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AN ACCURCY IMPROVEMENT OF THE CLINICAL EXAMINATION RESULT BY ISO-GUM AND QE

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Abstract The accuracy improvement of clinical examination starts to prevent from a misdiagnosis by uncertainty data. Recently it came to profit by it towards IT era for broader-based health care. The improvement accuracy was carrying out high quality data by ISO-GUM [1] and QE [2] technology. QE is useful for EQCS and EQA. It is the purpose that present development provides a patient with medical technology high level same as quality when and anywhere by EqQC for IT era. This research has continued applying for many years. The result has been reports every advance step of Blood Chemical Analysis (BCA).

Keywords: ISO-GUM, QA IT-era. Blood Chemical Analysis.

1. INTRODUCTION

IT medical system is meaning "the integrated healthcare network" and "the totalized medical management system to widely collaborate for multi various medical information".[12]

ISO published "Guide to express of Uncertainty in Measurement (GUM-GUM) [3]" as guidance for assuring all measurement result. It edited based on the documents of "Joint Committee for Guides of in Metrology" (JCGM document No.100), and published supplements added. The list of supplements is shown following. (The mark * is under plans).

Supplement 1: Numerical methods for the Propagation of distributions using a Markov Chain Monte Carlo (MCMC) method [4] :and it refer to in Fig.1.(JCGM101) [5]. Fig,1 shows the practical used procedure, it is example of concrete MCMC which National Institute of Standard and technology (NIST) is recommends [6], and it is profits by Gibbs sampling and Bayesian inference.

Supplement 2: Extension to any number of output quantities is useful models. (:JCGM102)

Supplement 3: Modeling for useful Multivariable Analysis (MA). (JCGM103).

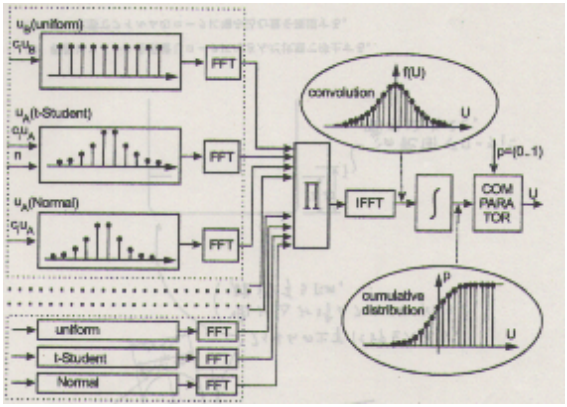


Fig1. MCMC of process by ISO-GUM in 2002 [6]

The GUM is due to added four new supplements

*Supplement 4: An introduction to be GUM and proposed "Law of propagation of uncertainty (LPU)" of ISO-GUM concretely. (JCGM104).

*Supplement 5: Concepts and basic principle of measurement uncertainty evaluation. (JCGM105)

*Supplement 6: The role of measurement uncertainty in deciding conformance to specified requirements (JCGM106)

*Supplement 7: Application of the least squares method (JCGM107)

Supplement 4 is related documents it performed at the following seven steps, it published in 2009

Step1. State the Problem
Step2. Identify the Decision
Step3. Identify the Inputs to the Decision
Step4. Define the Study Boundaries
Step5. Develop a Decision
Step6. Specify Acceptable Limits on Decision Errors
Step7. Optimize the Design for Obtaining Data.

Practical use MA of supplement 3 is required for BCA from tow or more uncertainty elements being inherent. The supplement 7 is using a least squares method for MA.

Quality Engineering (QE) has following procedure.

SQC: Statistical Quality Control

TQC: Total Quality Control

IQC & EQCS: Internal Quality Control and External Quality Control Scheme by Professional Test (PT)

IQA & EQA: Internal Quality Assurance & External Quality Assurance.

TQM: Total Quality Management

MSS: Management System Standard

CQC: Continue QC or (CQI: CQ Improvement)

GMS: General Management System

(For international quality level to IT-era)

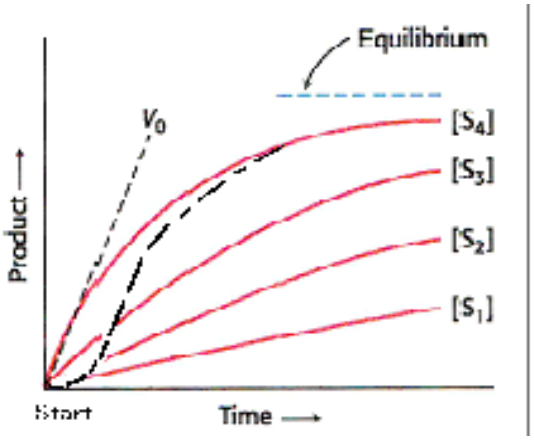
EqQC : Equivalent QC The high quality of same level when and anywhere

QE is starting analysis from hierarchical gradient- based motion estimation of fault factors though "Failure Mode and Effects Analysis (FMEA)". QE then determines the root cause of the fault element though "Root Cause Analysis (RCA)" and "Fault Tree Analysis (FTA)".

Recently, Fault-Injection technology is becoming very important.[7]

These are developed it based on tracer technology. In professional Test (PT), the procedure of QA decision it followed one by one step, in order to discern the importance level of fault/active input, it is execution by strategic sampling. In this research, the uncertainty factor contained in data is considering it as the fault.

The characteristic of the chemical kinetics reaction of measurement object is shown in Fig 2.



Fig,2 Chemical kinetics reaction curve

Sampling is defined in ISO 6550 series.

Research is advanced by practical use by GE and ISO-GUM. Both technologies had done its best in research of Decision level/Minimum Detectable Amount (DL/MDA). It is applied supplement 6. The result enables detection on the unstable region with the early resistance of start portion in a chemical kinetics reaction. (See Fig,2).

QA sets up the rated value conformance zone which can being assurance in probability density function (PDF) [8] of measurand. It is necessary to verity by an ISO14235-1 (see Fig.3) whether the uncertainty of measured value is suitable for assurance performance by coverage factor [9] that is used set up to upper limit and lower limit, and coverage interval stipulated by ISO-11929 for estimating from low dose samples..

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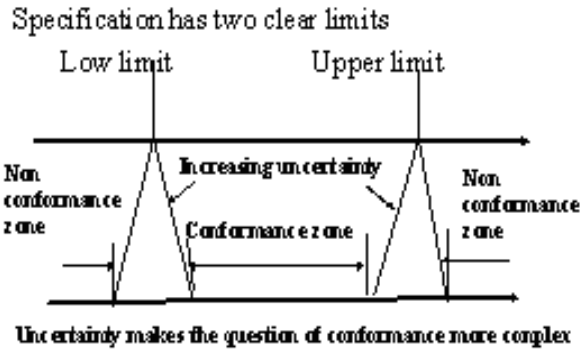

Fig.3. Conformance (Assurance) zone by ISO-14235-1

The coverage factor calculate synthetically from three types distribution in Fig,1 and it is obtained the formula of Welch-Satterthwaite (1) drawn chi-square test and likelihood function for conformation interval estimation..

$$V_{eff} = \frac{u_c^4(y)}{\sum_{i=1}^{N} \frac{c_i^4 u^4(x_i)}{v_i}} \qquad (1)$$

Where v_i is the degree of freedom of the input quantity. is combined standard uncertainty. u_c N is number of sample. Sampling plan is making by ISO 8550 series.

2. EXPRIMENT

2.1 Measurement method

A measurement object is improving the accuracy of calibration curve used for the quantitative analysis. It is important as intermediate accuracy in total system of measurement. Furthermore it has meaning importance when the standard substance is not being fixed.

The calibration curve makes measured result of the

several test reagents for different concentrations (doses) which is an arrangement harmonious in the shape of stairways. It is created by applying regression analysis to the measurand.

In this case, the test reagent of Radio Immuno-Assay (RIA) method was used in the experiments. It is one kind of BCA. In RIA, it measures by the competitive reaction of the antibody prepared first and the labeled antigen later added to the antigen. The labeled matter is I-125 radio-isotope for detectable maker.[11]

Experiment Objects are five sorts of homeopathic test reagents. It is chosen the Elastase-1 as principal samples. Furthermore, these using four sorts of additional regents as check sample are Plasma rennin activity, Thyroxin, Progesterone and Testosterone.

The concentrations of Elastaze-1 reagent are six doses: 50, 150, 500, 1500 and 5000 dose. The reagents of Thyroxin are 5 sorts dose which are 0, 3.0, 6.0, 12, and 24. The reagents of Progesterone are 6 sorts dose which are 1, 5, 25,100, 200 and 400. The reagents of Testosterone are 6 sorts dose which are 25, 50, 100, 250, 500 and 1000. Dose unit is concentration in international catalyst units (IU).

2.2 The experiment procedure

In this experiment, in order to assurance a measurement result, it calculated the uncertainty factor in the following four steps on produce and remove it from measurand.

In the first step, it calculates with the Analysis of Variance (ANOVA) which is basic statistics analysis .it is useful probability density function (PDF).

In the second, step, it is analyzed the uncertainty factor buried into the result obtained in the first step by the MCMC method. For this reason, it is created cumulative probability distribution.

In the third step, it is analyzed a multiplex variable factor by supplement. For reason, it is performed analysis of the factor to strategic data analysis to having fault partially in COF.

In the final step, it is verify the effect of the number of samples by 14253-1 using a effective free degree. This is important for calculation of coverage factor which determines the assurance interval in PDF.

2.3 The measurement theory

The enzyme kinetics reaction of BCA is follows the basic dynamic principles with a reversible reaction by between two molecules which are antigen and antibody. The reaction model of supplement 2 is useful a chemical kinetics of immunity with a reversible reaction in (2).

$$P+P^*+Q \underset{R_2}{\overset{R1}{\Leftrightarrow}} P^*Q+PQ+PI+P^*I \rightarrow P^*Q \qquad (2)$$

here are:

P: Antigen,

Q: Antibody,

P*: Labeled antigen with detectable marker,

PQ: Reaction compound,

P*Q: Reaction compound with P*,

$R_{1;}$ Association constant

R_2: Disassociation constant

R; Affinity.(Binding ratio P*Q/Po= %)

Po is total antigen Po=PQ+P*Q+PI+P*I

PI: Abnormal reaction compound.

Po is an invariant constant of nature in the "law of mass action". In this case, it must be the measured P*Q/Po of the effective binding ratio. Affinity is the same as the kinetic reaction rate. An affinity increases until the deactivation of saturation that the reaction is based on the reaction process in time series. The chemical kinetic reaction is accelerated as a quadratic differential polynomial equation with reaction time t. The equation is as follows according to three phases (3).

$$Ad(P^*Q)^2/dt_2+Bd(P^*Q)/dt+C(P^*Q) \qquad (3)$$

In (3), secondary order differentiation of the first item shows the rate of acceleration included a special resistance. It is shown to the portion of start on the reaction curve. A primary differentiation of the next item is reaction velocity. The last item is constant the amount of chemical compound after reached chemical equilibrium. Affinity is estimated as follow in (5)

$$d[P^*Q]/dt=R1[P^*][Q]-R2[P^*Q]\ldots \qquad (4)$$

$$k1[P^*][Q]=(R1-R2)[P^*Q]\ldots \ldots\ldots \qquad (5)$$

$$\text{An affinity R is in } (R1-R2)/R1 \qquad (6)$$

The final reaction state as stagnation phase is reached to d[P*Q]/dt=0 and change from (4) to (5). An affinity variable state is shown on the reaction curve at a time,

The value of affinity (%=P*Q/P_0) is determined by radioactivity remaining bound divided by the total amount of radioactivity added in the beginning the radioactivity. Chemical reaction is proportional to the concentration of

the labeled antigen. The unknown sample concentration can be calculated from calibration curve.

This research sets the data of affinity and regression analysis as the key object of improvement accuracy. [10]

3 Experiment result

3.1 First step data.

Fig 4 is quoted the PDF graph of measurand data which is pile up of the elatase-1 of six dose data obtained by Analysis of Variance (ANOVA), and it becomes basic data for carrying out this research.

Fig.5 is quoted the pareto graph that is pile up the quasi normal distribution curve, it is made of measurand by regression analysis.

Six of the quasi normal distribution in Fig 5 are abnormal distribution from which each perk position differs Ordinate is the account of frequency of total 320 sample sets. Abscissa is affinity (%) that is divided into 20 ranks between maximum and minimum affinity

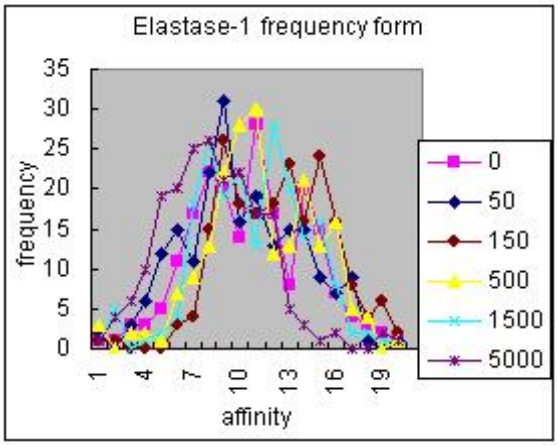

Fig4. A graph is piled up on six PDF the measurand of the erastase-1.

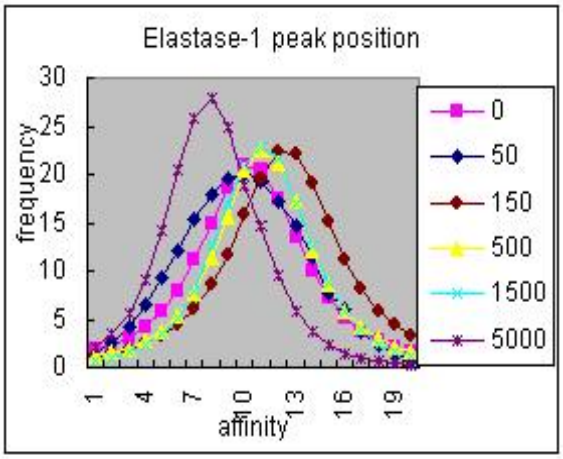

Fig.5 pileup graph of six quasi normal distribution curves

3.2 . Second step data

Fig.6 is quote a cumulative distribution frequency (CDF) of 5000 dose of Elastaze-1. The CDF curve has been the form of sigmoid and bending seen in some position. The bend of a curve suggested that abnormalities condition existed in a chemical reaction

PDF graphs are key data in his experiment..

In Fig.6, the reagent kit is divided into three groups and it shown influence to verify of difference between in reagent kits. The ordinate of is the account of frequency of total 320 sample sets which are divided into one group (100 samples set) and two groups (100 samples set). Fig.6 expresses the difference between three groups.

In Fig.6, the abscissa is shows affinity (%) which All graphs quote variation of affinity that divided the affinity into 20 ranks between maximum and minimum. The ordinate quotes generating frequency counts.

All of CDF result (including the four sorts of other dose) showed a state of an abnormal distribution similarity and not same form. It is seemed all sigmoid type. The abnormal distribution of PDF should be required to useful nonparametric test and nonlinear analysis.

This research analyzed of bend portion looked at by CDF in Fig.6. By ISO-GUM type B, acquire further measurement accuracy, it is necessary to analyze a fault element by FTA of QE. Here, it has to process of two stage least –squares by type B for abnormal distributions. Next work is selection of reference value. for key comparison in this research.

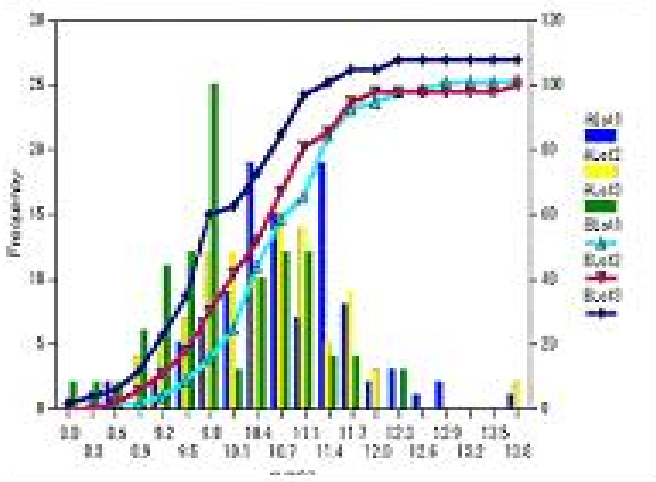

Fig.6 Elastase-1 5000 dose of 3 rots graph

3.3 Third step data

The results were quoted in Fig.7 and Fig.8.

Fig.7 shows data to MA of SD value which changes with storage days of the Elastase-1 reagent data.

Fig.8 shows data to MA of SD value which changes

with storage days of the Plasma Rennin Activity data. Both data has been same as form SD value in both are seen be unsteady with cycle that is variable by biorhythm of the 28 days period. The data of biorhythm is seen in the biomaterial..

The ordinate shows change state of SD. The abscissa shows the storage days of every seven days interval.

It is existence of what is considered to be down of reaction capacity and influence of deduction of the number of samples. The problem was found out for coverage factor of calculation to assurance by ISO-GUM from this data. The fall of SD value is meaning time of accuracy falling, and should avoid use.

The assurance of measurand is restricted to the data within 2 sigma by IQA at ISO standard, and in EQA, they are 3 sigma. Therefore, it cannot use the period when binding capacity declines.

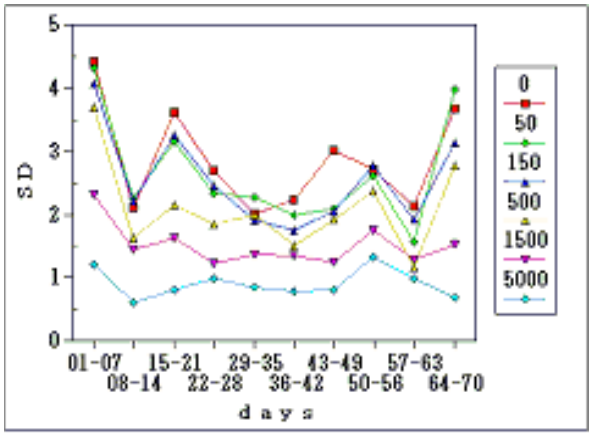

Fig.7 graph shows Elastase-1 test reagent data

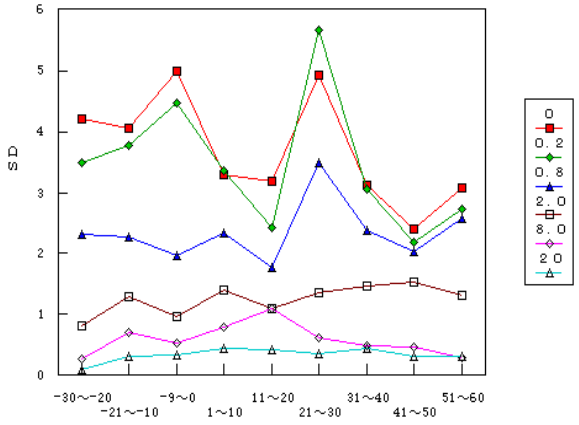

Fig.8 graph shows Plasma Rennin Activity data

Test reagent is made from biomaterial, it is the source of many uncertainty include. It is required to solve it in order from large factor which influence an accuracy and likelihood. Practical use of MA is important.

3.4 Final step data

This experiment verified the validity of using ISO-GUM and issued supplements. Furthermore, in order to investigate an information criterion number and likelihood test and it used MA in the time series data.

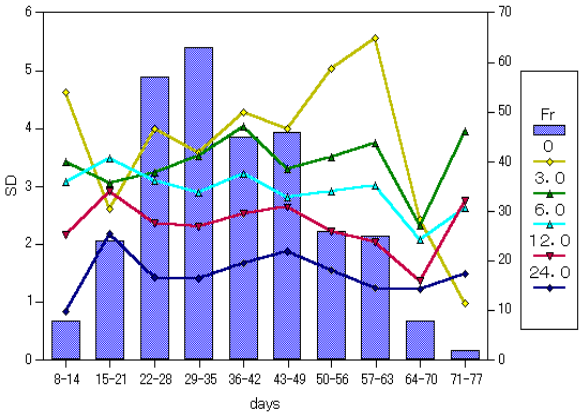

Fig.9 shows Thyroxin test reagent data

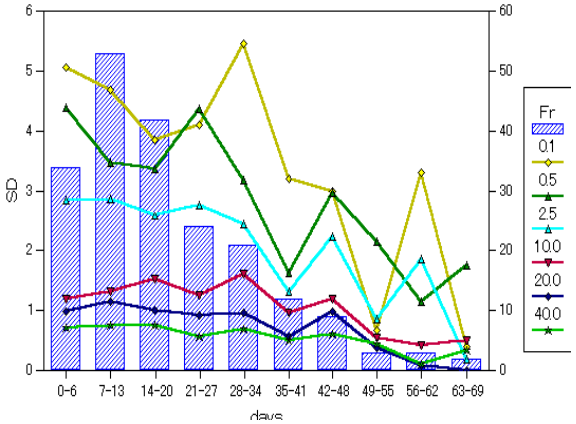

Fig.10 shows Progesterone test reagent data

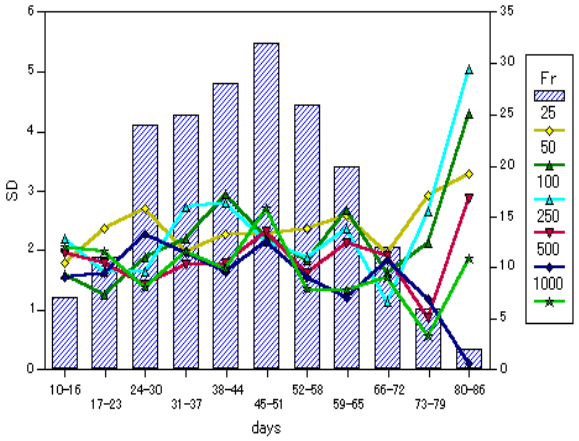

Fig.11. shows Testosterone test reagent data

Fig.9 shows the Thyroxin test reagent data of MA which considered the time series for storage days and number of sample.

Fig.10 shows the Progesterone test reagent data of MA which considered the time series for storage days and number of sample

Fig.11 shows the Testosterone test reagent data of MA which considered the time series for storage days and number of sample

The abscissa shows the storage days of every seven days interval. The ordinate shows change state of SD by line graph, and number of samples is shown changing state by bar graph,

LPU of ISO-GUM is effective by solving for every problem by Stratifies Fault-Injection (SFI)

The limit of the number of samples (likelihood) which will be critical accuracy performance of the measurement result has been solved. For information criterion, although it is the limit of the number of critical samples that is shown by likelihood. In this case, it required a more than ten for RIA.

4. CONCLUSION

Both accuracy improvements by ISO-GUM and GE are mining out the cause worsened thoroughly and removing it. When QA the standard value (true value) for calculating an error is not clear, it is difficult to perform QA.

The assurance of BCA is ambiguous Then ISO-GUM changed expression of ambiguous data into uncertainty (sigma) from error (%). QA object such as this, are PDF of a abnormal distribution, and CDF of sigmoid form is an object. The problem of uncertainty of estimating fault tolerance coverage though statistical processing of observation collected in fault-injection experiment, it considers Bayesian estimation methods for stratified sampling on MA By multi regression.

Whether a measurement result is possible an assurance performance judges, after synthesizing the result of the third step and the result of the final step.

These are described by procedure of supplement 4.

The result is required by improvement of accuracy also in BCA. To work improve further by practical use of new supplements. Revision of related ISO is progressing now.

The all experimental result is effective in accuracy improvement and useful for medical IT system.

Since the measuring object contains obstacles, measurement of biomaterial is the cause which worsens accuracy. It has corresponded many causes here.

Measurement Systems Analysis (MSA) is a specially designed experiment that seeks to identify the uncertainty components of variation in the measurement.

Medical Laboratory Quality System (MLQS) is offered essential in laboratory to the correct result for patient and donor by Good Laboratory Practice (GLP).

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