IMPACT of CALIBRATION on MEDICAL DEVICES
Medical Devices

- The Comprehensive Review of Potential Problems
- Establish Devices Alert & Patients safety
  - Reassurance
- Improving Systematic Approach
- Signify Metrology & Calibration aspect
Definition of Medical Devices

- any instrument, apparatus, appliance, or in combination, for its intended to be used for human beings for the purpose of:
  - diagnosis, prevention, monitoring, treatment of disease, injury or handicap, investigation, replacement of the anatomy or of a physiological process, control of conception

  electrical devices IEC/EN 60601 standard series
to acquire CE marking; EN ISO 14971 standard

Ref: COUNCIL DIRECTIVE 93/42/EEC
1999 Institute of Medicine report:

- Estimated 44,000 – 98,000 medical error deaths annually
- More than from highway accidents, breast cancer, or AIDS
<table>
<thead>
<tr>
<th>Root Causes of Sentinel Events (all categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Errors</strong></td>
</tr>
<tr>
<td><strong>Op/Post-op</strong></td>
</tr>
<tr>
<td><strong>Perinatal Deaths</strong></td>
</tr>
<tr>
<td><strong>Restraint Deaths</strong></td>
</tr>
<tr>
<td><strong>Transfusion Events</strong></td>
</tr>
<tr>
<td><strong>Ventilator Events</strong></td>
</tr>
<tr>
<td><strong>Wrong Site Surgery</strong></td>
</tr>
<tr>
<td><strong>Anesthesia-related Criminal Events</strong></td>
</tr>
<tr>
<td><strong>Delays in Treatment</strong></td>
</tr>
<tr>
<td><strong>Elopement</strong></td>
</tr>
<tr>
<td><strong>Infection-associated</strong></td>
</tr>
<tr>
<td><strong>Inpatient Suicides</strong></td>
</tr>
<tr>
<td><strong>Maternal Deaths &amp; Injuries</strong></td>
</tr>
</tbody>
</table>
Medical devices “use-errors”

1. Evidence medical errors to patient injuries and deaths.
2. Risk from
   - poor design of medical devices
   - how devices used and maintained.

User error means user made a mistake.
Medical devices “use-errors”

occur as a consequence of

• Operator error
• Poor interface design
• Incomplete labeling
• Incorrect documentation
• Misuse of the device
• User-device interaction
Sentinel Event Trends:
Medical Equipment Events Reported by Year

S. E. Alert #21
“Medical Gas Mix-ups”
July 2001

S. E. Alert #15
“Infusion Pumps”
November 2000

Medical Device Problem Reporting

- injuries and deaths related to
  - implants,
  - microprocessor-based medical devices,
  - supporting electronic, electrical equipment,
  - supporting pneumatic equipment
  - mechanical devices (reusable and disposable).
• burns from the fiber-optic lights used on endoscopes and headlamps
• anesthesia equipment misconnected breathing circuits and ventilator leaks
• misleading displays on medical devices
  - infusion pumps making serious errors,
  - misprogramming medication doses.

WALLSTREET JOURNAL  DECEMBER 23, 2008
It is only when medical devices go wrong that remind you how powerful they are.
- In India: Total No. of different kinds med-devices ~ 1.5 million, industry-size is ~1.5 Billion $

- Value of goods worldwide 260 Billion $
  - Line up to increase by 15-20% per year
  - About 5 Billion US Dollar by the year 2012
  - a larger number of patients need to be protected.
PROBLEMS

- Market always made to reduce costs
- Immoral manufacturers/importers try to move unsafe equipment's in.
- Machines are used inappropriately and without proper maintenance, calibration etc.
- Some electro medical equipment were imported without permission, license or any restriction
- No product-approvals of their origin.
- Freely-sold to healthcare facility
THE ESSENTIAL ELEMENTS

- No absolute safety guaranteed.
- It is a risk management issue
- Device effectiveness must be considered throughout its life span.
- Responsibility shall be shared by stakeholders

  Doctors
  Manufacturing Industry
  Hospital facility providers
  Insurance companies
VITAL PRINCIPLES

- Design and manufacture of devices must conform with safety principles
- Long term safety should be ensured
- Benefits of the devices must outweigh any side effects
- Medical devices should be useful for the intended purpose
FDA classifications

- Classified 1,700 different types of devices and grouped into 16 panels.
- Each type is assigned to one of three classes based on the level of safety and effectiveness.

Device Class and Regulatory Controls

- **Class I** General Controls (lowest risk)
  - With Exemptions (Limitations under 21 CFR Parts 862-892.9)
  - Without Exemptions (required 510k for marketing)

- **Class II** General Controls & Special Controls
  - With Exemptions
  - Without Exemptions (required premarketing submission 510k)

- **Class III** General Controls & Premarket Approval (greatest risk)
  - Application required for FDA clearance
All devices must:

- meet the essential requirements (irrespective of the class of the device)
- be subject to the reporting requirements (under the medical device vigilance system)
- (be CE marked)
510(k) Review of the new device

the evaluation of the performance compared to the predicate, including:

▪ the bias or inaccuracy;

▪ the imprecision:

▪ specificity and sensitivity.
Class

- Non invasive devices: I, IIa, IIb, III
- Invasive devices: I, IIa, IIb, III
- Active devices: I, IIa, IIb, III
ALWAYS CONFIRM CLASSIFICATION BY READING ALL RULES

Non invasive devices

Rules 1, 2, 3, 4

Invasive devices

Rules 5, 6, 7, 8

Active devices

Rules 9, 10, 11, 12

Special rules

Rules 13, 14, 15, 16, 17, 18
All non-invasive devices are in Class I.

Body liquid collection devices such as urine collection bottles, non-sterile dressings, plaster of Paris, cervical collars, hospital beds, wheelchairs, stretchers, stethoscopes, electrodes for EEG or ECG.
All non-invasive devices channeling or storing blood, body liquids or gases for the purpose of administration into the body are in **Class IIa**:
- infusion pump,
- Syringes pumps,
- tubing for anesthesia,
- breathing circuits,
- pressure limiting devices.
InVitro Diagnostic product (IVD)

- are those medical devices, reagents, and systems intended for use in diagnosis of disease
- examination of specimens taken from the human body.

21 CFR 809.3

Regulatory Authority:

- FDA act section 210(h),
- Public Health Service Act. section 35,
- Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.
FDA classifies IVD products

- to Class I-III according to the regulatory control level of safety and effectiveness.

General purpose reagent (GPR)

-a chemical reagent that has general laboratory application
- used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and
- is not intended for a specific diagnostic application
THE EU MEDICAL DEVICE DIRECTIVES

The Medical Devices Directive
(93/42/EEC, OJ L169: from bandages, tongue depressors, thermometers to contact lenses, stethoscopes, splints, heart valves and imaging equipment)

The In-Vitro Diagnostic Medical Devices Directive (IVDD) (98/79/EC OJ L331: reagents, control standards, test-kits, pregnancy test kits, Hepatitis B test kits)

The Active Implantable Medical Devices Directive (AIMDD)
(90/385/EEC OJ L189 p0017-0036): active implants e.g. heart pacemakers

Most countries have transposed these directives into a single national legislation (e.g. UK Medical Devices Regulations 2002)
MEDICAL IMAGING DEVICES  (*IN VIVO DIAGNOSIS*)

- X-ray projection imaging
- Computerised Tomography (CT)
- Ultrasound, Doppler imaging
- Magnetic resonance imaging (MRI)
- Radionuclide imaging
- Thermography
- *origin interactions with matter of atoms and nucleus* (*Ionizing radiation, radioactivity, acoustics, electromagnetic*).
RADIOTHERAPY DEVICES

- X-ray and electron, beams from accelerators
- Gamma-ray beams from isotope Co-60
- Brachytherapy treatment
- Dosimeters
- We used ionizing radiation, properties of atom nucleus, radioactivity, biological effects of ionizing radiation
CARDIAC-CATH LAB.
MEDICAL LABORATORY DEVICES

- sample separation, centrifugation
- electrophoresis, pH
- cell counters, spectrophotometers
- flow cytometer, microscopy
- HPLC (chromatography)

Clinical chemistry
- Haematology, immunology
- scintillation systems, genetic analysis

We measure

- biopolymers structure, galvanic cell
- properties of water and electrolytes, electric properties of living matter,
- sedimentation of particles, light absorption
Clinicians’ require rapid access to information to support critical care decisions.

- Microelectronics and biosensor tools using near bedside in a diminished form.
  - blood tests at the patient's side
  - portable ultrasound imaging devices
PHYSIOLOGICAL MEASUREMENT DEVICES

- Instruments for measuring physical and chemical variables in vivo
  - Thermometers
  - Cardiovascular physiology:
    - blood pressure monitors, flowmeters, Doppler US
  - Electrophysiology: ECG, EEG, EMG
  - Audiology and ophthalmology
  - Respiratory physiology:
    - spirometers, pulse oximetry, impedance pneumograph...
  - Endoscopes

We measure

thermodynamics, hydrodynamics, bioelectric, sound and light, etc.
Maximum Permissible Uncertainty?
PHYSICAL THERAPY DEVICES

- Electrotherapy
- UV and IR therapy
- Shortwave diathermy
- Ultrasound therapy
- Laser therapy

We measured & used

*Biological interactions of ultrasound, electromagnetic fields, electric current, infrared, visible and ultraviolet light, laser principle*
ENDOSCOPY
INTENSIVE CARE
WE measured & used

Biological interactions of ultrasound, electromagnetic fields, electric current, infrared, visible and ultraviolet light, laser principle, low temperatures, acoustic shock waves
LAPAROSCOPIC SURGERY
Robotic device for knee prosthesis implantation
Implants

Gastric antireflux prostheses
Breast prostheses
Cardiac valve prostheses
Cerebrospinal fluid shunts
Defibrillators
Infusion ports

Orthopedic Implants
Pacemakers
Stents
Tubal ligation clips
Vascular prostheses
Vena cava filters
Microprocessor-Based Devices

- increasing use of **microprocessors and software** in both implanted and external medical devices.
  - Programmable pacemakers,
  - long-term portable ECG recorders, and
  - ECG arrhythmia detection monitors,
    eg. cardiac arrhythmia detection software.
- accidents related to both hardware and software problems (rare and transient).
Pacemaker Implantation
to control a slow heart beat
Radio-frequency Catheter Ablation is used for patients who are experiencing palpitation caused by an abnormal electrical impulses in the heart.
PROSTHETIC DEVICES – “ARTIFICIAL ORGANS”

Artificial heart  Cochlear implant  Retinal implant

Cardiopulmonary bypass  Ventilator
Stents
- inserted into the damaged blood vessels, oesophagus etc.
- made of a metal—nitinol, which adopts the intended shape when heated to body temperature.
Suction catheter
I.V. cannulae
Umbilical cord clamp
Disposables

- following are involved in accidents:

  Anesthesia admin kits
  Breathing circuits
  Catheters
  Defibrillator paddle pads
  Embolectomy catheters
  Endotracheal tubes
  Sump pumps
  Suture needles
  Tampons
  Tracheostomy tubes
  Heart-lung bypass unit
  Hypodermic needles
  Infusion pump sets
  IV sets
  Luer-lock connectors
  Nasal oxygen cannulae
  Oxygen masks
HOME DEVICES (DEVICES FOR SELF-TESTING)

- 'self-testing`: device to be used by persons at home
  - thermometers,
  - BP-measuring
- test kits
  - used by patients
  - pregnancy,
  - glucose test etc)

Blood glucose meter
medical devices is necessary to inspect

- necessity of inspection applies to those devices that are in a direct contact with a patient can affect a patient's health or treatment.

- ensures the required level of effectiveness
- impact on risk arising from device malfunction
- preventive maintenance and quality control including calibration of the device appropriate for users

  - Faulty devices cause false diagnoses
  - unnecessary refer to special treatment or even worse
<table>
<thead>
<tr>
<th>Device Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Design/labeling error</td>
</tr>
<tr>
<td>- Device failure</td>
</tr>
<tr>
<td>- Device interaction</td>
</tr>
<tr>
<td>- Failure of accessory</td>
</tr>
<tr>
<td>- Software deficiency</td>
</tr>
<tr>
<td>- <strong>Improper maintenance, calibration, testing, repair</strong></td>
</tr>
<tr>
<td>- lack or failure of incoming inspection</td>
</tr>
<tr>
<td>- Improper modification</td>
</tr>
<tr>
<td>- Manufacturing error</td>
</tr>
<tr>
<td>- Packaging error</td>
</tr>
<tr>
<td>- Random component failure</td>
</tr>
</tbody>
</table>
Problem:
-Parents of infant used digital thermometer at home to check child's temperature read as 102.5. Family presented to ER with infant.

-In ER setting temperature obtained was 98.9. Sepsis work-up performed, including multiple lumbar puncture attempts. IV antibiotics administered.

-Parents brought thermometer in from home. When tested, the infant temperature was 103 on home thermometer and 99.2 on the hospital thermometer.

Model # KD-192
Problem:

- hospital using programmable drug library Infusion Pumps.
- Found multiple instances of the pumps "losing" their drug libraries.
- In troubleshooting the issue, B. Braun did send a software upgrade version which has not fixed the problem.
- the pumps running out of battery power. & as we have gotten a bad batch of batteries,
Problem:

- Infant warmer ignited while unit was in the Operating Room pending delivery of the infant. The unit was in operation but infant was not in the bed.
- A manufacturer's representative came to replace parts on the damaged unit and the heater elements on all four units in facility.
Adverse event type as malfunction and invalid/insufficient data.

The most frequently reported patient problems are:

• Elevated infant body temperature (2)

A problem involving a heating failure involving a power board, results in loss of temperature control within the patient compartment.

“Don’t Let Radiant Warmers Overheat Infants.”
Over the past year and a half, MedSun has received 8 adverse event reports involving infant radiant warmers and neonatal incubators associated with three manufacturers: submitted by 8 hospitals. Reported device problems are:

- Melting of incubator components or smoke
- Overheating of incubator occupant
- Failure of Incubator to heat
Infant Incubator

Problem:

The **Air Mode** was being used to preheat the incubator while awaiting the infant's return from surgery.

- When the infant was placed in the OmniBed, the bed was not put into Baby Mode.

- This caused the OmniBed to maintain an air temperature of 41.7 degrees C. This elevated air temperature resulted in an increase of the infant's temperature.
Apnea Monitors

A number of infant deaths can be traced to the failure of apnea monitors. Failures relate to:

- design limitations of the monitors
- misassumption of the clinical staff.
- improper use
- **SENSITIVITY**
  \[\leq 0.3 \, \Omega \text{ at maximum, no breaths at } 0 \, \text{bpm}\]
- **ECG FEATURES**
- **APNEA ALARM DELAY TIME** (±20%)
- **METER ACCURACY RATE** (±10%)
- **ALARM ACCURACY RATE**

Respiration monitoring is still an imperfect science.
INFUSION DEVICES
PATIENT-CONTROLLED ANALGESIC, ENTERAL FEEDING

RISK DEVEL : High

QUANTITATIVE TESTS

2.1 GROUNDING RESISTANCE (≤ 0.5 Ω)
2.2 LEAKAGE CURRENT (≤ 100 mA chassis)

2.10 FLOW ACCURACY

≤ 5% for critical IV pump applications;
≤ 10% for noncritical pump applications

2.11 MAXIMUM PRESSURE/OCCCLUSION ALARMS
The pump software can perform the actions:

- **Alarm**
  audio and video signals, e.g., occlusion.

- **Alert**
  visual signal issued to the user. Infusion should not be stopped.

- **Log**
  An entry made in the pump log.

- **Stop**
  Pump stops infusion.
Pump Actions
In response to a hazardous event

- Alarms for the generic infusion pump:
  - 1. Occlusion
  - 2. Air-in-line
  - 3. Dead battery
  - 4. Empty Reservoir
  - 5. No reservoir
  - 6. Dose limit
  - 7. Key pressed alarm

POST failure issued
- a. CPU test failure
- b. ROM / RAM CRC test failure
- c. Battery test failure
- d. Stuck key test failure
- e. Watchdog test failure
- f. Real Time Clock test failure
Safety Requirements

1 Infusion Control

1.1 Flow rate

1.1.1 The flow rate shall be programmable.

1.1.3 For a Small-volume pump provide flows 0.1 ml/hr to 99.9 ml/hr,

1.1.4 For a Large-volume pump 1 ml/hr. up to 999ml/hr),

1.1.5 Flow discontinuity at low flows (1 ml/hr or less)

1.1.6 The basal delivery rate shall be programmable up to 24 hours.

1.1.8 The pump should maintain a minimum rate of x ml/hr at all times during infusion
Infusion Control

- 1.1 Flow rate
- 1.2 Flow rate accuracy
- 1.3 Volume to be infused
- 1.4 Bolus Dose
- 1.5 Drug reservoir
- 1.6 Pump suspend
- 1.7 Data retention
- 1.8 Reverse delivery
- 1.9 Air-in-line alarm
- 1.10 Occlusion alarm
Problem: Morbidly obese post-op patient had cardiac arrest.

Underwent five unsuccessful rounds of defibrillation using the Zoll M series biphasic defibrillator charged to 200 joules for pulseless ventricular tachycardia rhythm.

The team applied a different manufacturer's biphasic defibrillator that allows 360 joules defibrillation. The rhythm was captured and converted to normal sinus rhythm with a single biphasic shock at 360 joules.
Review of 843 postimplant defibrillator tests from 31 centers.

The overall failure rate was 3.1% (24/764). Defibrillator failure is associated with a high risk of sudden cardiac death, routine defibrillator testing may be justified.

- Low Energy Biphasic
- Ability to arrest arrhythmia within a max-energy of 360 Joules
- Should have Automatic Lead switching to see ECG measure and compensate for chest impedance for a range of 25-150 ohms
- Charging time of less than 3 sec for maximum energy.
ระยะของการออกแบบ กำหนดเกณฑ์ 1:1:1.5 (1 = 1mV)
ช่วงที่ตัดสินว่าอยู่ในเกณฑ์ ช่วงที่อยู่นอกเกณฑ์ ช่วงของเกณฑ์ยอมรับ (อยู่ในเกณฑ์)
ช่วงของความไม่แน่นอน (ตัดสินไม่ได้)
ช่วงไม่เป็นไปตามเกณฑ์
Electrosurgical Units

- high voltage and high power
- can cause serious electrical burns.

Do not contact either the active or dispersive electrode while the unit is activated.
2. QUANTITATIVE TESTS
2.1 GROUNDING RESISTANCE (≤ 0.5 Ω chassis, footswitch; > 20 MΩ return electrode (except grounded output units))
2.2 CHASSES LEAKAGE CURRENT (≤ 100 mA chassis)
2.3 OUTPUT ISOLATION (Manufacturer’s specification or ≥ 80%)
2.10 OUTPUT CURRENT/POWER
Pulmonary Function Test

- 2 techniques
  - open and closed circuit technique

Evaluate the quality of test
Comparison with a set of published

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male Formula</th>
<th>Female Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>M -2.601 + 0.122A - 0.00046A² + 0.00023H² - 0.00061AH</td>
<td>F -5.914 + 0.088A - 0.0003A² + 0.056H - 0.0005AH</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>M -7.697 + 0.123A + 0.067H - 0.00034A² - 0.0007AH</td>
<td>F -10.603 + 0.085A - 0.0019A² + 0.12H - 0.00022H²</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>M 19.362 + 0.49A + 0.829H - 0.0023H² - 0.0041AH</td>
<td>F 83.126 + 0.243A + 0.002A² + 0.08H - 0.0036AH</td>
</tr>
</tbody>
</table>
Pattern of Abnormal Function

- **Obstructive**
- **Restrictive**
  - Pulmonary parenchyma
  - Extraparenchyma
    - Inspiratory dysfunction/
      stiff chest wall
    - Inspiratory and expiratory
dysfunction
Medical Lab. Devices
FDA-approved test system brought into the lab

standard requires the following:

- "(b)(1)(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:
  - (A) Accuracy.
  - (B) Precision.
  - (C) Reportable range of test results for the test system."
Inaccuracies in analytical results

All measurement gives rise to inaccuracies or ‘errors’

Errors arise because of unavoidable variation in the physical and chemical procedures involved in making a measurement.
invitro diagnostic product (IVD)

medical devices, reagents, and systems intended for use in diagnosis of disease or other conditions

- examination of specimens taken from the human body.
- 21 CFR 809.3

Regulatory Authority:
- FDA act section 210(h),
- Public Health Service Act. section 35,
- Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.
Clinical Diagnostics,
Immunodiagnostic Products Troponin I Reagent Pack

reported inconsistent quality of test results,

- **false negative result**
- Falsel high positive troponin result
- doctor send a patient home with heart muscle damage, delay in treatment and potentially death
- may lead to unnecessary surgery, which carries risks of harm to patients.
Critical Results:
Indicate a life-threatening condition that may be corrected by appropriate and timely intervention.

<table>
<thead>
<tr>
<th>TEST</th>
<th>Units</th>
<th>Low Value</th>
<th>High Value</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>umol/L</td>
<td>N/A</td>
<td>&gt;80</td>
<td>0-17 years old only</td>
</tr>
<tr>
<td>Bilirubin, Total</td>
<td>mg/dL</td>
<td>N/A</td>
<td>&gt;15.0</td>
<td>0-30 days old only</td>
</tr>
<tr>
<td>BUN</td>
<td>mg/dL</td>
<td>N/A</td>
<td>&gt;90</td>
<td>Called for selected patients - see below.* First Instance rule applies for inpatient results that are called.</td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/dL</td>
<td>&lt; 6.0</td>
<td>&gt;12.0</td>
<td></td>
</tr>
<tr>
<td>Calcium, Ionized</td>
<td>mg/dL</td>
<td>&lt; 3.00</td>
<td>&gt; 6.50</td>
<td></td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>%</td>
<td>N/A</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td>&lt; 40</td>
<td>&gt; 400</td>
<td>Pediatric &gt;300</td>
</tr>
<tr>
<td>Lactate</td>
<td>mmol/L</td>
<td>N/A</td>
<td>&gt; 4.0 (ED)</td>
<td>&gt; 10.0 (All Others)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>mg/dL</td>
<td>&lt; 1.0</td>
<td>&gt; 5.0</td>
<td></td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>%</td>
<td>N/A</td>
<td>&gt;3.0</td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>mmHg</td>
<td>&lt; 20</td>
<td>&gt; 70</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>units</td>
<td>&lt; 7.25</td>
<td>&gt; 7.65</td>
<td></td>
</tr>
<tr>
<td>pO2</td>
<td>mmHg</td>
<td>&lt; 55</td>
<td>N/A</td>
<td>&lt;55 Arterial, Capillary &lt;40 mmHg</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>&lt; 3.0</td>
<td>&gt; 6.0</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>mg/dL</td>
<td>&lt; 1.0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>mmol/L</td>
<td>&lt; 120</td>
<td>&gt; 165*</td>
<td>*First instance rule applies</td>
</tr>
<tr>
<td>Troponin</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 0.05</td>
<td>Inpatients - First Instance rule applies</td>
</tr>
</tbody>
</table>

*First instance rule applies

*BUN called if >90 for all ED patients. Inpatients: First instance called to B6/6, F6/6, PP41, PN51, PS54, D4C4. Outpatients: Not called to OPTX, OPTXC, DIAL, EASD, PERD, KIDNEY, C5/3
<table>
<thead>
<tr>
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<th>Units</th>
<th>Low Value</th>
<th>High Value</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>≥ 150</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 35.0</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Caffeine</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>≥ 40.0</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 15.0</td>
<td></td>
</tr>
<tr>
<td>Carb. Metabolite</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 3.7</td>
<td>Also called if metabolite &gt;50% of parent</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 300</td>
<td>Inpatients - Not called to B4/6 (Abd. TX) Outpatients - Called</td>
</tr>
<tr>
<td>Desipramine</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Digoxin</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 2.5</td>
<td></td>
</tr>
<tr>
<td>Doxepin</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 130.0</td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>mg/dL</td>
<td>All results</td>
<td>All results</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 15</td>
<td>Inpatients - Not called to B4/6 (Abd. TX) Outpatients - Called</td>
</tr>
<tr>
<td>Felbamate</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 100</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 12.0</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500 ng/mL</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>mg/dL</td>
<td>All results</td>
<td>All results</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 20.0</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>parent + metab. &gt;8.0</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>mmol/L</td>
<td>N/A</td>
<td>≥ 1.50</td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>mg/dL</td>
<td>All results</td>
<td>All results</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 500</td>
<td>Also called if total tricyclic is &gt;500</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>mg/dL</td>
<td>N/A</td>
<td>&gt; 3.0</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 50.0</td>
<td></td>
</tr>
<tr>
<td>Phenytin</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 30.0</td>
<td></td>
</tr>
<tr>
<td>Phenytoin, Unbound</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 3.0</td>
<td></td>
</tr>
<tr>
<td>Plasma HGB</td>
<td>mg/dL</td>
<td>N/A</td>
<td>&gt; 100</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 15.0</td>
<td></td>
</tr>
<tr>
<td>Salicylate</td>
<td>mg/dL</td>
<td>N/A</td>
<td>&gt; 50</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 20</td>
<td>Inpatients - Not called to B4/6 (Abd. TX) Outpatients - Called</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>ng/mL</td>
<td>N/A</td>
<td>&gt; 15</td>
<td>Inpatients - Not called to B4/6 (Abd. TX) Outpatients - Called</td>
</tr>
<tr>
<td>Theophylline</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 20.0</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 12.0</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 30.0</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>mcg/mL</td>
<td>N/A</td>
<td>&gt; 150.0</td>
<td></td>
</tr>
</tbody>
</table>
Methods requiring validation

- Lab. Developed or in-house methods
- Modified Standard methods, or use outside their intended range

  - Determine the conditions under which such results can be obtained
  - Determine the limitation of the method

  complete validation or verification of capability

Implementation

- Document the method
- Train testing staff
- Develop QC criteria
- Provide for future review (at least yearly)
The technics used involve one or more of:

- **Use of RM or CRM.**
- **Comparison of result with other validated/standard methods**
- **Inter laboratory comparisons**
- **Assessment of uncertainty**
- **Systematic assessment of the factors influencing the result**
Reference measurement method for metabolites and substrates

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Reference method / procedures</th>
<th>Applicable matrices</th>
<th>Measurement principle/techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>DGKL reference method</td>
<td>lyophilized, fresh or frozen serum</td>
<td>Absorption spectrometry</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Doumas reference method for total bilirubin</td>
<td>lyophilized, fresh or frozen human serum</td>
<td>Spectrophotometry</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>NIST definitive method</td>
<td>lyophilized, fresh, or frozen human serum</td>
<td>ID/GC/MS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>CDC Abell-Kendall method</td>
<td>lyophilized, fresh, or frozen human serum</td>
<td>Spectrophotometry</td>
</tr>
</tbody>
</table>
Reference system for Enzyme Analysis

Reference measurement procedure (IFCC)

Primary reference material
(e.g. extremely well characterized and purified enzyme)

Secondary (matrix-matched) reference material

Manufacturer's standing measurement procedure

Manufacturer's product calibrator

End-user's routine measurement procedure

Routine sample

RESULT
calibration verification
CLIA ’88 define in 42 CFR 493 in section 493.2.

- Assay of materials of known concentration
  - in the same manner as patient samples
  - to support/confirm the instrument or
  - test system’s calibration
  - throughout the reportable range
for patient test results”
Perform calibration verification procedures:

At least once every 6 months and whenever any of the following occur:

- Introduced a complete change of reagents
  - unless lab. can demonstrate that reagent lot numbers does not affect the range used, and control values are not adversely affected.
- There is a major preventive maintenance or replacement of critical parts.
- Control material reflect trend or shift, are outside of the lab’s acceptable limits.
- The lab’s schedule for verifying the report range requires more frequent calibration verification."
Validation of the new instrument performance

- Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:

  (A) Accuracy.
  (B) Precision.
  (C) Reportable range of test results for the test system."
Calibration verification

- should be performed at least once every 6 months and whenever the following occur:
  - A complete change of reagents is introduced, unless it is demonstrated that control values are not affected
  - There is major preventive maintenance or replacement of critical parts
  - Control results indicate that there may be a problem with the test system
  - There is an environmental change, including instrument relocation, as applicable
  - There is an instrument replacement
Immunoassay of thyroid hormone

- Lot of antibody changes,
- A specimen carryover factor.
- The specimen and reagent pipetting errors,
- Changes of calibration materials,
- Reagent aging:
  - Different operators failing to warm reagents to recommended temperatures,
  - Failing to properly follow calibration

Errors arise because of variation in the physical and chemical procedures involved in making a measurement.
Immunoassay of thyroid hormone

- QC specimen results (means of duplicates) at four concentrations H (high), N (normal), LN (low normal), and L (low) from 591 consecutive in-control T4 RIA batches over 29 months.
- Changes of QC specimens are indicated by vertical lines. Horizontal lines indicate means and 95% confidence intervals for each QC lot. Closed arrows indicate where four changes of calibrators occurred. Two open arrows indicate statistically significant effects possibly associated with reagent lot changes.
Traceability

The result of a measurement

must be assured to a calibrator and controls

through available reference material or reference method,

national or international standards

through an unbroken chain of comparisons

all having stated uncertainties.
The metrological traceability of values assigned to calibrators and controls must be assured through available reference materials and reference measurement procedures.
Standards harmonized for traceability

- **ISO/FDIS 17511**
  Traceability of values assigned to calibrators and control materials

- **ISO/FDIS 18153**
  Traceability of assigned values for catalytic concentration of enzymes in calibrators and control materials

- **ISO 15193 / EN 12286**
  Presentation of reference measurement procedures

- **ISO 15194 / EN 12287**
  Description of reference materials

- **ISO 15195**
  Requirements for reference measurement laboratories
ISO/FDIS 17511 and ISO/FDIS 18153

Metrological Traceability

- primary calibrator
- secondary calibrator
- working calibrator
- product calibrator
- routine sample

- primary reference measurement procedure
- secondary reference measurement procedure
- manufacturer’s selected measurement procedure
- manufacturer’s standing measurement procedure
- user’s routine measurement procedure

definition of SI-unit
Blood Glucose Test Strips ; Class 1 Recall

- Test strips are counterfeit (fake) versions

Could give incorrect blood glucose values, result in a patient taking either too much or too little insulin, lead to serious injury or death
Method Selection

- must use methods that meet client needs and are appropriate for the tests.
  - National or international standard methods
  - Publish methods
  - Manufacturer methods
  - Lab. Development methods
- Lab. can perform a test to more than one methods
Methods for Glucose Measurement

**Hexokinase** (spectrophotometric or fluorinetric indication)

\[
\text{Glucose} + \text{APF} \xrightarrow{\text{Hexokinase}} \text{Glucose-6-PO}_4 + \text{ADP}
\]

\[
\text{Glucose-6-PO}_4 + \text{NADP} \xrightarrow{\text{G-P dehydrogenase}} \text{6-Phosphogluconate} + \text{NADPH} + \text{H}^+
\]

**Glucose oxidase** (oxygen consumption indication)

\[
\text{Glucose} + \text{O}_2 \xrightarrow{\text{Glucose oxidase}} \text{Gluconic acid} + \text{H}_2\text{O}_2
\]

**Glucose oxidase** (hydrogen peroxide reaction) followed by Trinder Reaction

\[
\text{H}_2\text{O}_2 + \text{pheol} + 4\text{-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{quinoneinine dye} + 2\text{H}_2\text{O}
\]

**Glucose oxidase** (amperometric indication; sample-capillary blood)

**Glucose dehydrogenase** (colorimetric, poorer specificity)
Compare different blood glucose methods

- The first three different blood glucose determination methods were compared with the reference method.
- 1) o-toluidine with glacial acetic acid, lower
- 2) o-toluidine without glacial acetic acid, higher
- 3) neocuproine (with Technicon AutoAnalyzerII), lower
- 4) hexokinase glucose-6-phosphate dehydrogenase (reference method).
# Cholesterol in Blood and Plasma

## Determination on Three Different Methods

<table>
<thead>
<tr>
<th>Bias and Precision at the</th>
<th>Highest Level of Traceability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Reference Method</strong></td>
<td>Isotope dilution mass spectrometry</td>
</tr>
<tr>
<td></td>
<td>Measured cholesterol <strong>ONLY</strong> (Expensive)</td>
</tr>
<tr>
<td><strong>Secondary Reference</strong></td>
<td>Abell-Kendall spectrophotometry</td>
</tr>
<tr>
<td></td>
<td>Measured Cholesterol &amp; Other Sterols (Inexpensive)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bias and Precision at the</th>
<th>Lowest Level of the Traceability Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End User Routine Methods</strong></td>
<td>Multiple Methods for Same Measurand</td>
</tr>
<tr>
<td></td>
<td>Multiple Instrument Platforms (Indicator Differences)</td>
</tr>
</tbody>
</table>
Why Test & Calibration?

What you cannot measure you cannot control
drift
temperature
humidity
mechanical stress
components of medical equipment
calibration
detected
corrected or compensated
drift
performance degrades
test results unreliable
performance quality suffer
Hospital Require Their Medical Equipment to be:

Performing to the expected standards of
  - accuracy,
  - reliability,
  - free of hysteresis and linear

Safe & Effective
Economic & Available

Met regulations, accreditation requirements and standards.
necessity of inspection

Inspection is a special calibration with

- additional functional tests defined by the Rules on Metrological Requirements.

-only for those instruments

- type test has already been performed
- type approval certificate has been issued

with the Rules on Metrological Requirements
laboratory instrument calibrations

- system suitability
- supplier's calibration procedure
- Equipment qualifications (IQ/OQ)
- Calibration Labeling
- Impact Assessments on Critical Systems / Instruments
- Evaluate Equipment / Process Tolerances, Upper / Lower Spec Limits, Calibration failure Limits, Alarm Set Points, Alert Set points.. Etc
Calibration verification 42 CFR 493 in section 493.2.

Test system’s calibration: Assay of materials of known concentration in the same manner.

Perform at least once every 6 months and whenever the following occur:

- A complete change of reagents
- There is major preventive maintenance
- Control results found problem with the test system
- Environmental change eg, instrument relocation,
- There is an instrument replacement
Guide to Inspections, measuring, and test equipment – 21 CFR 820.72

assure, measuring and test equipment is

- suitable for its intended use

- capable of producing valid results

- performance qualification of the equipment.

• assure the software has been validated for its intended use.

• Verify equipment, checked, calibrated and inspected
CEN and ISO: traceability of IVD MDs

- Reference measurement procedures
- Reference materials
- Traceability of values assigned to calibrators and control materials
- Traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials
- Medical Lab. - Require 15195

  ISO/FDIS 15193
- EN 12287:1999, ISO/FDIS 15194
- prEN ISO/FDIS 17511
- prEN ISO/FDIS 18153
- Reference measurement laboratories prEN ISO/FDIS 15195