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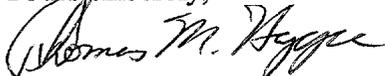
Docket No. 00N-1394  
Dockets Management Branch (HFA-305)  
Food & Drug Administration  
5630 Fishers Lane  
Rockville, MD 20857

Dear Dockets Manager:

On behalf of i-STAT Corporation, 104 Windsor Center Drive, East Windsor, NJ 08520, Talisman Group hereby submits comments on the "Review of criteria used to determine whether specific laboratory tests are waived from certain requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA)". A public hearing on these matters was held on August 14 - 14, 2000 in Gaithersburg, MD. Attached are hard copies of comments as well as a reproduction of a slide presentation made by Michael Groves of i-STAT-STAT Corporation.

Thank you for the opportunity to submit these comments. On behalf of i-STAT Corporation and Talisman Group, we are

Yours sincerely,



Thomas M. Happe  
Executive Director  
Talisman Group

cc: Michael Groves, Vice President, International Sales & Operations, i-STAT  
Clara A. Sliva  
U. S. Food and Drug Administration  
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00N-1394

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i-STAT Corporation would like to thank the U. S. Food and Drug Administration for the opportunity to submit comments on issues surrounding the waiver of laboratory tests under the CLIA '88 Waived Status regulations.

## **SUMMARY**

The Congressional intent with CLIA '88 was to resolve inter-laboratory variation and allow for a range of oversight that is dependent on the complexity of operating a system. Because of the CLIA Act of 1988, oversight of areas such as quality control, proficiency testing and personnel was placed into the regulator's hands, creating a three tiered system of classification. Systems that meet the lowest of these categories, namely the waived category, would fulfill the objective of providing the widest access to testing systems while making sure that such systems are so simple and accurate as to render the likelihood of erroneous results by the user negligible is clearly an important objective for all testing. Meeting this objective has the potential to lower costs and turn-around-time for routine clinical testing. These are benefits to the overall quality of care provided by today's physician and received by the patient, particularly in rural areas.

By the 1988 time frame some tests already met the lowest oversight category, namely "waived", and were in frequent use by non-laboratory trained professionals. Since then manufacturers have designed technically advanced systems that demonstrate industry's ability to remove areas of concern in the performance of certain laboratory testing by focusing on the areas of concern addressed by the CLIA'88 act. For example, new technology, particularly the single-use or unit-use technology, removes the operator from areas such as calibration and quality control testing, moving the responsibility for the product quality back to the manufacturer. Hence, if a system is designed such that the user cannot affect the results through the testing methodology and cannot alter patient results based upon quality control or proficiency test results, it is clearly designed for the laboratory untrained user. Such a system should be a very clear candidate for the waived category - it is redundant for the user to be required to perform frequent QC and be submitted to proficiency testing on a routine basis for such a system. However, very few of these new systems that are performing tests that were not on the initial waived category list of tests have been cleared for waiver. The causes of this are many fold, but the most apparent of these was the use of an unclear and impractical process.

i-STAT Corporation believes that a quantitative waived test should produce an analytical result equivalent to current precision and accuracy as performed in a CLIA-licensed laboratory, staffed with laboratory trained professionals. There is no reason to establish higher accuracy standards for tests in the waived category than in the other categories. Indeed, in making a determination of a system's performance, significant consideration should be given to the supportive data of 510k cleared Class II test devices. Accuracy should be established by professional laboratory personnel in professional settings.

Precision performance and Comparison of Methods testing should be established between the laboratory untrained user and laboratory trained user settings. Standard statistical techniques, already commonplace in the FDA 510k setting, are sufficient to provide the basis for acceptance or rejection of performance characteristics of proposed waived devices. Using the resource of the professional laboratory community and the *in vitro* diagnostic manufacturer and with the participation of untrained users, the FDA should be able to confidently make rulings on the acceptability of proposed tests and test systems for waived status.

**Creating a clearly articulated, practical waiver process for the clearance of tests utilizing today's and tomorrow's technology will deliver the widest access to state-of-the-art testing for patients. Better access to testing will improve the timeliness and accuracy of diagnosis, thereby improving care. The patient benefits and the practice of medicine is better for it.**

#### **SPECIFIC COMMENTS:**

The FDA has solicited comments in the area of the criteria to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible." i-STAT believes that this determination will be obvious if the device proposed for waived status is capable of being put into the hands of users without formal laboratory training and produces equivalent results as those produced in the hands of trained laboratory users.

i-STAT Corporation believes that a properly designed test system capable of being utilized by laboratory untrained users that produces a "CLIA-licensed" equivalent result will, inherently, produce accurate results. Use of multiple fail-safe mechanisms dictate that the device be fully automatic and not prone to producing inaccurate results. Examples of appropriate fail-safe mechanisms are detection of inappropriate sample application such as the amount of sample used, bubbles in a sample, , calibration failure, electronic controls failure, etc. Automatic detection of such anomalies for waived tests should be performed by the test system without intervention on the part of the operator.

i-STAT Corporation believes that the alternative criteria used by FDA in determining that a test can be waived, namely that it will "pose no unreasonable risk of harm to the patient if performed incorrectly" should refer to the ability of the testing system to not report results if the system is not performing correctly, not, the value of the test in making a diagnostic decision. Firstly, there is a very real opportunity to confuse the waived category with the home use category. For tests cleared through the 510(k) route for the waived category, and not cleared through the home use route, it is clear that these are designated for health care professionals who are caring for a patient. Therefore, the risk of harm issue is not related to the patient interpreting the results, rather it must relate to the robustness of the testing system in providing a fail-safe approach that suppresses

results if the system is used incorrectly, as there is a health care professional interpreting the results before making a therapeutic decision. In other words, the risk of harm needs to be interpreted in terms of the test system in the hands of a health care provider rather than a lay person using the product at home. Secondly, technology has been shown to be capable of advancement in logarithmic fashion. To create a set of hard and fast rules and statistical "criteria" for this determination applicable to all possible devices would be a formidable task, quite possibly becoming obsolete due to technological advances in the future. Rather, the FDA should design flexibility into the criteria used to determine risk of harm to the patient. The FDA should allow for discretionary authority in this area. Manufacturers seeking waived status of their devices should be allowed to demonstrate the fail-safe design of their device to remove any concerns that may exist due to device failure. All devices are not necessarily created equal. Consideration should be allowed for use of industry experts to aid the FDA in this area.

#### Accuracy, Imprecision and Interferences:

Utilization of the current FDA 510k clearance process for Class II tests, assures that the issues of accuracy, precision and equivalency are addressed by the manufacturer for laboratory trained professionals. Only those areas in which untrained users can influence a system should be evaluated in terms of whether a system should fall under the waived category or not. For example, it would seem inappropriate to ask a non-laboratory trained user to verify the absence of interferences or to determine the accuracy of test systems by using highly complex reference methods.

i-STAT Corporation believes that the establishment of accuracy performance of a waived test is best left in the hands of professional laboratory personnel trained in these areas of laboratory analysis. That being said, a waived test in the hands of laboratory untrained health care workers should be capable of producing test results of equivalent accuracy as those results produced in a CLIA-licensed moderately complex laboratory. Comparison of the waiver test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, or to a previously cleared Class II medical device are various procedures that can be utilized to establish and document accuracy component of a waived test. With the exception of using the laboratory untrained user for generation of comparative results, accuracy studies do not belong in the hands of laboratory untrained users. As stated above, this is an area that is covered in the current 510(k) substantial equivalence submission and should not be unnecessarily repeated, except to demonstrate no deviation between laboratory and non-laboratory trained users.

i-STAT Corporation believes that standard precision estimate statistics (e. g. ANOVA) are adequate to determine precision characteristics in the untrained user setting. Comparisons between laboratory untrained and laboratory trained users (using identical materials) should demonstrate equivalent precision performance at both settings. Again, the imprecision should be the same in the hands of the laboratory untrained and trained user.

i-STAT Corporation feels that interference studies are appropriately conducted by trained professionals. The actual setting where interference testing is performed does not have influence on level or degree of interference performance. Interference performance tends to be a static event unrelated to operator technique, particularly on test systems that have fail-safe mechanisms for the detection of adequate specimen volume and other analytical parameters. Likewise, environmental studies or flex (stress) studies are appropriately performed under controlled laboratory conditions by the manufacturer. Whether of a waived status or not, these studies should be implemented based on appropriate risk analysis performed by the manufacturer.

#### Statistical Sampling:

To determine the right numbers of samples to be tested, consideration needs to be made of the variables to be studied and the intrinsic imprecision of the system being tested. There have been many schemes developed to address this area. On the one hand one could resort to the comparison of methods experiment in the traditional clinical laboratory based on the National Committee for Clinical Laboratory Standards (NCCLS). In this they recommend no less than 40 specimens be run in duplicate for the test method as well as the comparative method. The NCCLS guideline further states that consideration should be given to components such as range of measurement, reportable range, extended range, duplicate measurements, pooled specimens, sample sequence, and time and duration of the study. i-STAT finds that most labs have significant difficulty in complying with the NCCLS guidelines, often due to the difficulty of obtaining samples that cover the range. Due to the complexity of the NCCLS EP9-A protocol, i-STAT Corporation believes that more simplistic testing should be performed at proposed waived test sites than is recommended by NCCLS. On the other hand, the current FDA recommendations suggest that a minimum of 20 untrained operators at 3 separate sites be utilized for demonstration of waivability of a test. We believe that the precise study protocol should be statistically valid and does not need to conform to the current protocol. For example, if intra-site variability is more important, one may choose fewer than 20 people at each site and instead use more sites.

In order to keep the system flexible, FDA should not discount various other analytical performance quality specifications published in the field of clinical chemistry<sup>1</sup> but should refrain from enacting hard and fast rules of acceptability.

#### Samples to be Used:

The NCCLS EP9-A Approved Guideline for Method Comparisons<sup>2</sup> recommends that human specimens be utilized for a methods comparison experiment. They are often the best samples to

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<sup>1</sup> Fraser, C.G. and Petersen, P.H. Analytical Performance Characteristics Should Be Judged against Objective Quality Specifications. Clin. Chem. 1999; 45:321-323.

<sup>2</sup> Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline; EP(-A), Vol. 15, No. 17.

use when studying imprecision. Some artificial sample types (aqueous controls, human blood-based control, etc.) are notoriously difficult to use and therefore will naturally yield poorer test results in the hands of laboratory untrained users, but this says nothing of the system performance when used on patient samples – the real intent of the testing system.

On the other hand, use of artificially prepared specimens out any significant health risks to laboratory untrained personnel during the performance study phase of waived test studies, since commercial preparations are screened to be negative for the common infectious diseases. Therefore, the FDA should allow use of real or natural patient specimens and/or prepared human specimens, depending on the specific test(s) being studied. For tests that have special matrix requirements or other analytical requisites not attainable by use of artificial matrices, fresh human samples should be used. Most succinctly stated, the specimen type utilized should reflect as closely as possible the actual specimen type intended to be analyzed by the waived test. **The type of specimen used in studies designed to demonstrate equivalency between laboratory trained and laboratory untrained users should represent the most appropriate specimen matrix for the test under consideration. Use of inferior or incompatible specimen materials will produce misleading information in some cases, particularly systems designed for use with whole blood.**

#### Reading Level and Means of Communicating Instructions:

The background of untrained users should be carefully considered. i-STAT Corporation feels that healthcare professionals outside of the traditional area of the clinical laboratory are capable of using certain waived tests. Paramedics, firefighters, physicians, phlebotomists, physician assistants, nurses, visiting nurses and nurse practitioners are examples of healthcare personnel capable of utilizing technology in many tests. While these personnel are not trained in the strict science of laboratory medicine, they are generally trained in the areas of universal precautions and phlebotomy. As such, they are proficient at obtaining and handling patient specimens, dressing and treating wounds and the general hygiene practices consistent with quality patient care in the area of infection control.

i-STAT Corporation believes that the background of users of waived tests should depend on the application of the test system. For example, the educational level for systems intended for waived tests in the healthcare field include the physician office, paramedic, visiting nurse and visiting respiratory therapist settings should be of at least a high school education. The personnel in these settings typically hold education levels higher than that of the 12<sup>th</sup> grade. But in some applications, a lower level of schooling may be anticipated. Being stringent as to the reading level for all waived tests, and especially requiring a grade 7 standard, applies the standards used for clearance of a home use test to that for a waived test. Is this appropriate? For example, it requires one not to use the word “specimen” in the instructions as this is not a grade 7 word. Yet anyone one of the health care list mentioned in the paragraph above would use the word specimen when referring to a whole blood sample.

Instructional materials that are capable of educating and instructing users in the health care profession should result in the education of "untrained laboratory users" such that performance equal to that of trained professional laboratory users is demonstrated. Use of state-of-the-art instructional materials, such as VCR videos, World Wide Web presentations and other PC-based graphical presentations should be encouraged by the FDA. For example, interactive Web sites have the ability to not only monitor testing activity but can instantaneously provide users with up to the minute instructions, notices and new practices and recommendations for the waived test system being used. Today's pervasive presence of the World Wide Web makes this technology available today. The FDA should allow and encourage device manufacturers to disseminate information in this manner.

### **CONCLUSION:**

The FDA should make sure that the rules for categorizing tests as waived should be clearly articulated, based upon sound scientific principles that can be found in the literature. This will allow manufacturers to design systems for the waived category to ensure that the highest quality of testing together with the widest access to state-of-the-art testing for patients. Better access to testing will improve the timeliness and accuracy of diagnosis, thus improving care. The patient benefits and the practice of medicine is better for it

The attached presentation is that of Michael Groves Ph.D., Vice President of International Sales and Operations, i-STAT Corporation, East Windsor, NJ. These slides were presented to the FDA Public Workshop, "Review of the criteria used to determine whether specific laboratory tests are waived from certain requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), August 14 – 15, 2000, held in Gaithersburg, VA.

Comments for  
Division of Clinical Laboratory  
Devices, Public Workshop,  
August 14-15<sup>th</sup>, 2000

Michael R. Groves Ph.D.  
Vice President, International Sales and  
Operations

i-STAT Corporation

# Congressional Intent with CLIA 88

- Resolve inter-laboratory variation
- Make sure the right level of oversight is applied:
  - ◆ QC
  - ◆ PT
- Make sure the appropriate level of personnel are involved in the testing

# Manufacturers Response

Design systems that are intrinsically stable with no user influence on results:

- No user calibration, or adjustment
- ⇒ User results are a subset of the factory finished goods data set
- No sample manipulation by user
- Design a Quality Control System appropriate to the technology (Electronic Quality Control)

# Questions to Ask of the System

- Can the personnel affect the results?
  - Can the application of traditional liquid QC provide information that alters the acceptance of the results?
  - Can PT detect inter-laboratory variation?
- ⇒ If the answers to all three of these is no, then why burden the user with requirements in these areas?

Lab A

Lab C

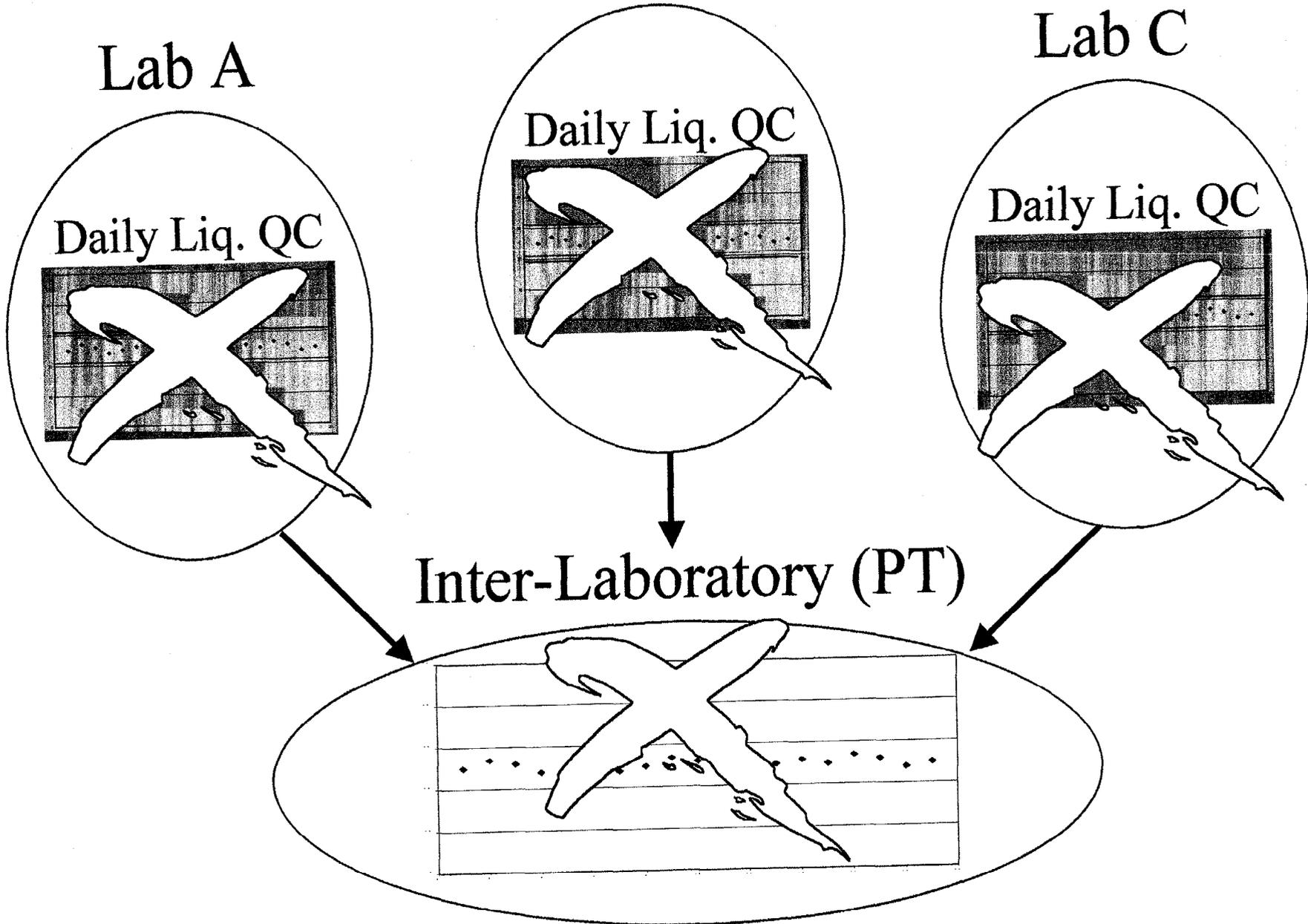
Lab A

Daily Liq. QC

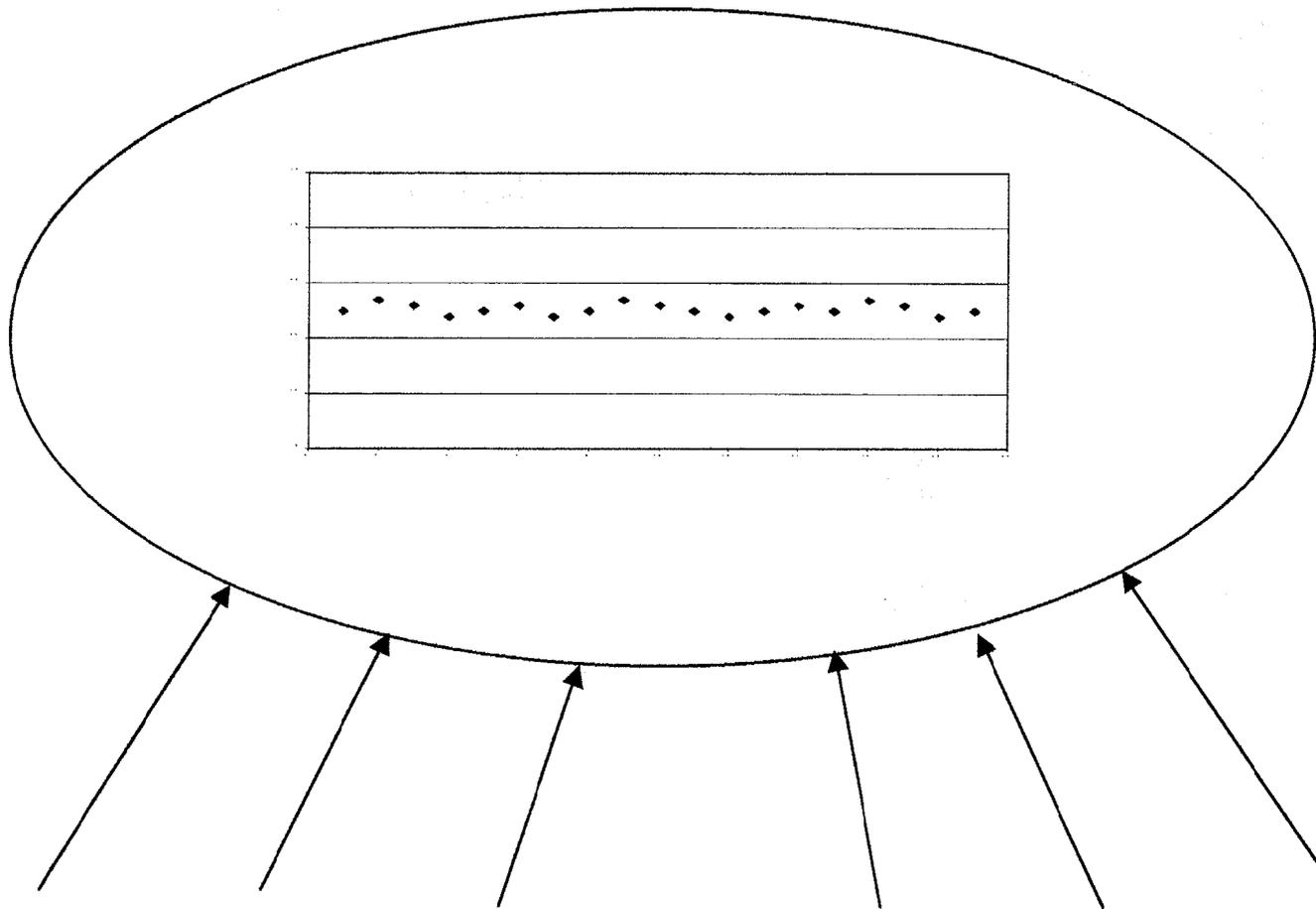
Daily Liq. QC

Daily Liq. QC

Inter-Laboratory (PT)

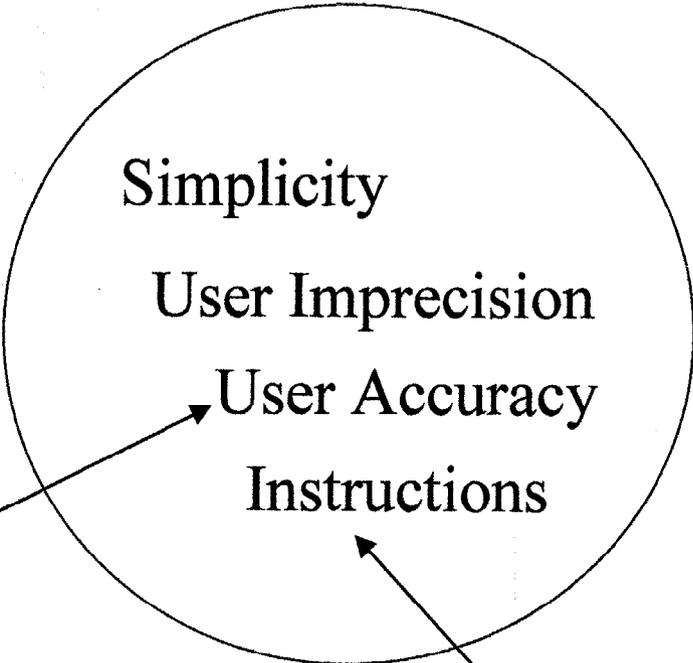
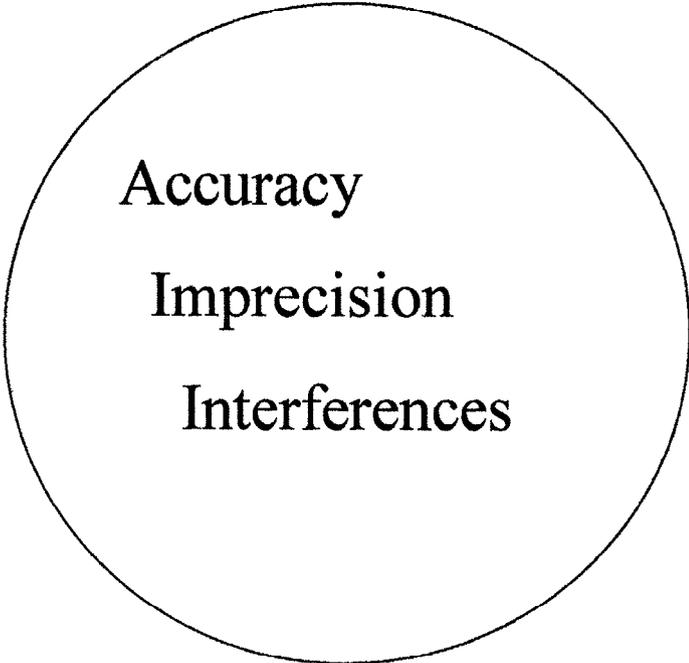


# Manufacturer's PT ??



# 510 k Process

# Waived Category

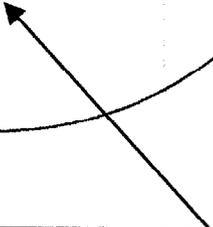
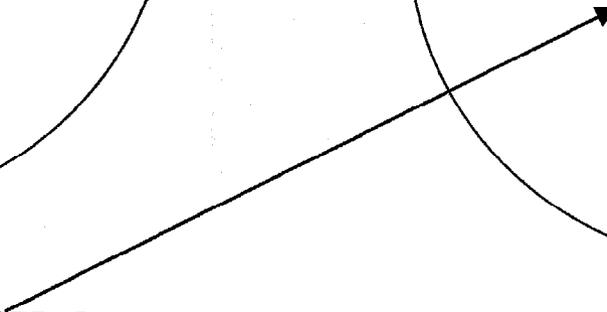
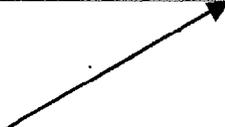


Versus a CLIA Mod. Or  
High Complexity Lab

7<sup>th</sup> Grade Level  
Written or Verbal?

Real Specimens  
or Artificial?

Web or Video?



# Statistical Validity of Study Data?

Intra-site Variation – 20 Users each site

- Statistically Valid
- Could be difficult to obtain
- Real world?

Inter-site Variation – 3 Sites

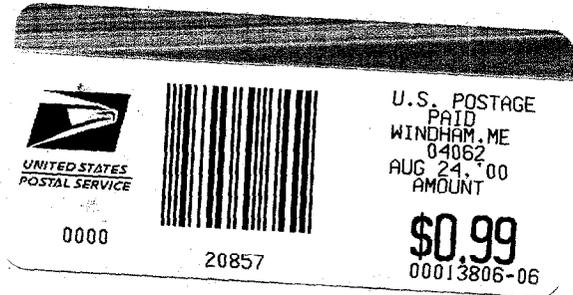
- Statistically Valid?

Proposal

- 5 Sites & 5 Users?

FIRST CLASS

FIRST CLASS



# FIRST CLASS MAIL

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TO:

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