30% of these samples is between 120- 200 mg/dL, in 15% of these samples is between 201- 300 mg/dL, in 10% of these samples is between 301- 400 mg/dL, and in 5% of these samples is >400 mg/dL. The two data sets are statistically analyzed to compute the Bias [7] between the 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 ISO 15197:2003. This requires that at least 95% of individual glucometer values fall within $\pm 20\%$ of the Reference Method glucose values for all samples with glucose concentrations ≥ 75 mg/dL, or fall within ± 15 mg/dL of the Reference Method glucose values for samples whose glucose concentrations < 75 mg/dL.

III. Results And Discussion

3.1   Global distribution of the product batches tested Total of 567 batches of 'Blood glucose test strips' have been tested by the BKL till date, that were specific for use with 155 different kinds of devices manufactured in Europe, USA, Japan, Israel, Australia, India, China, Korea, Taiwan and Malaysia as shown in Fig 1. This number is not representative of the total volume of the import as the total number of batches tested is conditioned by the laboratory's capacity to test a certain number of batches per year. However the profile of the samples tested may be reflective of the profile of the imports. 40 % of the batches tested were from Taiwan and designed for use with 74 different kinds of Glucometer devices. It was followed by Korea with 25%, Europe with 16%, China with 11%, USA with 3% and negligible relative share of batches from Australia, Israel, Malaysia and India.
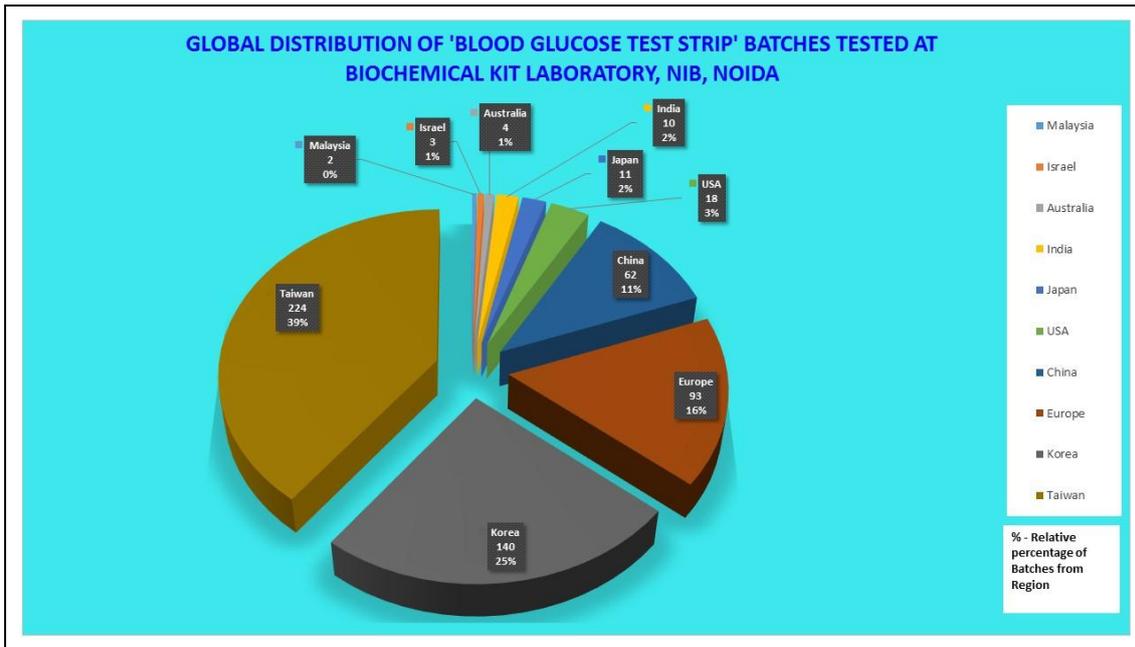
Figure 1 'Blood Glucose Test Strip' product batches received from different regions of the world and the relative proportion shown as percentage of batches tested.
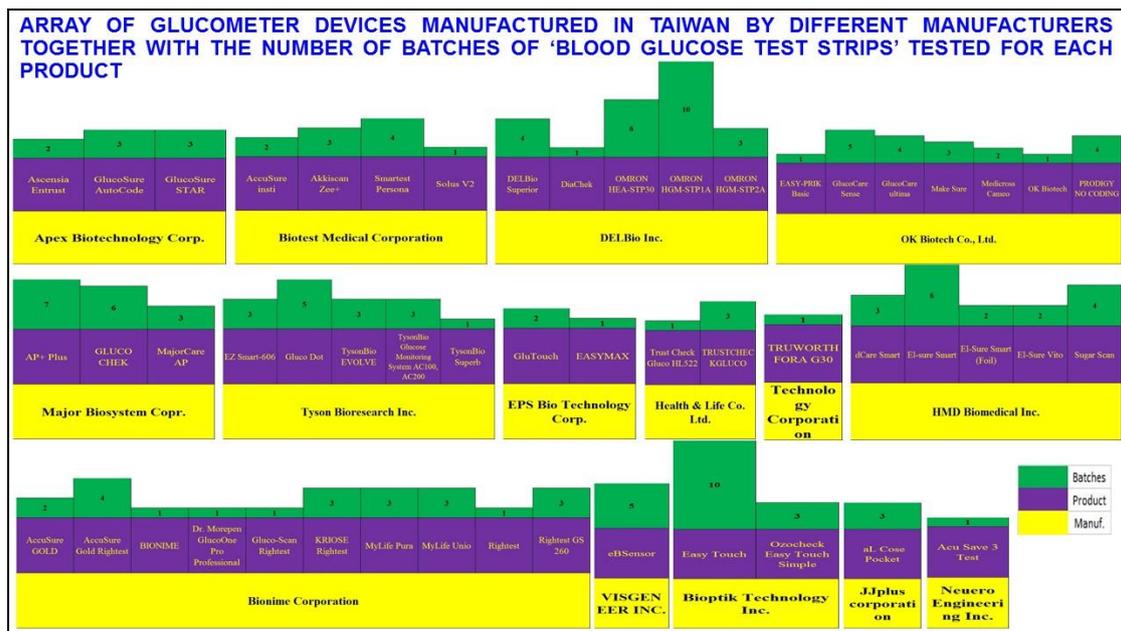
Figure 2 Different glucometer devices manufactured by the same manufacturer under different trade names in Taiwan.
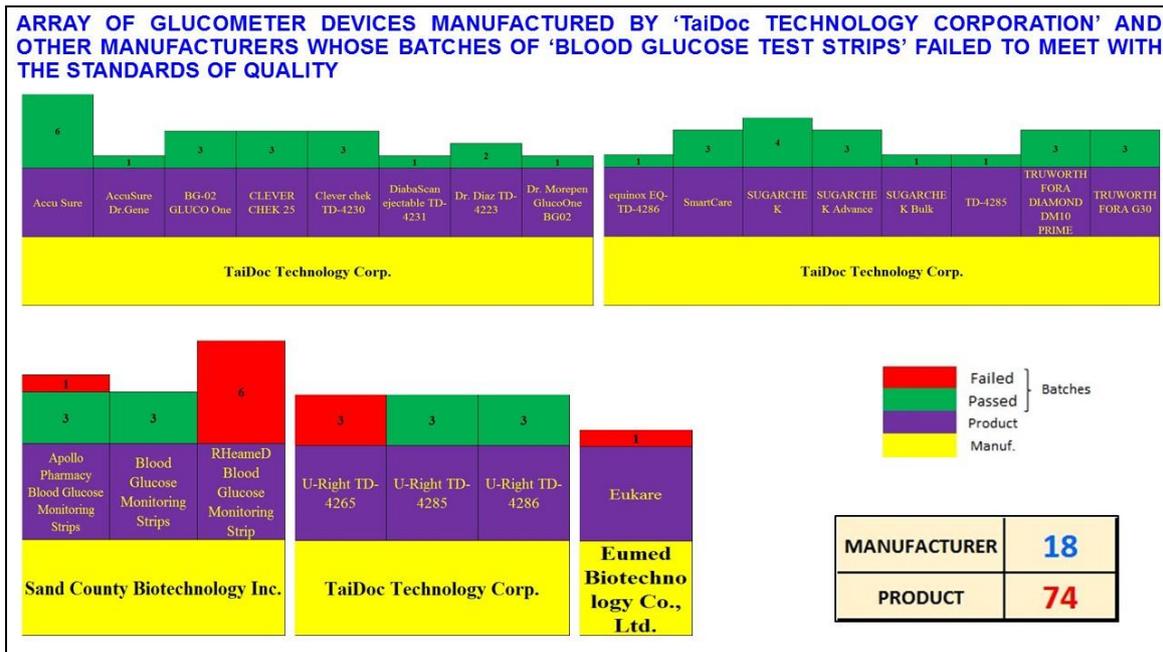
Figure 3 Array of products by 'TaiDoc Technology Corporation'. Glucose Test Strip batches that have failed to meet with the standards of quality have been manufactured by the three manufacturers from the Taiwan region.

The 224 batches received from the Taiwan region has the maximum number of manufacturers; seen in Fig 2 and Fig 3. Very few test strip batches for a particular device are seen to be repeatedly imported. 74 different products by 18 different manufacturers from this region have been tested. TaiDoc Technology Corp. is the biggest manufacturer amongst them with 19 different products. 27 different products by 7 manufacturers from Korea; shown in Fig 4 and 16 different products by 5 manufacturers from China ; shown in Fig 5, have been received and tested.
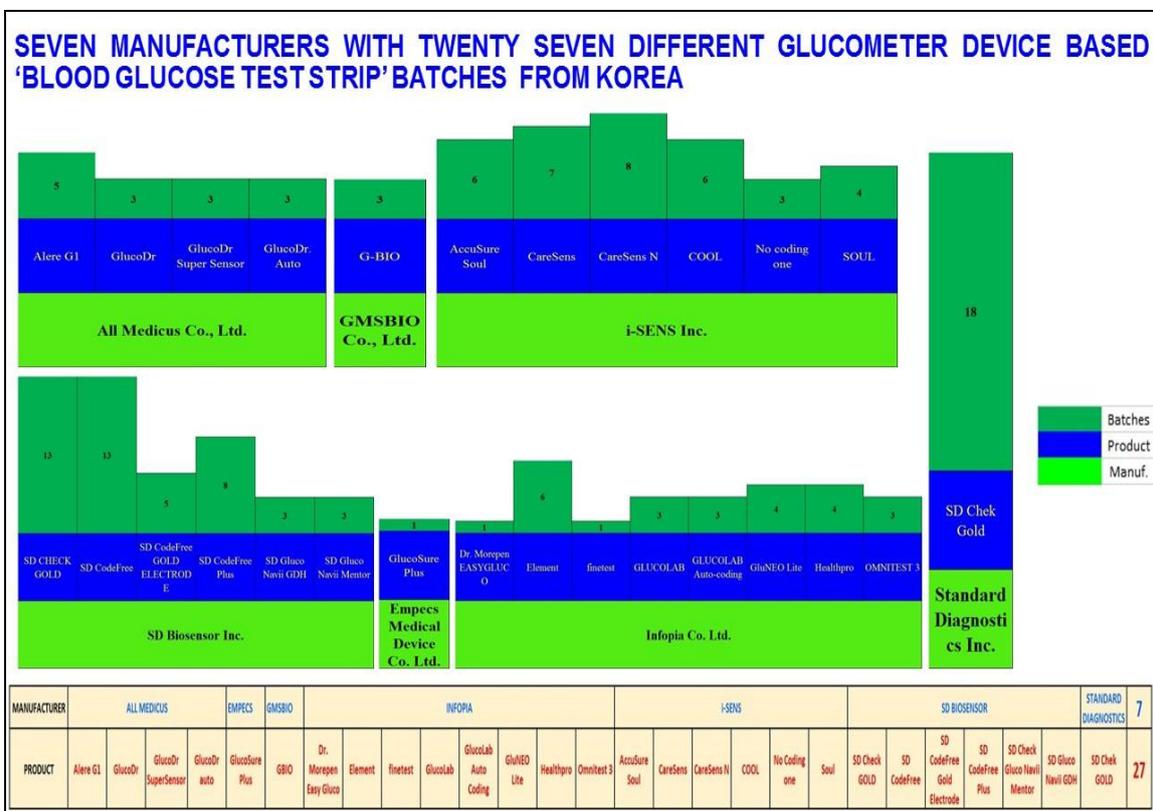
Figure 4: Products tested from seven different manufacturers belonging to Republic of Korea.
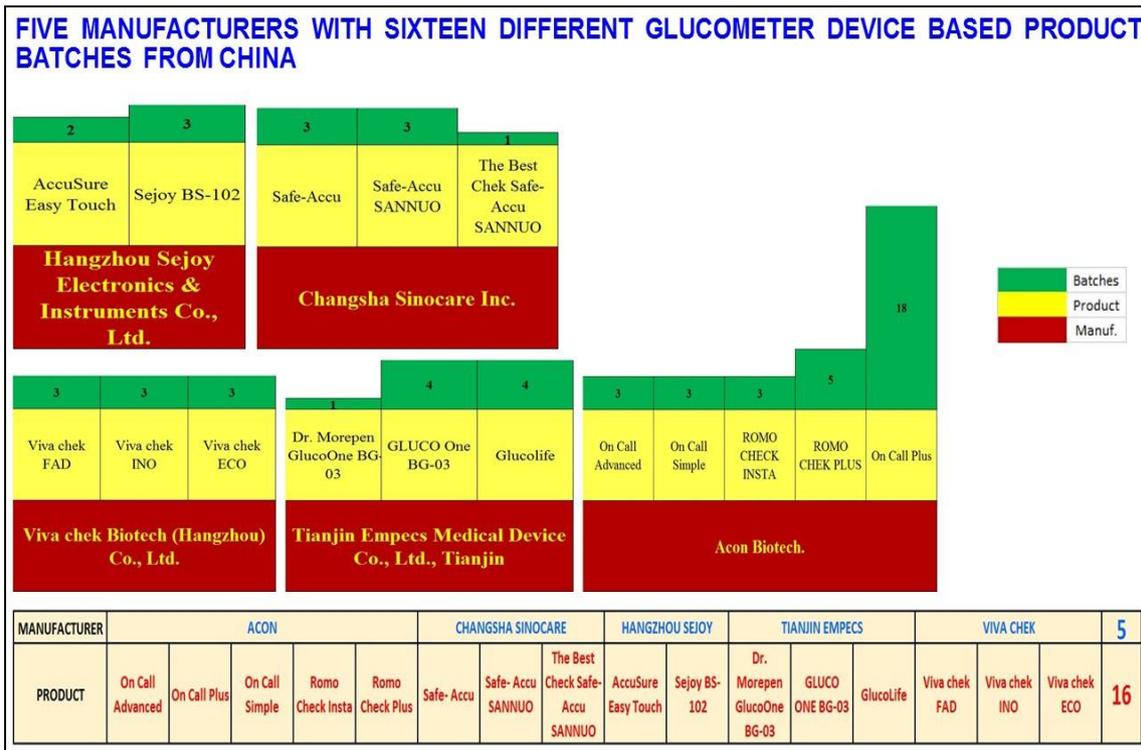
Figure 5: Array of products from five different manufacturers belonging to the Peoples' Republic of China.

From the USA 8 different products by Abbott Diabetes Care, Bayer Healthcare, Arkray, Roche Diagnostics and Lifescan have been tested; Fig 6. Products from Abbott, Lifescan and Roche Diagnostics have also been received from Europe besides those from B Braun, Convergent Technologies and 77 Electronika; Fig 7.
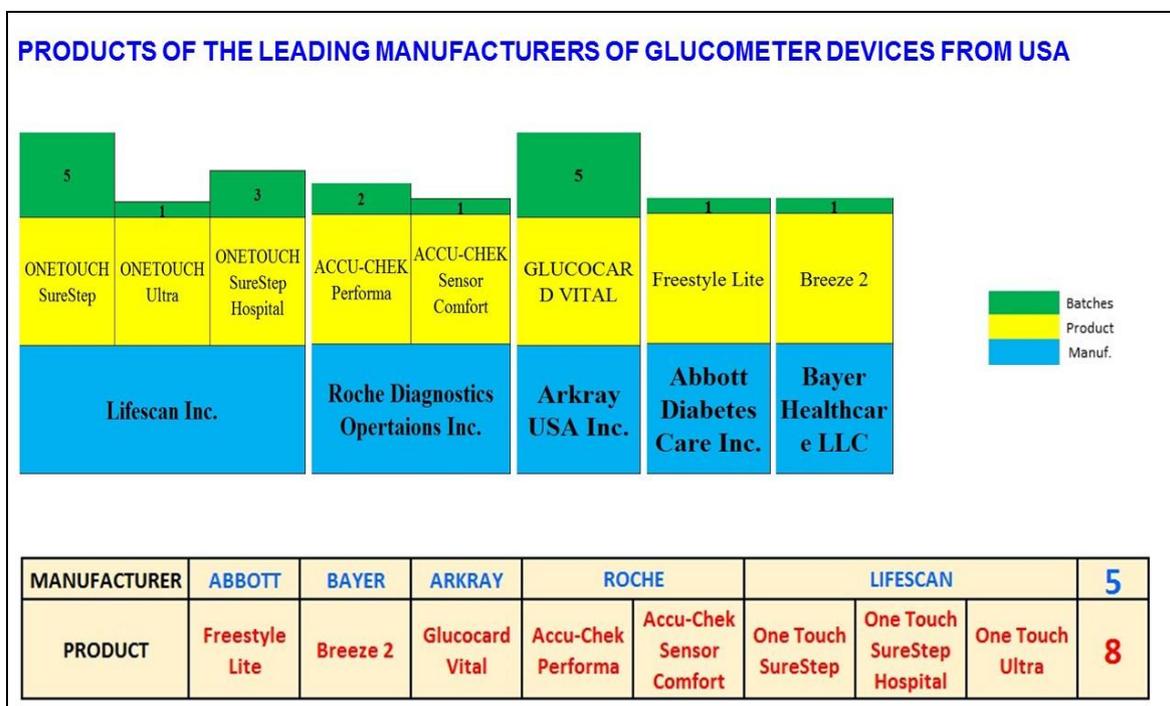
Figure 6: Glucose strip batches for leading brands as Accu-Chek, One Touch, Glucocard, Freestyle and Breeze 2, which have been tested.

Figure 7: Figure showing twenty different products by eight leading manufacturers from Europe whose product batches have been tested.

Meril Diagnostics, Sensa core Medical Instrumentation and Biosense Technologies were the indigenous manufacturers, Fig 8; 4 different products from whom have been tested.
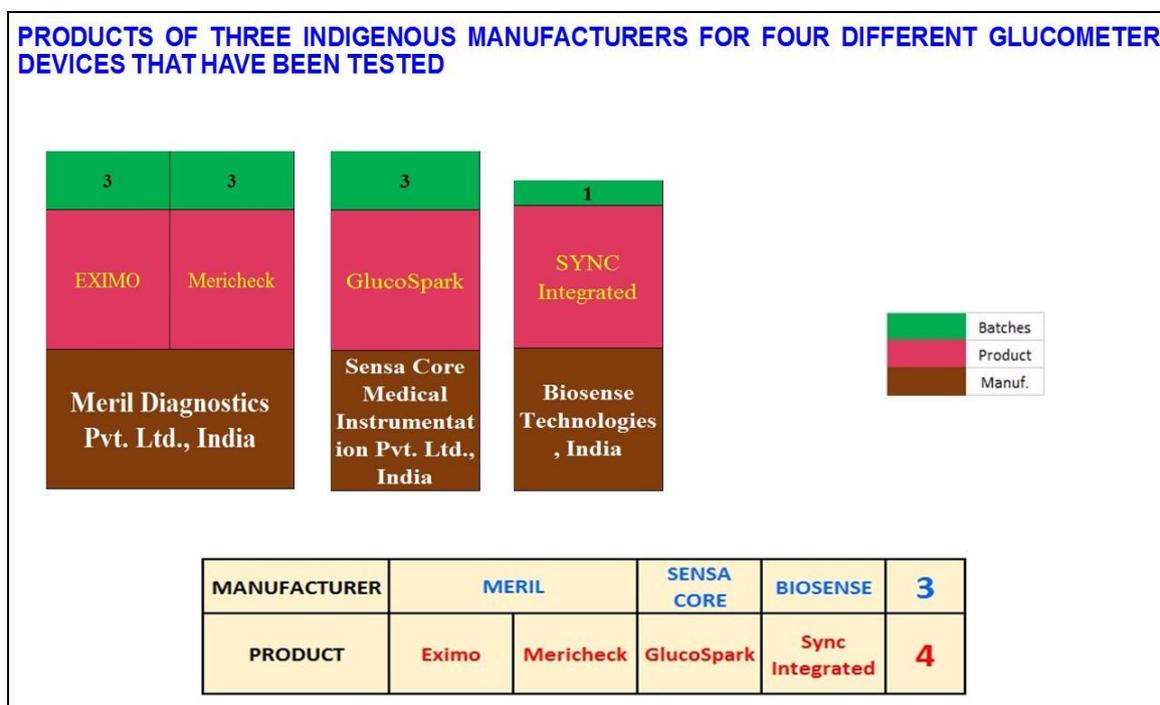
Figure 8: Three indigenous manufacturers from India whose 'Blood Glucose Test Strip' batches for four different glucometers have been tested.

3.2. Fulfillment of other regulatory requirements by the manufacturers Though submission of supporting documents such as Manufacturer's in- house Quality Control Protocols specific for the product, and Batch specific Certificate of Analysis (CoA) and Quality Control Test Results from source is part of our regulatory requirement; relevant information is seldom submitted by the manufacturer, as a result of which the protocols

and parameters employed for quality checks at the manufacturing level cannot be ascertained. None of the manufacturer's CoA are prepared with reference to the applicable guideline, ISO 15197: 2003. Most CoAs are generated without the testing of the product on human blood samples. Dimensions of the strip, environmental temperature, description of the control solution ranges, appearance, packaging inspection, etc. are other irrelevant parameters that form the basis of the CoA that are submitted by the manufacturers.

3.3. Trends in 'Precision' and 'Accuracy' parameters of the product batches tested Of the total of 567 batches that have been tested till date, only 11 batches have been found to be Not of Standard Quality (NSQ). Product performance trend analysis chart for certain manufacturers with respect to the parameters 'Precision', 'Bias' and 'System Accuracy' have been plotted for multiple batches of their products tested. In the trend analysis at Fig 9 for 42 batches of Roche products tested, % CV found to be < 5 for almost all the batches, the Bias is within ±10% at 95% confidence interval and 100% of the glucometer values are within ± 15mg/dL/ 15% of the Reference Method values in the System Accuracy analysis. An observable dispersion in values of System Accuracy and Bias can be seen only in batches tested before 2013, i.e. before the introduction of the latest edition of the applicable guideline ISO 15197.
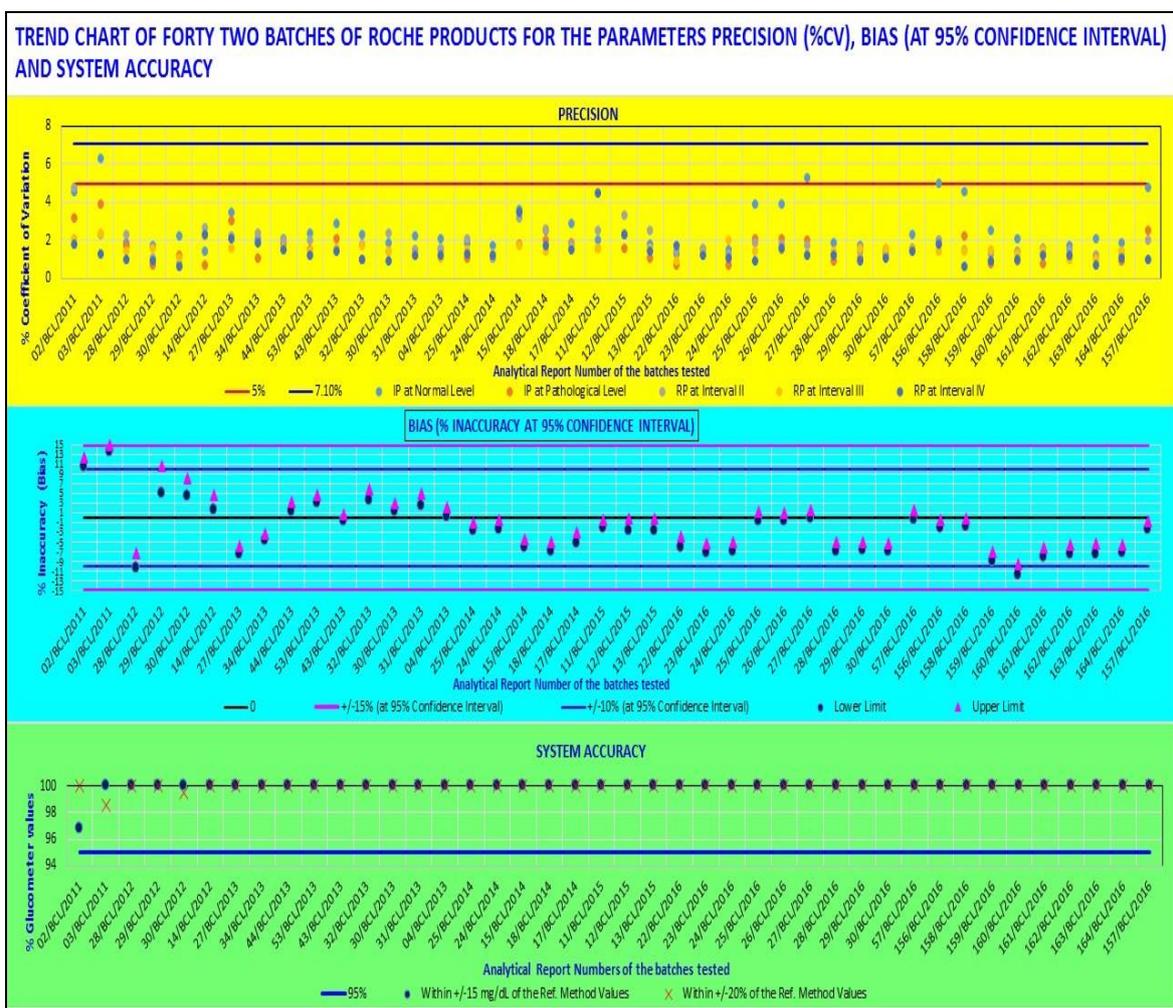
Figure 9: Trend Chart for performance of forty two batches of Roche products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.

A similar trend for 39 product batches from Lifescan can be seen in Fig10 with the exception seen in the System Accuracy analysis when more than a few batches are seen to have only 95% of the glucometer values within ± 15mg/dL/ 15% of the Reference Method values. Fig 11 shows the 17 batches of Arkray products to have consistently high level of precision. While the Bias is mostly between ±10%; 98- 100% of the glucometer values are within the acceptable range from the Reference Method in the System Accuracy analysis.
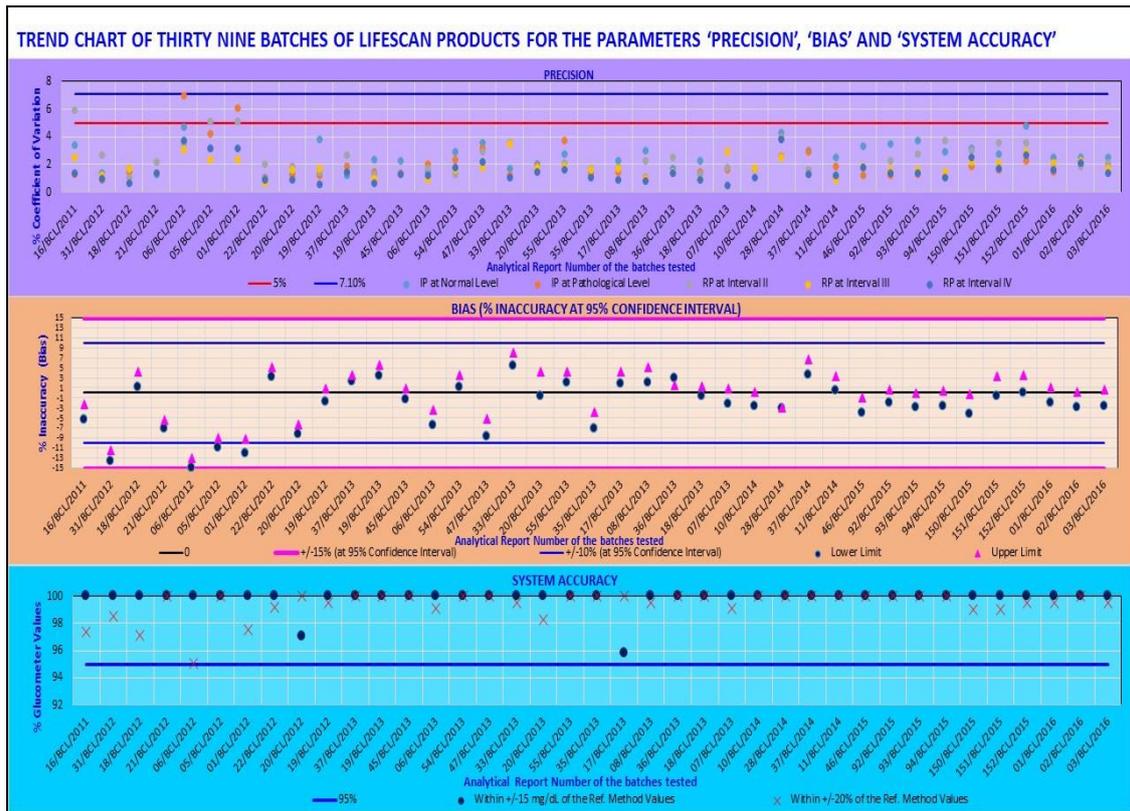
Figure 10: Trend Chart for performance of thirty nine batches of Lifescan products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.
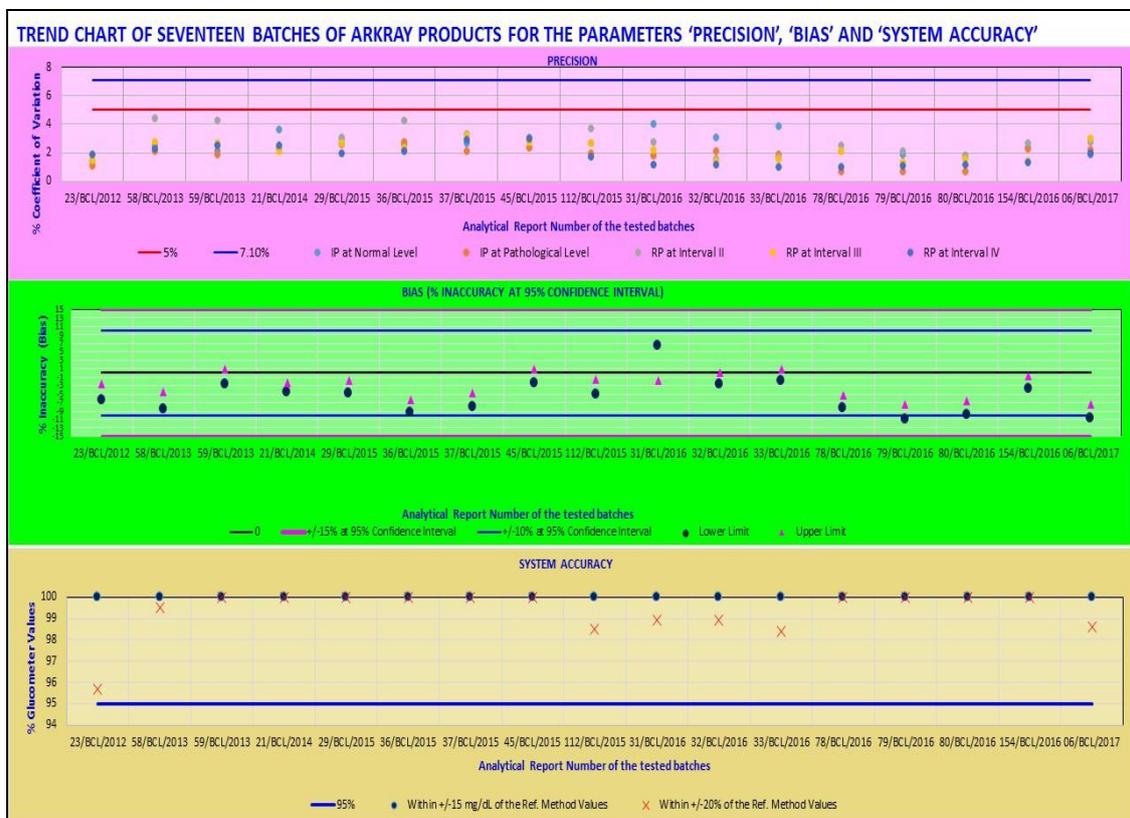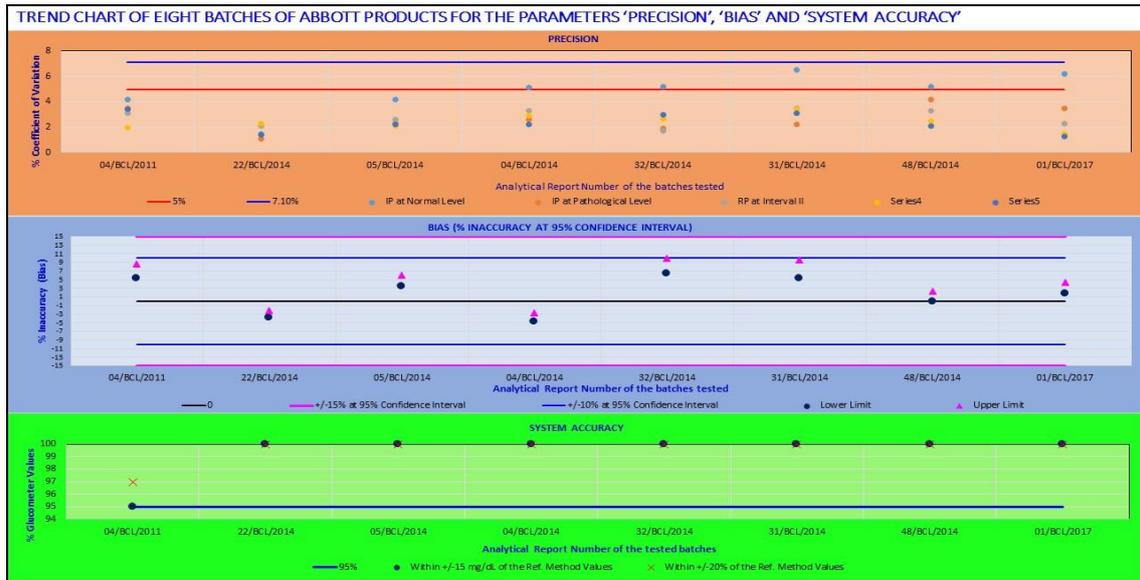

Figure 11: Trend Chart for performance of seventeen batches of Arkray products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.

Only 8 batches of Abbott products have been tested and their trend can be seen in Fig 12.
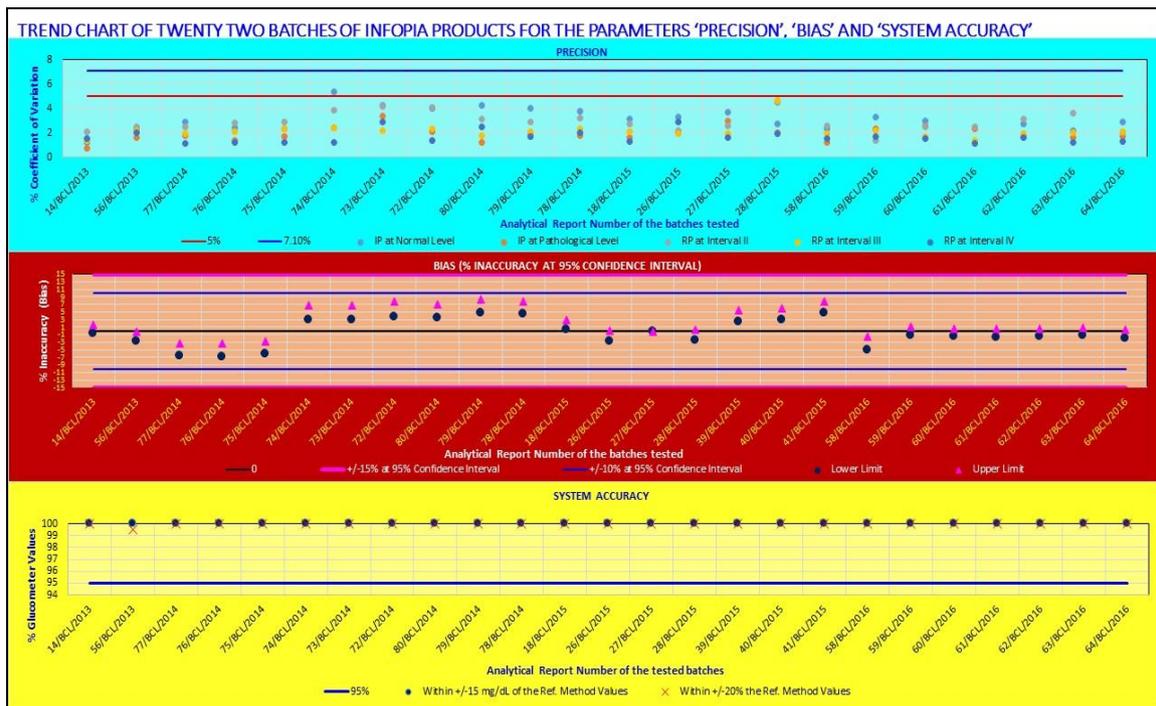

Figure 12: Trend Chart for performance of eight batches of Abbott products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'

SD Biosensor, i- sens and Infopia are the three manufacturers who have submitted multiple batches for testing. The trend analysis of their products are at Figs 13, 14 and 15 respectively. The consistently superior quality of manufacturing by Infopia is noticeable in Fig 15.
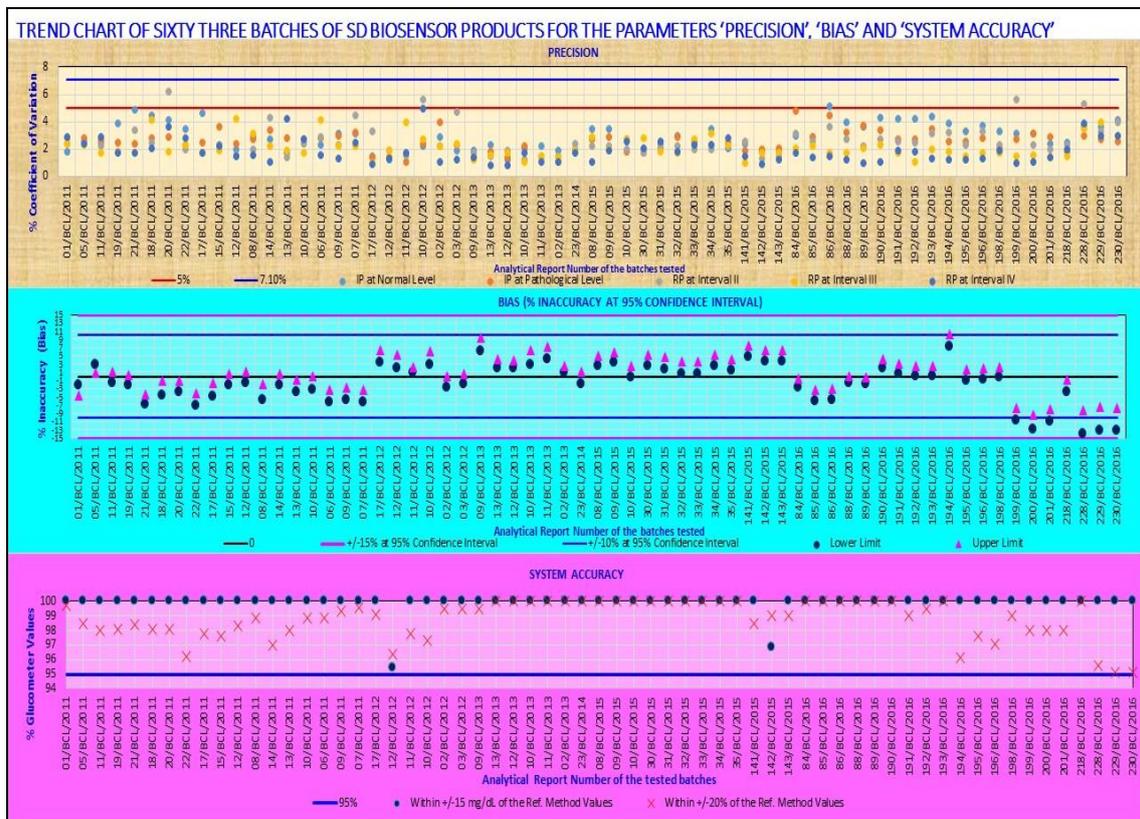
Figure 13: Trend Chart for performance of sixty three batches of SD Biosensor products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.
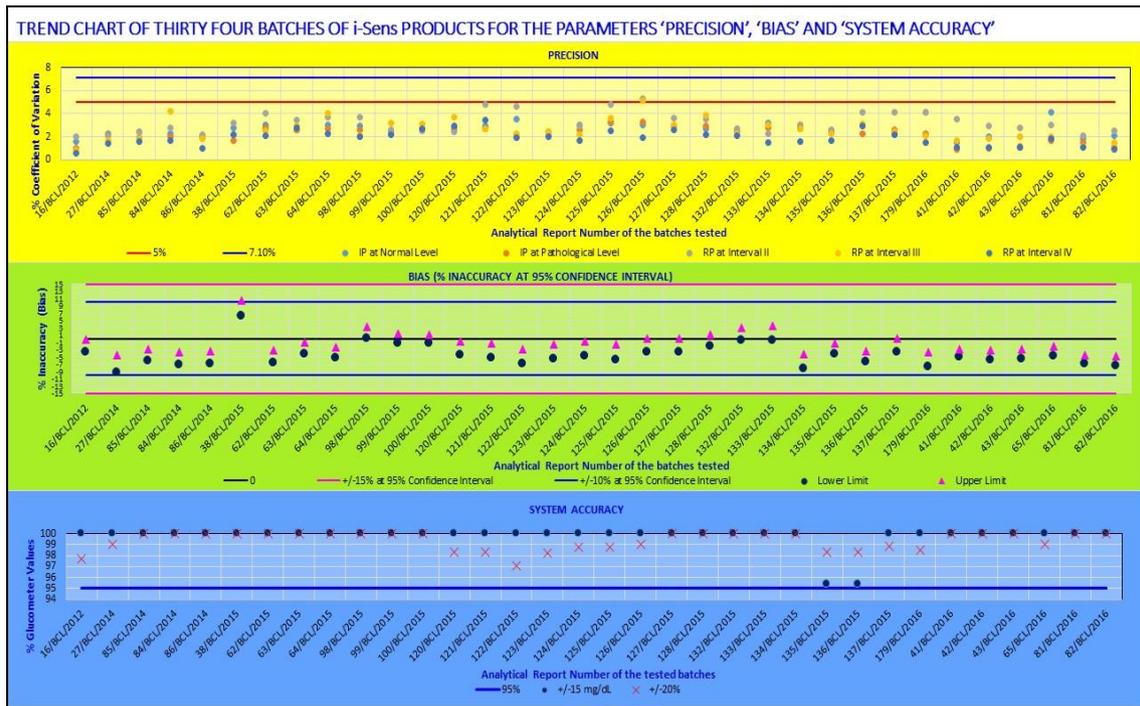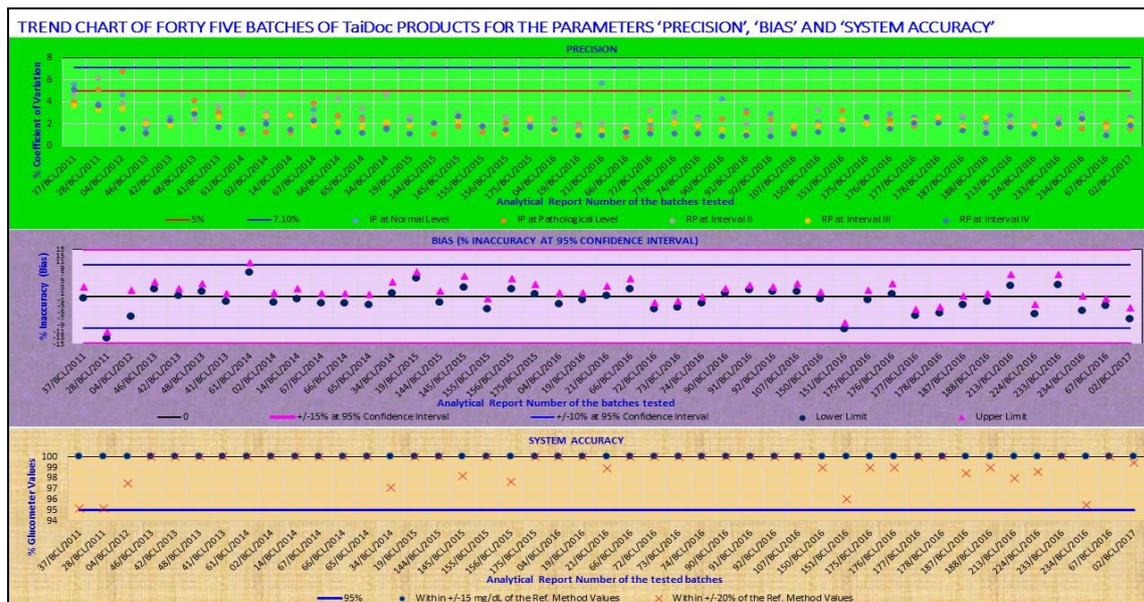
Figure 14: Trend Chart for performance of thirty four batches of i-Sens products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.

Figure 15: Trend Chart for performance of twenty two batches of Infopia products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'.

48 batches of products by Taidoc Technology Corporation have been tested till date; 3 of which have failed to meet ISO 15197: 2003 criteria. Trend analysis of the remaining 45 can be seen at Fig 16. Quality of manufacturing seems to have improved after 2013. Incidentally, the other 8 batches of products that have failed are by Sand County Biotechnology and Eumed Biotechnology; also from Taiwan. Though 62 batches of products from China have been tested, they have come intermittently from several manufacturers and hence a trend analysis could not be done.

Figure 16: Trend Chart for performance of forty five batches of TaiDoc products with respect to parameters 'Precision', 'Bias' and 'System Accuracy'

IV. CONCLUSION

The Glucometers market in India is dominated by products largely originating from Taiwan, China, Korea, Europe and USA. Based upon the Limits of Acceptance for the 'System Accuracy' parameter as per ISO 15197: 2003 and that of the 'Repeatability' and 'Intermediate' Precision parameter as per WHO: reference document 2002; only about 2% of the products have failed the 'Standard Quality' mark. 75% of these products are of Taiwan, China and Korea origin. Unlike the European and American manufacturers, the names of product by the manufacturers from Taiwan, China and Korea region keep on changing, with some exceptions as On Call Plus by Acon Biotech, China, SD Check Gold and SD CodeFree by SD Biosensor, Korea and Easy Touch by Bioptik Technology, Taiwan. The rationale behind frequent changes of product name and device model by manufacturers from South East Asia region is not clear. Availability of a new model from a particular manufacturer through the same importer means limitations in availability of consumables (strips) for the older product. This understandably affects the interests of the end user with the previous model of the device, who is not only ill; possibly financially challenged, and yet faces the eventuality of having to buy another SMBG product. It is pertinent to speculate whether above trend is related to the probable absence of Current Good Manufacturing Practices (cGMP) at the manufacturing sites belonging to these regions or absence of proper regulatory mechanisms for real time monitoring of product quality as is evident from the paucity of quality control related document support for the batches imported from these regions.

Acknowledgements

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