Risk Management in IVD Producer Relation between manufacturer and user

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IVD Manufacturer Requirements

International Standard ISO 13485-2016

Medical Devices Quality Management Systems
Requirements and Regulatory purposes

7 Product realization

7.1 Planning of product realization

The organization shall plan and develop the processes needed for product realization. Planning of product realization shall be consistent with the requirements of the other processes of the quality management system (see 4.1).

In planning product realization, the organization shall determine the following, as appropriate:

a) quality objectives and requirements for the product;

b) the need to establish processes, documents, and provide resources specific to the product;

c) required verification, validation, monitoring, inspection and test activities specific to the product and the criteria for product acceptance;

d) records needed to provide evidence that the realization processes and resulting product meet requirements (see 4.2.4).

The output of this planning shall be in a form suitable for the organization's method of operations.

The organization shall establish documented requirements for risk management throughout product realization. Records arising from risk management shall be maintained (see 4.2.4).

NOTE 1 A document specifying the processes of the quality management system (including the product realization processes) and the resources to be applied to a specific product, project or contract, can be referred to as a quality plan.

NOTE 2 The organization may also apply the requirements given in 7.3 to the development of product realization processes.

NOTE 3 See ISO 14971 for guidance related to risk management.

Purposes

Ensuring product safety

Decreasing the systems strategic costs as a result of identifying and improving problems before sale

Reducing costs by providing an appropriate instruction in order to understand the reason and the time of error occurrence

Reducing the Legal responsibilities against the product

Scope

This plan should be support from elimination of risk in following steps:

Design Process

Production Process

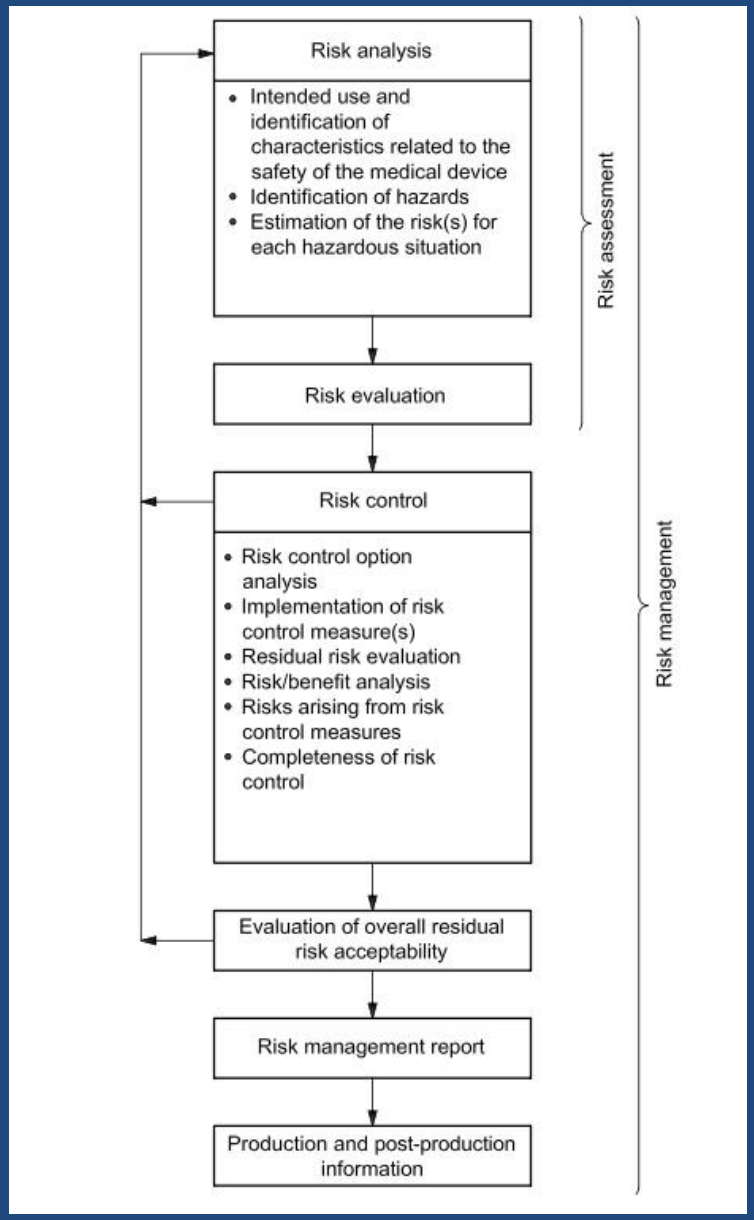
User

Supplier management

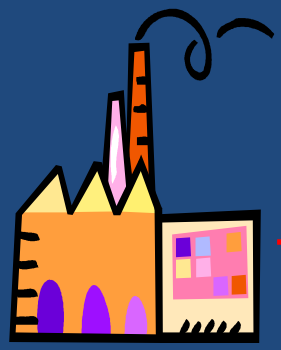
International Standard

ISO 14971

Medical Devices – Application of Risk Management to Medical Devices


Risk analysis
• Intended use and identification of characteristics related to the safety of the medical device
• Identification of hazards
• Estimation of the risk(s) for each hazardous situation
Risk evaluation
Risk control
• Risk control option analysis
• Implementation of risk control measure(s)
• Residual risk evaluation
• Risk/benefit analysis
• Risks arising from risk control measures
• Completeness of risk control
Evaluation of overall residual risk acceptability
Risk management report
Production and post-production information
Risk assessment
Risk management

Assess the Risk of Harm Due to Failures



Defective IVD:
Hazard

Incorrect or delayed test result:
Hazard

Incorrect or delayed medical treatment:
Hazardous Situation

Injury or death:
Harm

ISO 14971:2007(E)

Annex H
(informative)

Guidance on risk management for *in vitro* diagnostic medical devices

Intended use

the measurement system, analyte, sample matrix, examination procedure (qualitative, semi-quantitative or quantitative), type of operator and site of use.

quantitative examinations for beta-human chorionic gonadotropin (ß-hCG) concentration for serum, plasma or urine samples.

Indications for use

the medical applications and patient populations

ß-hCG results can be used for detecting pregnancy, for screening pregnant women for fetal Down's syndrome, and for monitoring certain cancers. Each medical application may have different requirements for measurement sensitivity, specificity, precision and trueness.

H.2.2 Identification of possible use errors

H.2.2.1 Use errors

Use errors include actions not intended by the manufacturer, such as procedure shortcuts, optimization attempts and improvization, as well as omissions of actions intended by the manufacturer, such as those prescribed in the instructions for use.

– use of an IVD medical device with an inappropriate calibrator, reagent, instrument or sample matrix
– attempt to optimize an examination procedure in order to improve its performance characteristics
– abbreviation of an examination procedure (taking “shortcuts”)
– neglect of instrument maintenance
– operation in adverse environmental conditions

H.2.3 Identification of characteristics related to safety

H.2.3.2 Performance characteristics of quantitative examination procedures

precision (imprecision)
trueness (bias)
analytical specificity
Detection limit

Performance requirements depend on the medical application. A falsely high or falsely low result can lead to an incorrect diagnosis or delayed treatment, and the consequent harm to the patient could depend on the concentration of analyte and magnitude of bias.

H.2.3 Identification of characteristics related to safety

H.2.3.3 Performance characteristics of qualitative examination procedures

Qualitative examination procedures are only intended to detect the presence or absence of an analyte.

Diagnostic sensitivity
Diagnostic specificity

A positive result when the analyte is absent or a negative result when the analyte is present can lead to incorrect diagnosis or delayed treatment and to harm to the patient.

H.2.3.4 Dependability characteristics

When physicians depend on IVD examination results to help make urgent medical decisions, such as in an intensive critical care setting, timely results can be as important as accurate results. Failure to produce a result when it is needed could result in a hazardous situation.

H.2.3.5 Ancillary patient information

In some cases, examination results can require demographic information about the patient, as well as pertinent information about the sample or its examination for proper interpretation:

sample type

sample description

measurement units

reference intervals

age

gender

genetic factors

which might be entered manually by a laboratory analyst or automatically by a laboratory computer system

If an IVD medical device is designed to report ancillary information with the examination result, failure to associate the correct information with the examination result could affect the proper interpretation of the result and lead to a hazardous situation.

H.2.4.3 Identifying hazards in fault conditions

Failure modes that can result in not meeting the performance characteristics required for medical use should be considered when identifying IVD hazards in fault conditions:

- within-batch inhomogeneity
- batch-to-batch inconsistency
- non-traceable calibrator value
- non-commutable calibrator
- non-specificity (e.g., interfering factors)
- sample or reagent carryover
- measurement imprecision (instrument-related)
- stability failures (storage, transportation, in-use)

H.2.4.3 Identifying hazards in fault conditions

Failure modes that can result in delayed results in urgent care situations should be considered when identifying IVD hazards in fault conditions:

- **unstable reagent**
- **hardware/software failure**
- **packaging failure**

H.2.4.3 Identifying hazards in fault conditions

Failure modes that can result in incorrect patient information should be considered when identifying IVD hazards in fault conditions:

- **incorrect patient name or identification number**
- **incorrect birth date or age**
- **incorrect gender**

H.2.4.4 Identifying hazards in normal use

Incorrect results can also occur in normal use, even when the IVD medical device meets the performance characteristics claimed by the manufacturer.

***uncertainty of measurement**

*** biological variability of patient samples**

***choice of a cut-off value or other factors.**

***unexpected influence in the sample matrix**

*** natural heterogeneity of the analyte: antibodies and other proteins in blood samples are mixtures of different isoforms**

H.2.5.2 Estimating severity of harm

The medical use of an IVD examination result determines the potential harm that an incorrect result can cause to a patient.

Estimating the severity of harm requires an understanding of the medical use of the IVD examination results, the analytical performance requirements for each application and the extent to which medical decisions are based on IVD examination results.

H.2.5.3 Estimating probability of occurrence

the probability that use of an IVD medical device will result in harm depends on the cumulative probabilities associated with a series of events.

– the probability that the IVD medical device will produce an incorrect result
– the probability that the laboratory will fail to detect the result as incorrect and will report the incorrectresult
– the probability that the physician will fail to recognise the result as incorrect and will be led to take (or not take) action
– the probability that the patient will be harmed by the physician's action or inaction

Laboratories can recognize a result as incorrect for reasons such as:

– the quality control system identified a change in performance of the examination procedure
– the value of the measured property is not compatible with current situation
– the result exceeded a critical limit that required the examination result to be verified
– the difference compared to the patient's previous result exceeded an expected or plausible amount.

When estimating the probability of occurrence, consider that not all laboratories have effective detection systems that can prevent incorrect results from being reported.

Physicians can recognize a result as incorrect for reasons such as:

- **the result is physiologically impossible**
- **the result is inconsistent with the patient's clinical status**
- **the result is contradicted by other data**

H.2.5.4.2 What is the possibility that the incorrect IVD examination result would be detected by a user/laboratory?

– Are control materials provided with the IVD medical device?
– Are controls integrated into the device to detect the fault condition?
– How effective would the controls be in detecting the fault condition?
– Are there other quality assurance measures that might detect the incorrect result (e.g., critical value system, plausibility checks)?
– Would error messages allow a user to correct the problem and obtain a valid examination result upon reexamination?

For example, the message "not enough blood" on an instrument for self-testing is intended to prompt the user to repeat the examination.
– If the device is intended for laboratory use, do laboratories have effective systems for detecting such an incorrect result?

What is risk?
Industrial Model

Risk - Function of 3 factors:

Occurrence- Probability or frequency of failure

Detection-Probability that failure will be detected before harm

Severity-Consequence or harm

Risk Control

Risk control option analysis

Often there will be more than one way to reduce a risk. There are three mechanisms listed:

a) inherent safety by design
b) protective measures in the medical device itself or in the manufacturing process
c) information for safety

Inherent safety by design

- precision of the measuring system
- trueness of the calibrator values
- analytical specificity of IVD reagents (e.g. better antibody)
- detection limit or quantitation limit of the examination procedure
- reliability of the instrument (e.g. prevention of spurious results)
- discrimination between positive and negative samples
- automation of mistake-prone procedural steps
- positive sample identification (e.g. bar-coding)
- ease of use (e.g., as identified by studies of human factors)

Protective measures

If improving the design of the IVD medical device is not practicable, then perhaps additional controls can be incorporated into the device to detect conditions that produce incorrect results

– sample integrity checks to detect unacceptable samples (e.g., hemolysed)

– removal of foam (if the sampling device has a liquid level sensor) or fibrin clots from the sample

– on board sensors and software checks to detect adverse system conditions (e.g., incorrect temperature, spectrophotometer drift, plugged pipetting mechanism)

– built-in controls to detect calibrator, reagent or instrument failures

– alarms, error messages or algorithms that suppress incorrect results

– plausibility algorithms to identify improbable results

Information for safety

Performance characteristics

Laboratory directors and healthcare providers need to know the relevant performance characteristics in order to determine if the IVD medical device is suitable for their use. This information is supplied by the manufacturer.

– analytical specificity (e.g., effects of interfering or cross-reacting substances)
– trueness (i.e., acceptable bias)
– precision
– detection limit or quantitation limit
– accuracy (combination of precision and trueness)
– diagnostic sensitivity (fraction of true positive results in patients with disease)
– diagnostic specificity (fraction of true negative results in patients without disease)

Information to prevent production of incorrect results

Instructions for use, procedural limitations and environmental specifications are necessary to help users prevent incorrect (hazardous) results:

– sample collection, storage and preparation requirements
– known interfering substances
– validated measuring interval
– warnings about improper use that can contribute to incorrect results
– limitations regarding specific patient populations
– warnings about inappropriate clinical conditions or inappropriate sample types
– proper cleaning methods
– preventive maintenance procedures and maintenance intervals;
– reagent storage requirements and expiration date

Kit Name:								
Design								
Date:		**Revision: 01**	**Revision Date:**				**Prepared by:**	
Hazard	Characteristic	Known or suspected Problem	Potential Effects	Severity	Occurrence	Risk Index	Recommended Action	Comments
1a	Material/component including biological and chemical component	Chemical material (stop solution)	Burn or corrosive	1	2	2	Use of safe material or diluted Advisory notice in IFU	
1b		Biological material	health risk to user	5	2	10	Use of negative sample for preparation of reagent, use of recombinant antigen, , Inactivation of biological source, advisory notice in IFU	
1c		Variability in Antibody	Failure product	4	2	8	Raw material QC	
2a	Reagents	Microbial Contamination or chemical Contamination	Instability of conjugate and control	4	4	16	Microbial assessment, filtration, adding preservative	
2b			Colour change in Chromogen	4	3	12	Stability testing Visual inspection after production Use very clean vials	
3a	Measurement or Detection	Different serotype	False Negative	5	3	15	Use of Antibodies to detect all serotype	
3b		Different Genotype	False Negative	5	3	15	Use of Antibodies to detect all genotype	
3c		Interference substance	False positive	5	2	10	Comparison test Interference test	
3d		Interference Antibody Heterophile ,disease state or physiologic	False positive	5	4	20	Comparison test Interference test	
3e		Virus Type	False Negative	5	5	15	Use of antibody to detect type Use of panels for validation	
4a	Environment Influences	storage temperature condition	Instability	2	5	10	Accelerated Stability Full term Stability In use Stability Label and IFU	
4b		handling situation	Instability	2	5	10	Simulation stability test Packaging material QC	

Status at Initial										Status After Risk Minimization		
Hazard	Potential Failure	Potential Effect	Severity	Potential Causes of Failure	Current Control	Occurrence	Risk Index	Recommended Action	Action owner	Severity	Occurrence	Risk Index
U1-Assay method	Acceptable sample is not define	Inaccuracy or imprecision	4	Untrained operator	IFU recommendation	2	8	Clear recommendation in IFU	QA, Production	4	1	4
U2-Assay method	Reagent Preparation (Wash solution)	Inaccuracy or imprecision	2	Untrained operator	IFU recommendation	3	6	Use additional Label	Production, RD	2	2	4
U3-Essential accessories	Reader washer or micropippet are not calibrated	Inaccuracy or imprecision	3	Poor GLP	IFU recommendation	2	6	Recommended to use ELISA Check kit and training on Lab site	Sale and QA	3	1	3

How Mitigate Risk in Industry

Occurrence : Design for Safety

Disclose safety characteristics

Detection: Built in control mechanisms

Provide alert to identify problems

Severity : Provide instruction for safety use and precaution for use errors

Inform laboratory of limitation and advise how to monitor performance

ISO 13485 : 3.6

labelling

written, printed or graphic matter affixed to a medical device or any of its containers or wrappers, or accompanying a medical device, related to identification, technical description, and use of the medical device, but excluding shipping documents

Table H.1 — Examples of possible use errors and labelling risk controls

Use error	Risk control
Non-calibrated instrument	Specified calibration interval
Reagents that have lost reactivity	Expiration date on reagent packaging
Inadequate equipment maintenance	Maintenance instructions
Mixing of incompatible reagent lots	Lot identification and instructions
Examination of non-commutable body fluids	Specification of suitable sample types
Incorrect sample preparation	Sample preparation instructions
Incorrect reagent storage	Storage requirements, including critical factors (temperature, light, moisture, etc.)
Confusion of reporting units (e.g., mmol/l or mg/dl)	Units displayed or printed with each result
Improper instrument installation	Installation instructions; qualification procedure
Incorrect instrument operation	Operating instructions, with critical steps identified
Incorrect sample dilution	Dilution requirements, including acceptable diluents

Instruction for use

Introduction or Explanation of assay
Principles
Kit content
Warning & Precaution
Specimen collection & Handling
Procedure (materials required, notes)
Assay Procedure (preparation of reagent)
Quality Control or validation
Calculation
Limitation
Expected Values
Performance characteristics
References

Laboratory - Manufacturer Partnership

- **Developing a quality plan surrounding a laboratory device requires a partnership between the manufacturer and the laboratory.**
- **Some sources of error may be detected automatically by the device and prevented, while others may require the laboratory to take action, such as analyzing surrogate sample QC on receipt of new lots of reagents.**
- **Clear communication of potential sources of error and delineation of laboratory and manufacturer roles for how to detect and prevent those risks is necessary.**

What is Risk Management in Clinical Lab?

Use of policies / procedures designed to minimize the occurrence of patient harm due to an incorrect test result

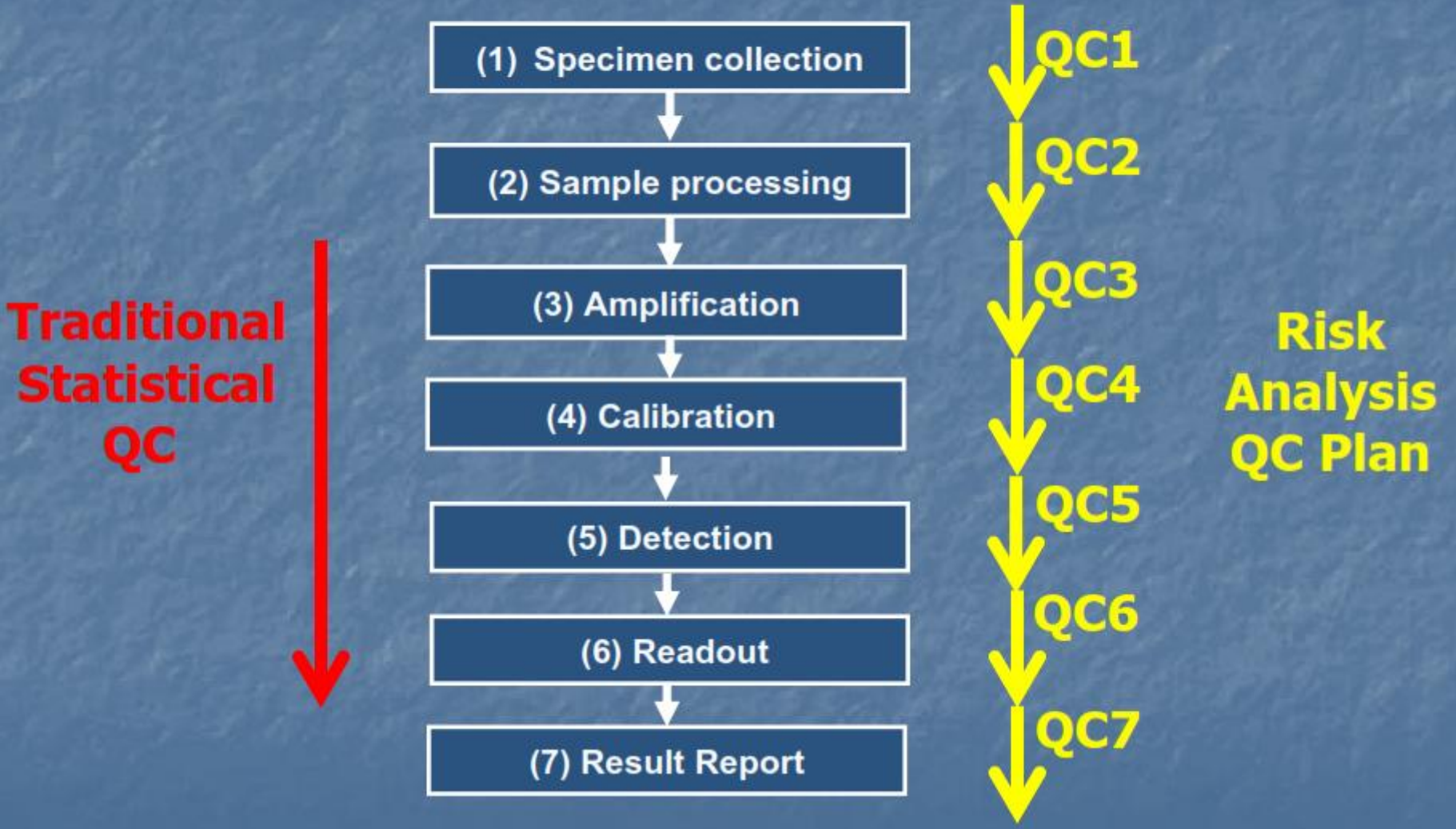
- **Run QC material to ensure the instrument is performing properly**
- **Monitoring refrigerator temp where reagents are stored**

Example QC Plan

QC Plan	Frequency	Recovery	Disclosure
Analyst/operator controls			
Standard Operating Procedure	Yearly SOP review	Director review	No
Operator training	Every operator	Supervisor review	No
Operator checklists	Daily	Supervisor review	No
System maintenance	Manuf. Schedule	Manuf. Repair	No
Operator competency	Yearly	Re-train	No
Built-in analyzer controls			
Electronic checks	Manuf.	Manuf. Instructions	No
Function tests	Manuf.	Manuf. Instructions	Sample condition
Process tests	Manuf.	Manuf. Instructions	No
Calibration checks	Manuf./Reg.	Supervisor review	No
Stable control materials			
Statistical QC	Startup + Monitor	TS guidelines	No
Trueness control	Calibration	TS guidelines	No
Periodic EQA, PT	3/year	CA plan	No
Patient data analysis			
Implausible values	Each sample	Repeat test	Yes

TS = Trouble-Shooting; CA = Corrective Action

SQC vs Risk Analysis



Thank You

SQC and Risk Analysis