# IMPACT of CALIBRATION on MEDICAL DEVICES

นพ.วิรัตน์ วงศ์แสงนาค

# *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

Ref: COUNCIL DIRECTIVE 93/42/EEC

- 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

# BACKGROUND

1999 Institute of Medicine report:

- Estimated 44,000 – 98,000 medical error deaths annually
- More than from highway accidents, breast cancer, or AIDS

# Root Causes of Sentinel Events (all categories)

Medication Errors

Op/Post-op

Perinatal Deaths

Restraint Deaths

Transfusion Events

Ventilator Events

Wrong Site Surgery

Anesthesia-related

Criminal Events

Delays in Treatment

Elopement

Infection-associated

Inpatient Suicides

Maternal Deaths & Injuries

# 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

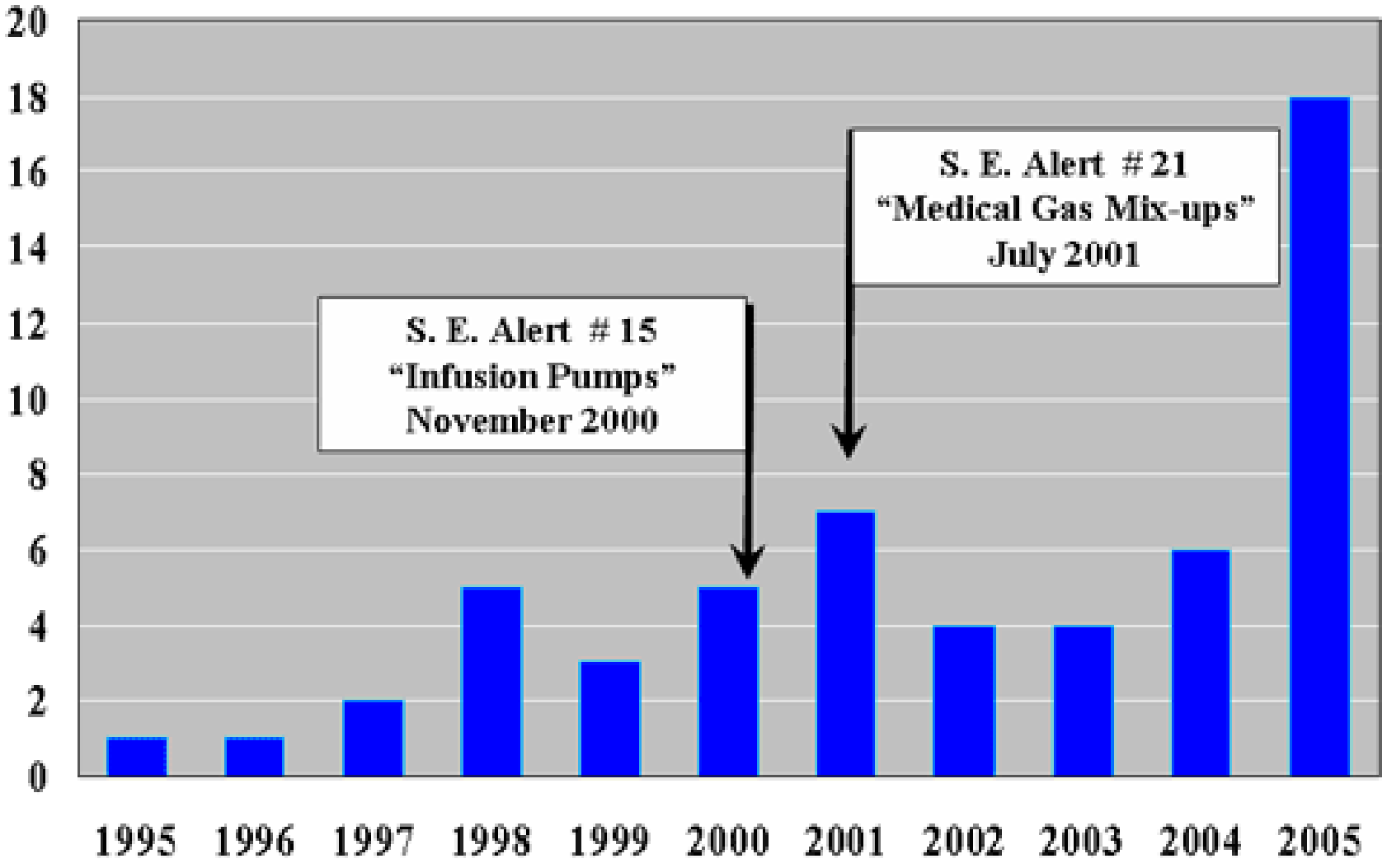
# Medical devices “use-errors”

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



# 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).

# TOP 10 TECHNOLOGY HAZARDS FOR MEDICAL-DEVICE USE

- 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.*

# AMOUNT USED & NEED

- 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 it's 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 types 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

# GENERAL REQUIREMENTS

- 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 |

RULE 1 -

All non-invasive devices are in Class I

# DEVICES THAT DO NOT TOUCH THE PATIENT SKIN

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

# RULE 2 – CHANNELING OR STORING FOR EVENTUAL ADMINISTRATION

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,

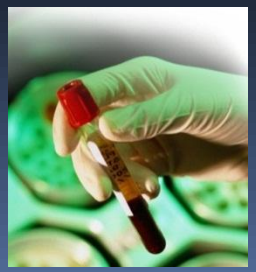
tubing for anesthesia,

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.
- IVD Code classification of FDA lists in 21 CFR 862, 21 CFR 864, and 21 CFR 866.

## 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

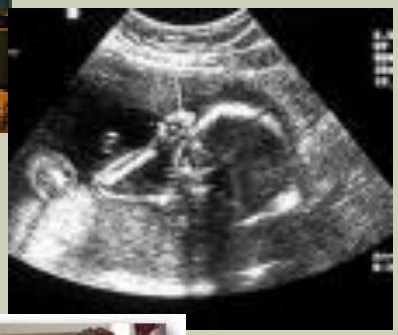
- The **Active Implantable Medical Devices Directive (AIMDD)** (90/385/EEC OJ L189 p0017-0036): *active*

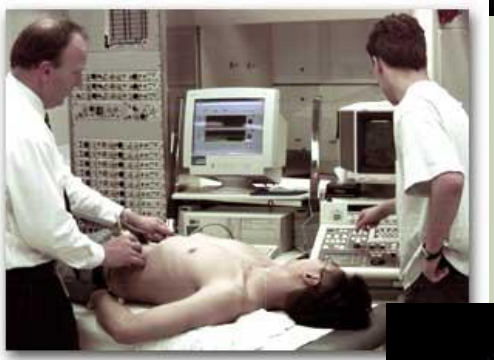
  implants e.g. heart pacemakers

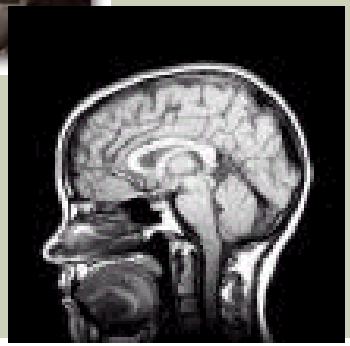
- **Most countries have transposed these directives into a single national legislation (e.g. UK Medical Devices Regulations 2002)**

# 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*).







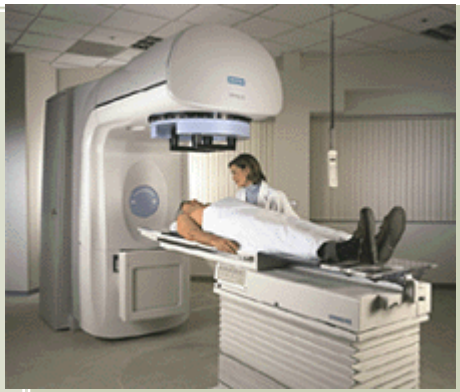
# RADIOTHERAPY DEVICES

- X-ray and electron, beams from accelerators
- gamma-ray beams from isotope Co-60
- Brachytherapy treatment
- Dosimeters
- We used *Ionizing radiation,*

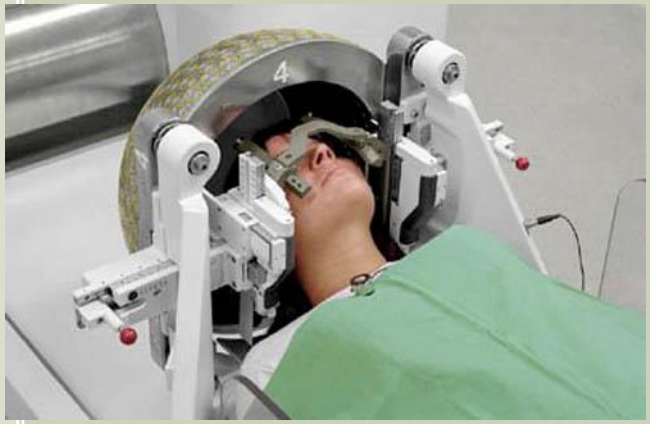
  *properties of atom nucleus,*

  *radioactivity,*

  *biological effects of ionizing radiation*

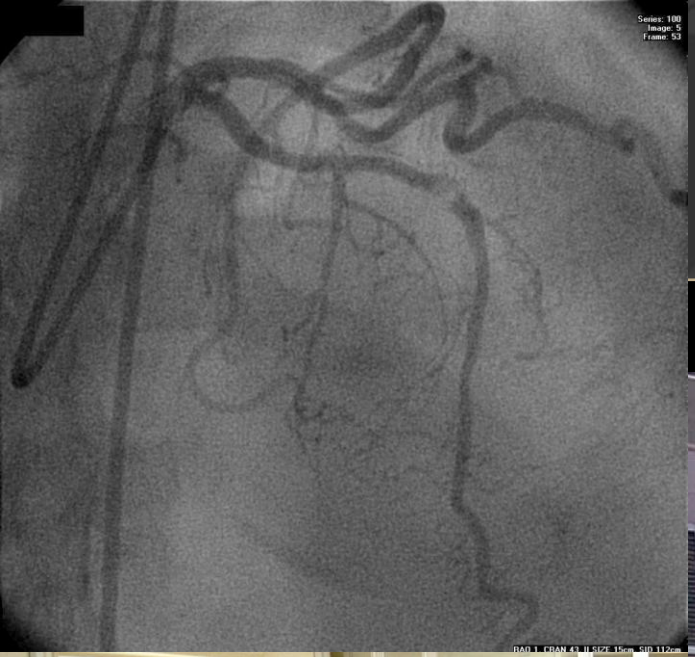


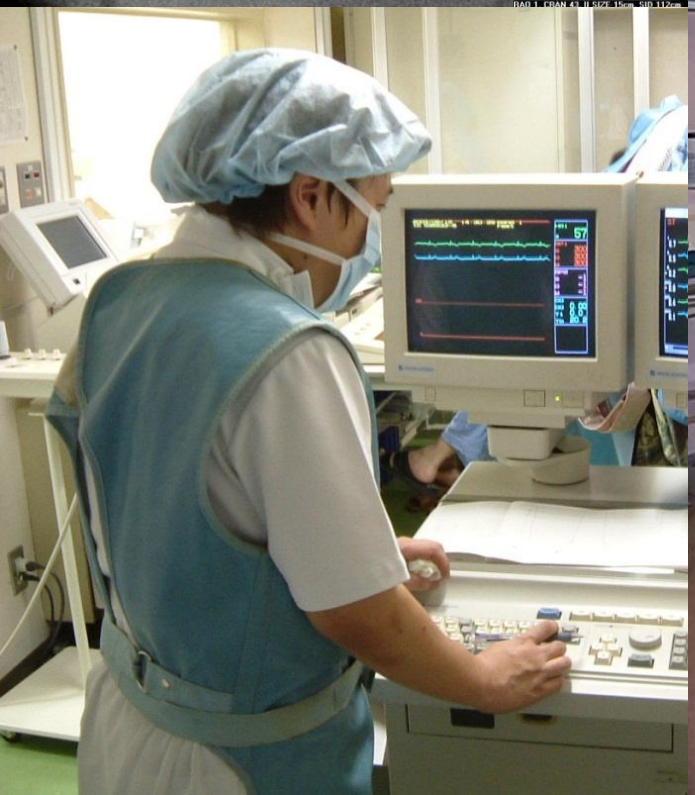
Linear accelerator

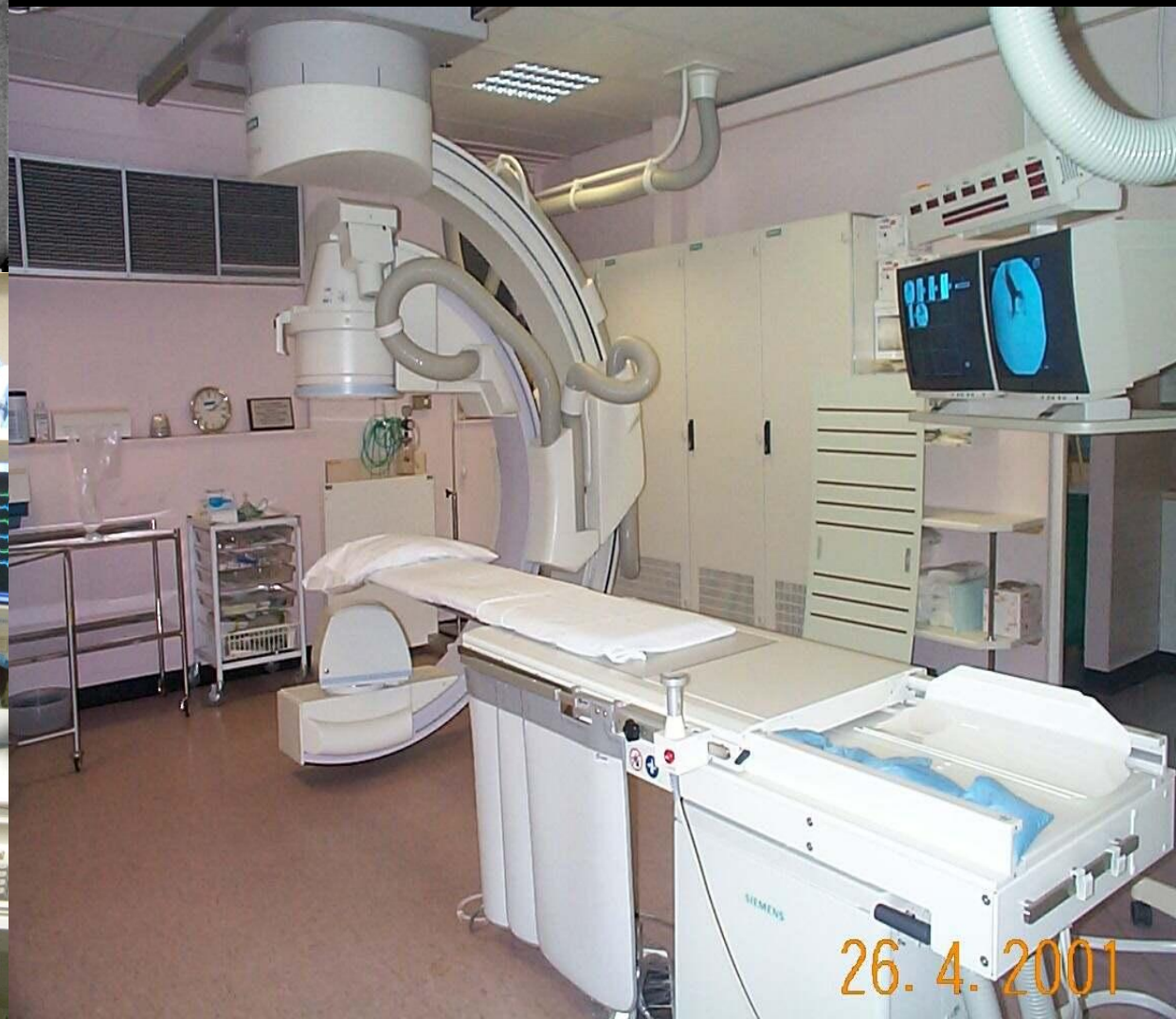


Gamma knife

# 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

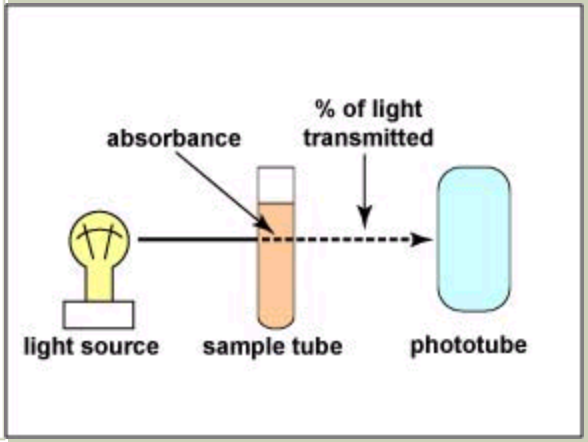
- We measure

biopolymersstructure, galvanic cell

properties of water and electrolytes,

electric properties of living matter,

sedimentation of particles, light absorption



# POINT OF CARE (POC)

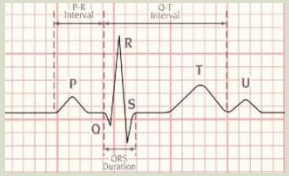
- Clinicians' require rapid access to information to support critical care decisions
- Microelectronics and biosensor tools using near bedside in a diminished form.
  - blood tests at the patient's side
  - portable ultrasound imaging devices

# PHYSIOLOGICAL MEASUREMENT DEVICES

- Instruments for measuring **physical and chemical** variables *in vivo*

- Thermometers
- Cardiovascular physiology:

  blood pressure monitors, flowmeters, Doppler US

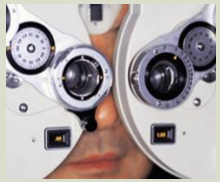


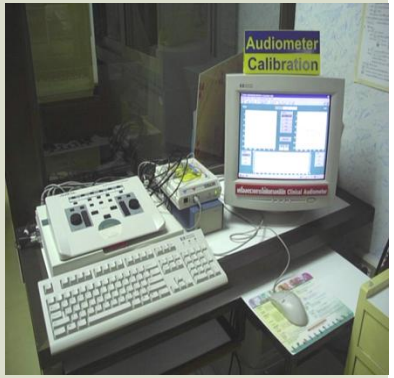

- Electrophysiology: ECG, EEG, EMG
- Audiology and ophthalmology
- Respiratory physiology:

  spirometers, pulse oximetry,

  impedance pneumograph….


Measuring lung capacity using a spirometer.

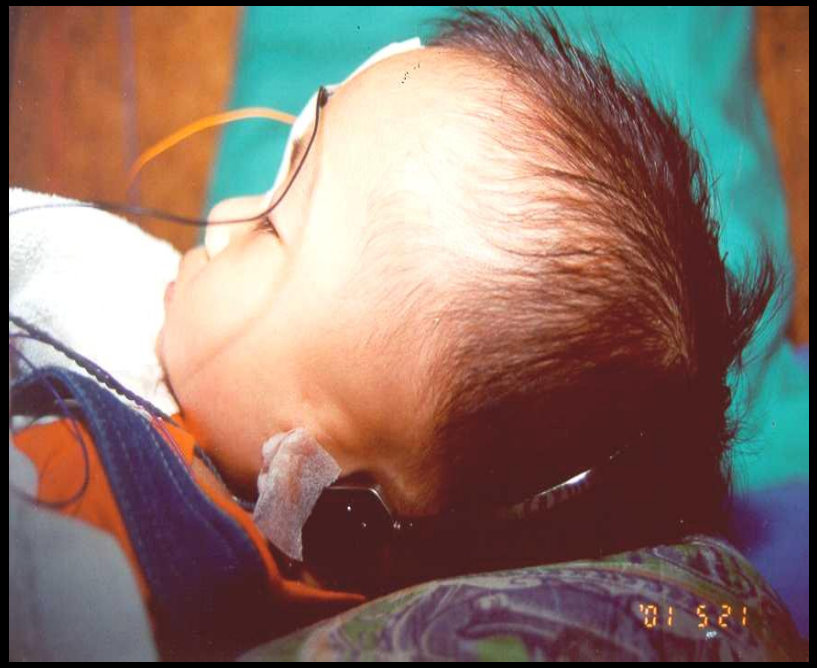


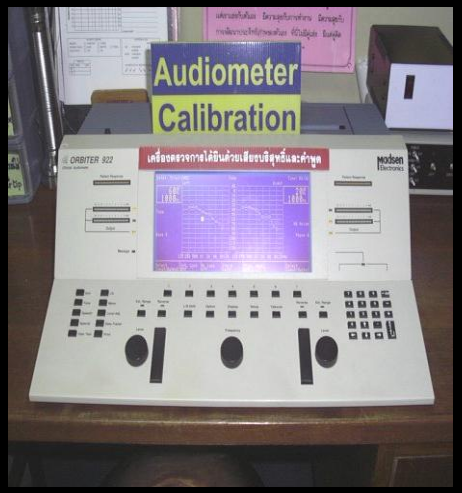



- Endoscopes

We measure

***thermodynamics, hydrodynamics, bioelectric, sound and light, etc.***

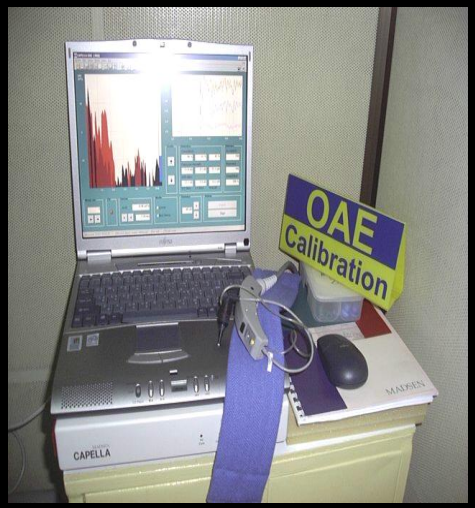






**Maximum Permissible**

**Uncertainty ?**




เครื่องตรวจหาระดับ hearing ใน auditory pathway ไปจนถึง brainstem

ABR-auditory brainstem response

# PHYSICAL THERAPY DEVICES

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

We measured & used

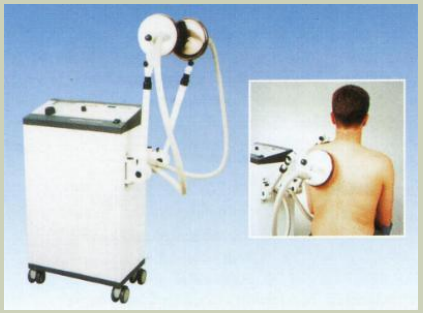
***Biological interactions of ultrasound,***

***electromagnetic fields,***

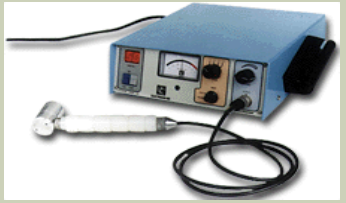
***electric current, infrared,***

***visible and ultraviolet light,***

***laser principle***



Shortwave diathermy

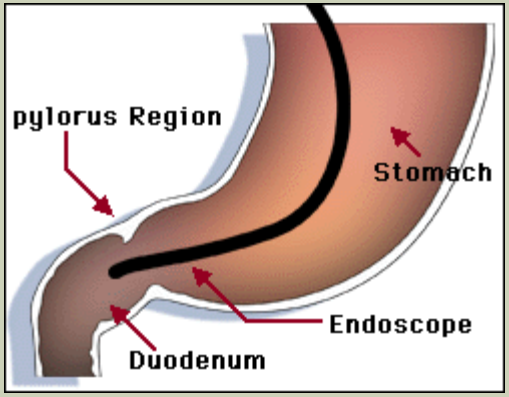


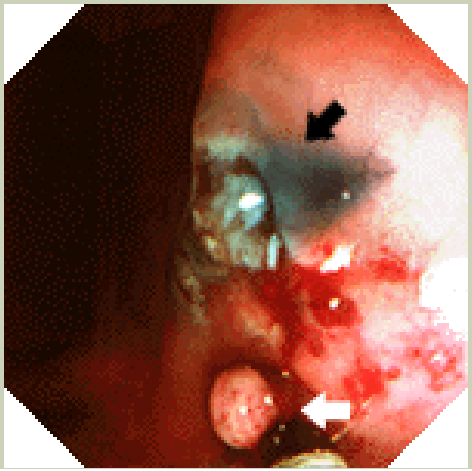
Ultrasound therapy unit

Muscle stimulator

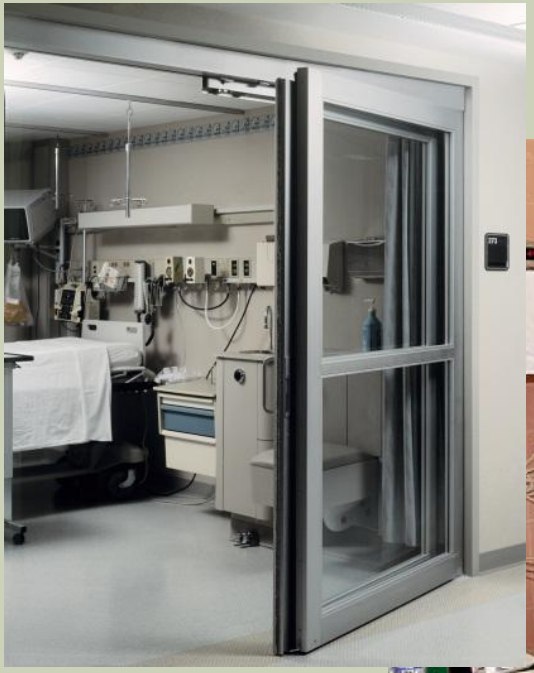
Laser therapy unit

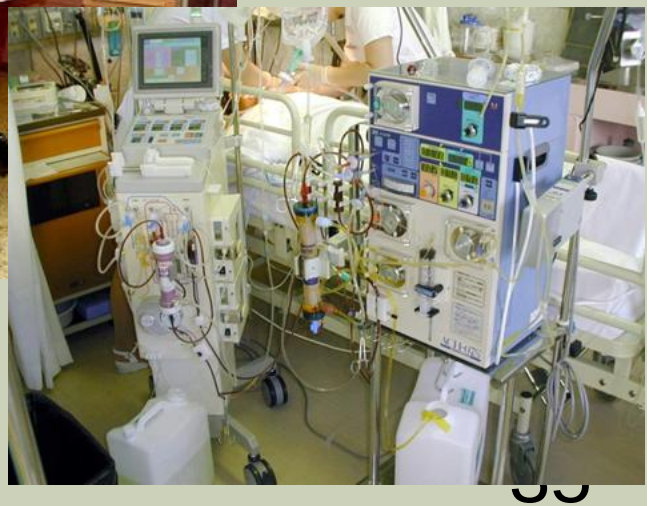
# ENDOSCOPY



# INTENSIVE CARE





# SURGICAL DEVICES, LITHOTRIPSY

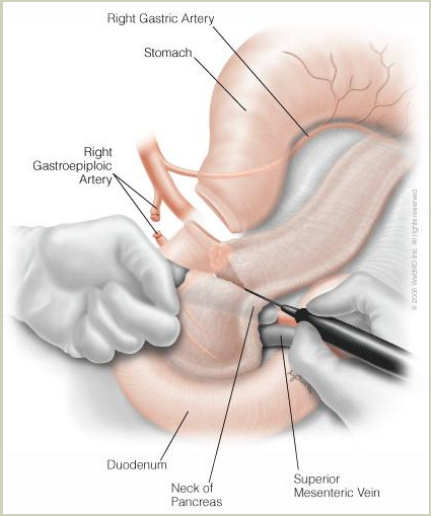
anaesthesia

cryosurgery

Operating lamps

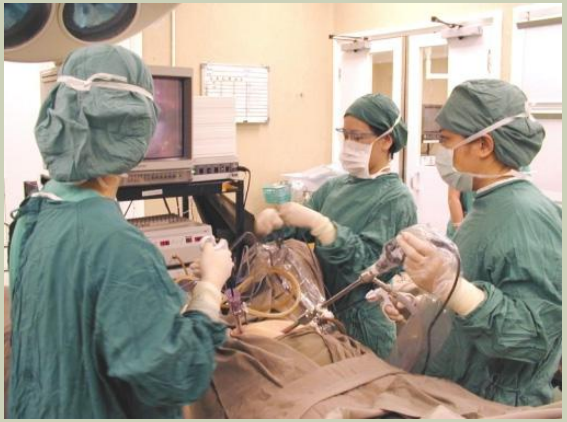
WE measured & used

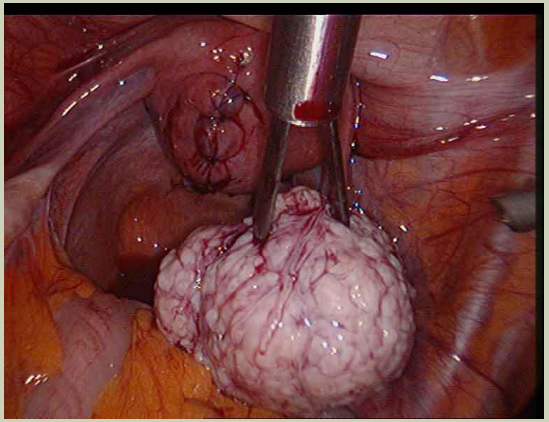
Biological interactions of ultrasound, electromagnetic fields, electric current, infrared, visible and ultraviolet light, laser principle, low temperatures, acoustic shock waves

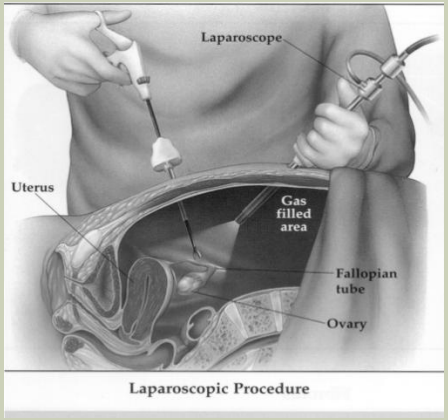


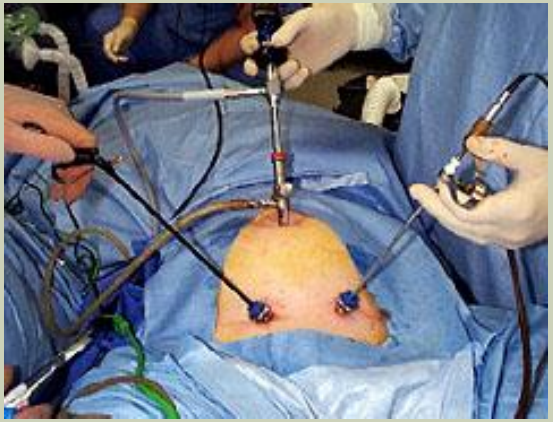

electrocautery

# LAPAROSCOPIC SURGERY

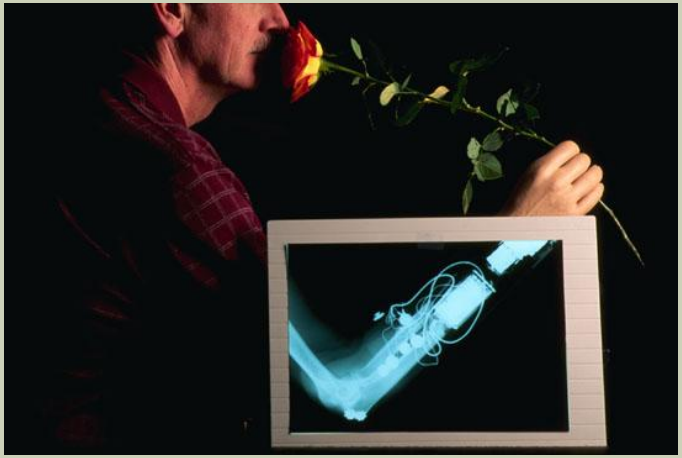


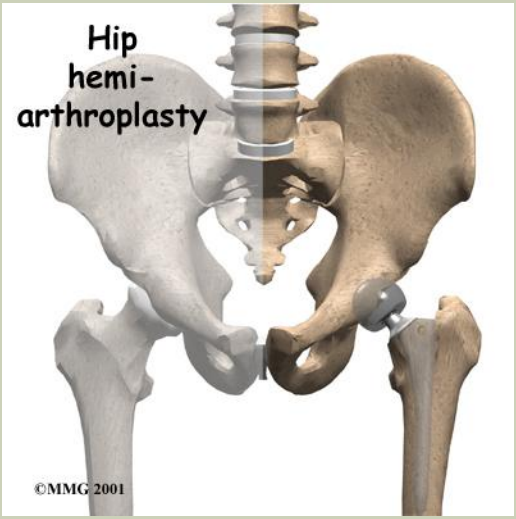


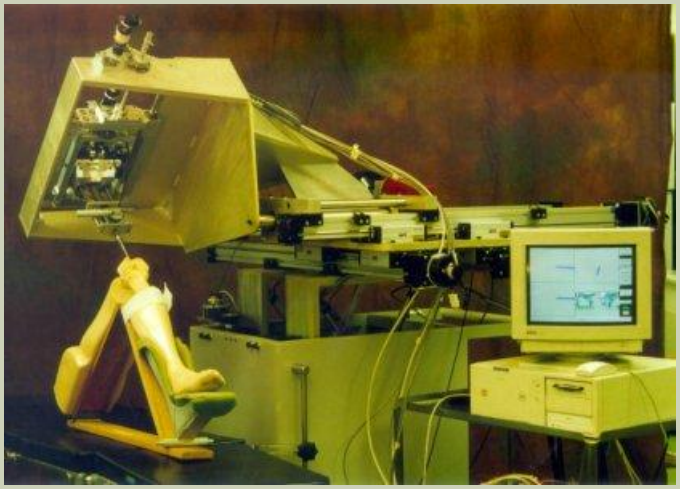


# PROSTHETIC DEVICES - IMPLANTS



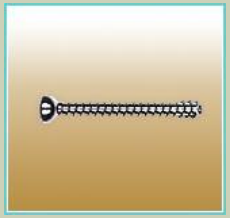


Robotic device

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

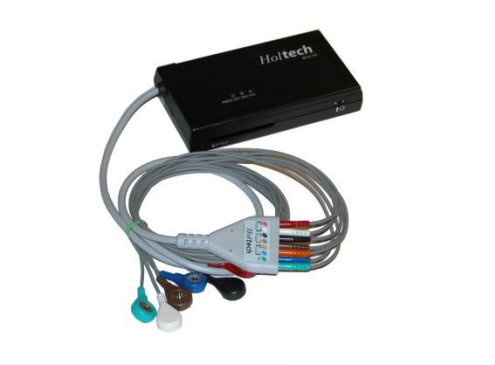
Vascular prostheses

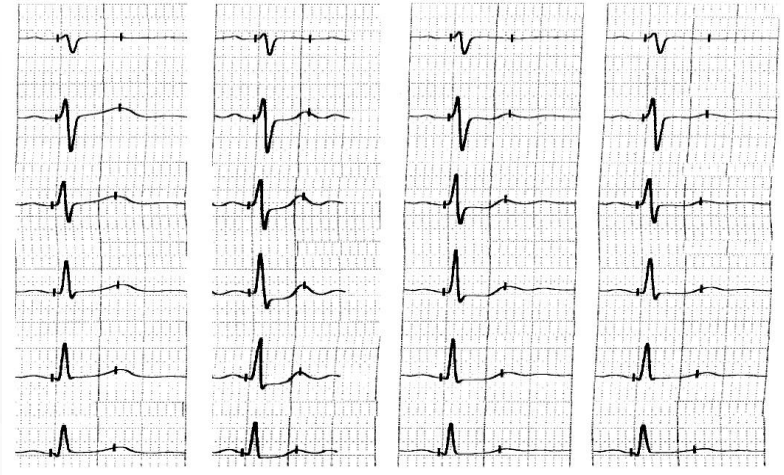
Vena cava filters

# Microprocessor-Based Devices

- increasing use of microprocessors and associated software in both implanted and external medical devices.
  - Programmable pacemakers,
  - long-term portable ECG recorders, and
  - ECG arrhythmia detection monitors,

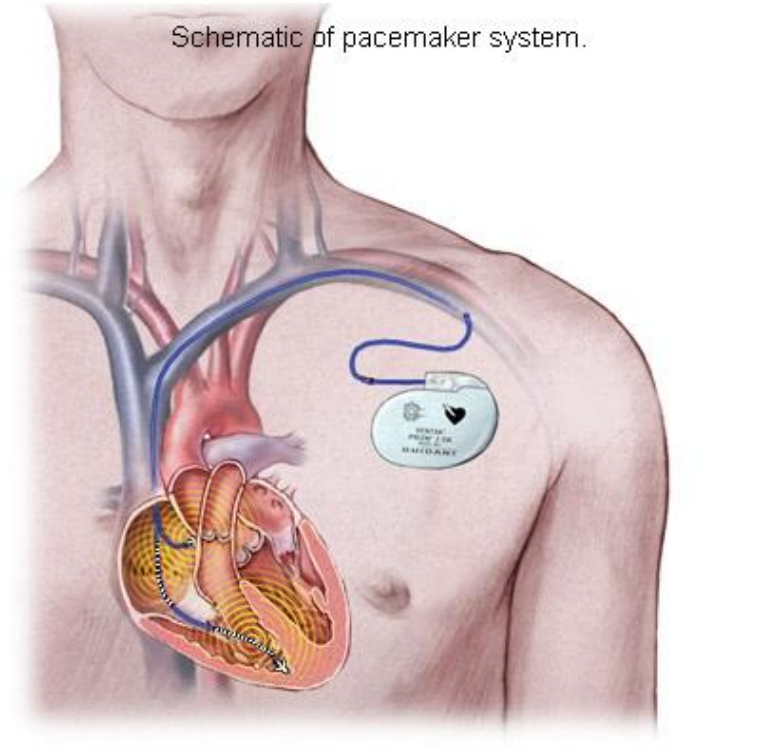
    eg. cardiac arrhythmia detection software.
- accidents related to both hardware and software problems (rare and transient).

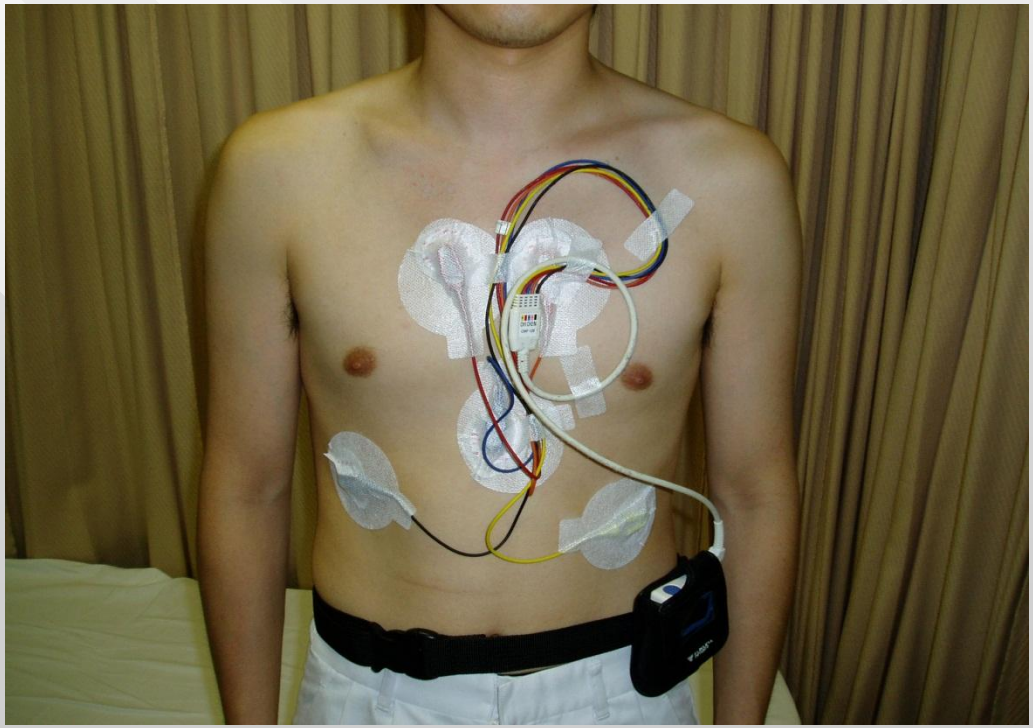


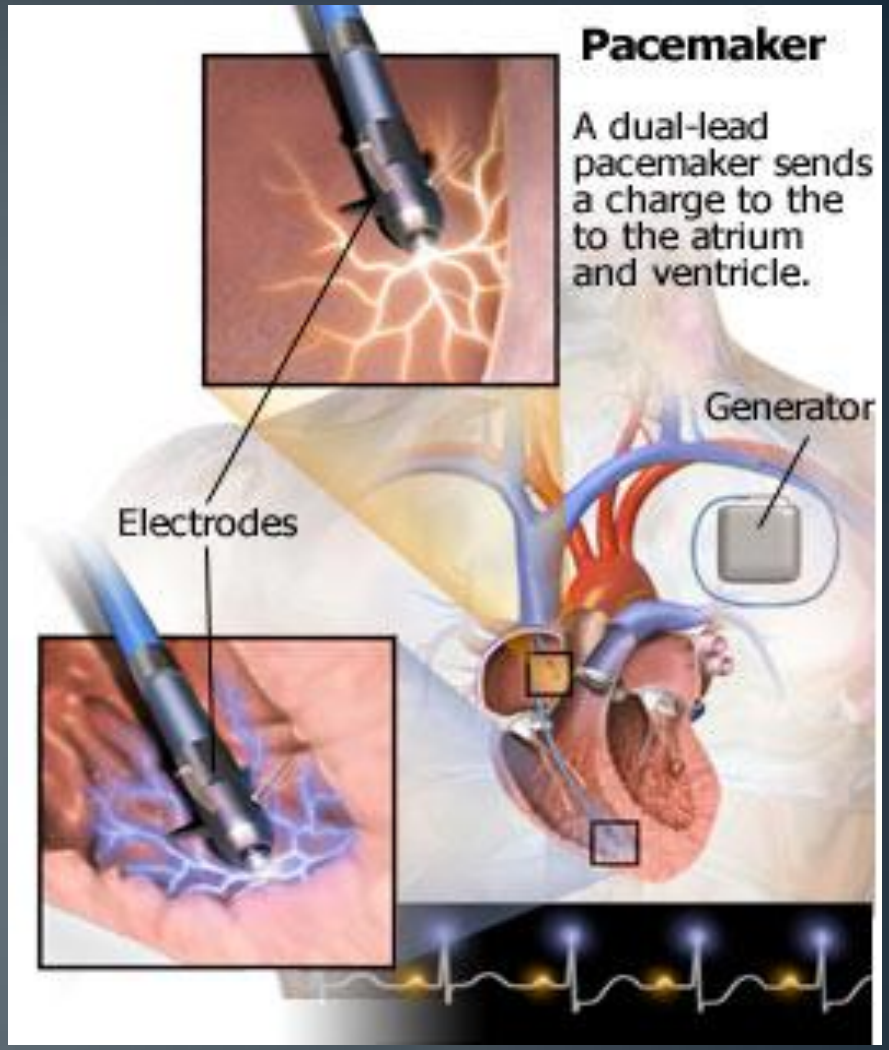

# Pacemaker Implantation

to control a slow heart beat



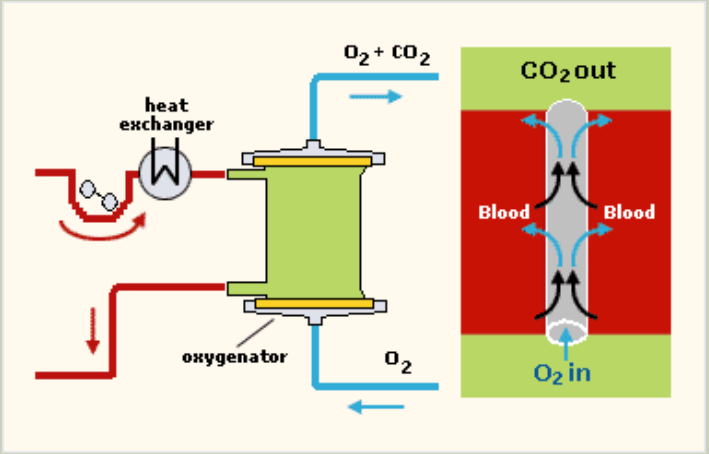
# Radio-frequency Catheter Ablation



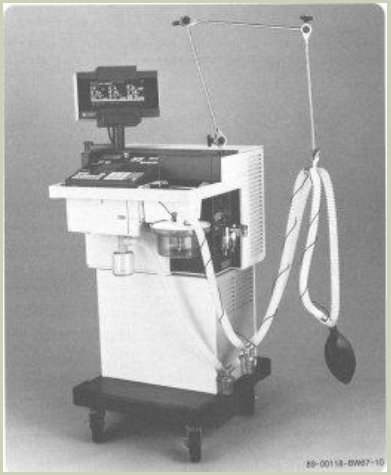

is used for patients who are experiencing palpitation caused by an abnormal electrical impulses in the heart

# PROSTHETIC DEVICES – "ARTIFICIAL ORGANS"

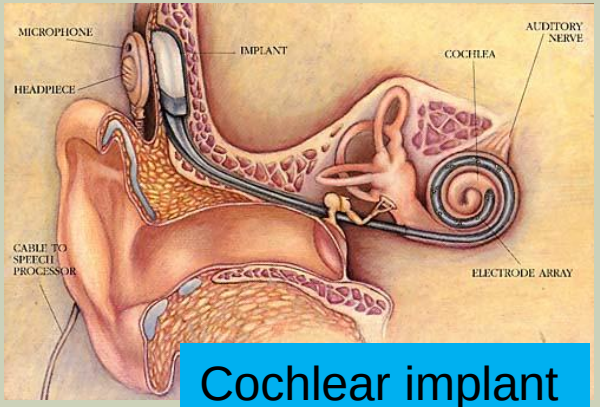
Artificial heart



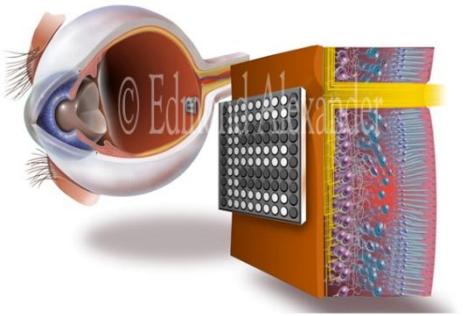

Cardiopul-monary bypass



Ventilator

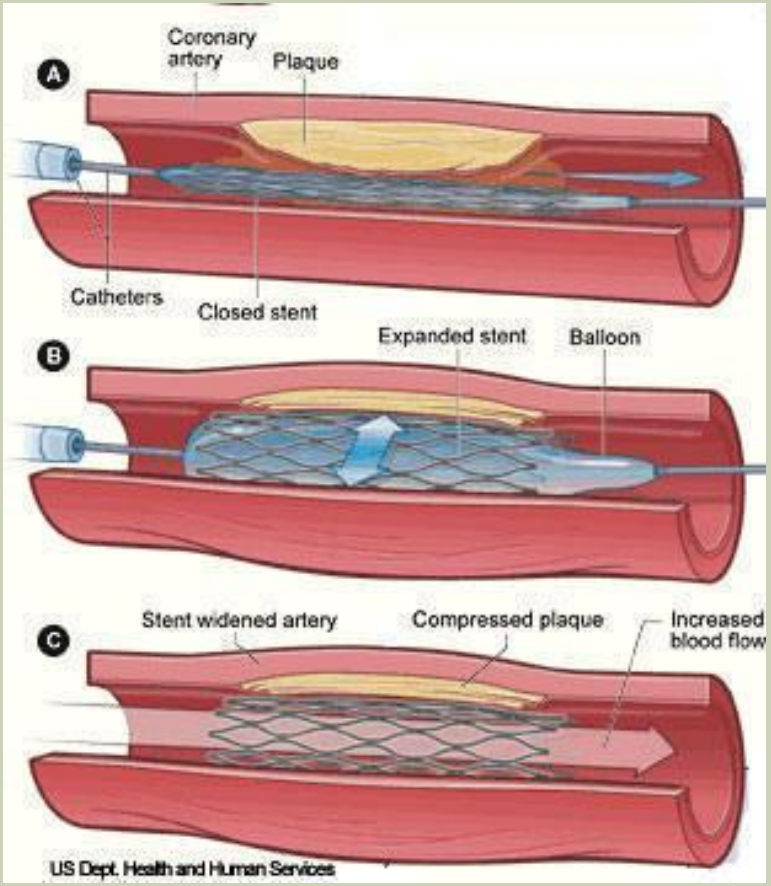


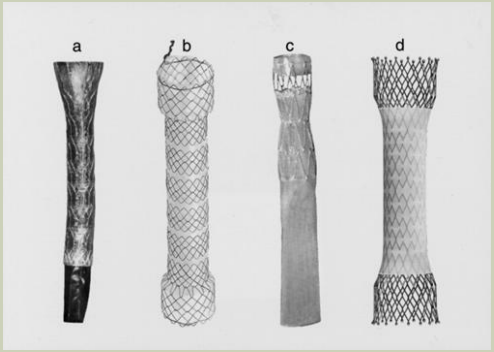

Cochlear implant



Retinal implant

# PROSTHETIC DEVICES –"ARTIFICIAL ORGANS"



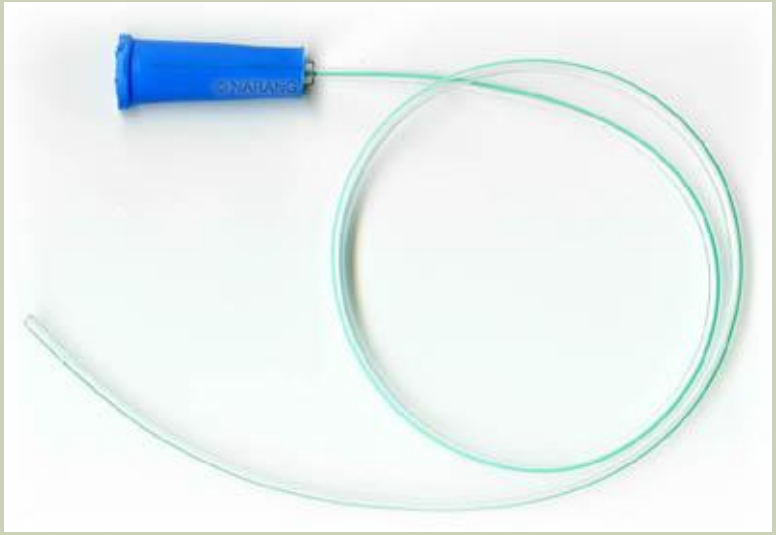




- **Stents**

  - inserted into the damaged blood vessels, oesophagus etc.

  - made of a metal– nitinol, which adopts the intended shape when heated to body temperature.

# DISPOSABLE MEDICAL DEVICES



Suction catheter

I.V. cannulae


Umbilical cord clamp

# Disposables

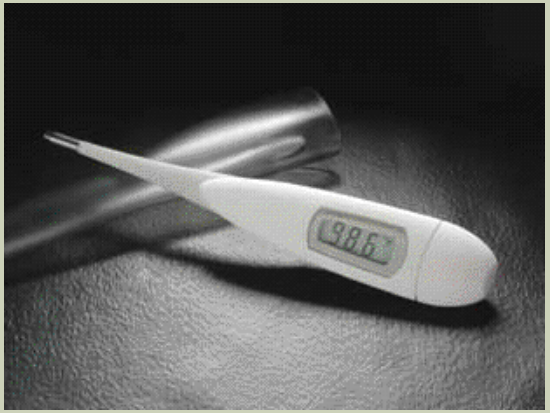
- following are involved in accidents:

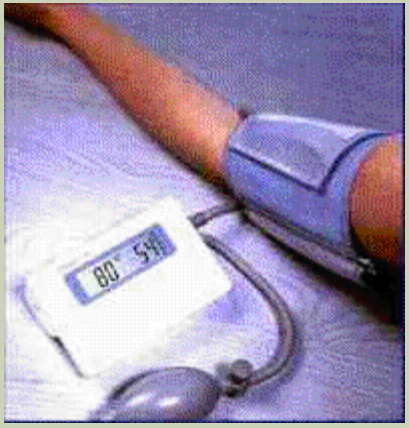
Anesthesia admin kits
Breathing circuits
Catheters
Defibrillator paddle pads
Embolectomy catheters
Endotracheal tubes
Heart-lung bypass unit
Hypodermic needles
Infusion pump sets
IV sets
Luer-lock connectors
Nasal oxygen cannulae
Oxygen masks
Sump pumps
suture needles
Tampons
Tracheostomy tubes

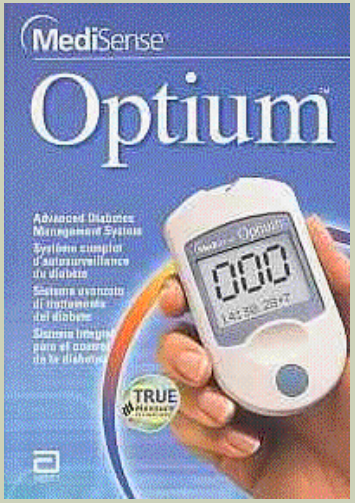
# HOME DEVICES (DEVICES FOR SELF-TESTING)

- '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

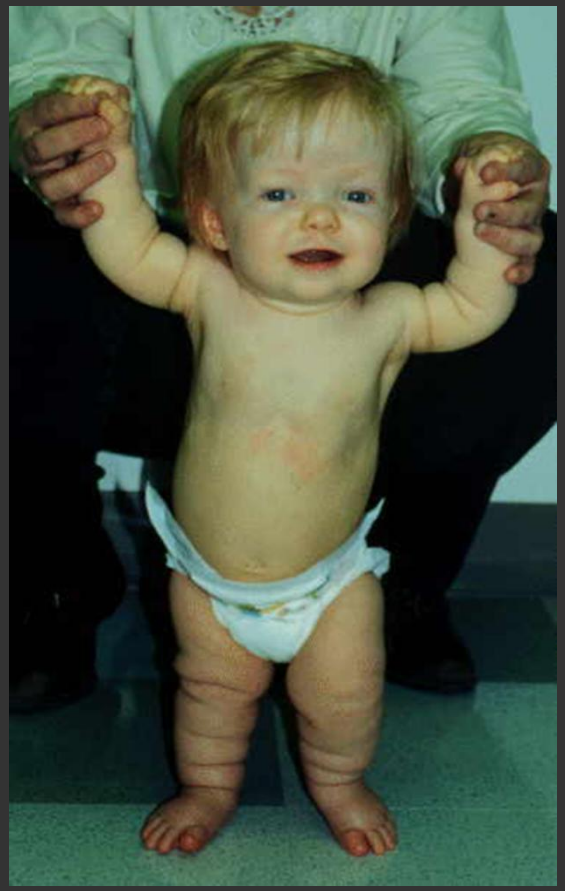
- necessity of inspection applies to those devices that are
  in a direct contact with a patient
  can affect a patient's health or treatment.

- 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

# Device Factors

- Design/labeling error
- Device failure
- Device interaction
- Failure of accessory
- Software deficiency
- Improper maintenance, calibration, testing, repair
- lack or failure of incoming inspection
- Improper modification
- Manufacturing error
- Packaging error
- Random component failure



# Digital Thermometer

- Model# KD-192

  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.

# Infusion Pump

- Model# Outlook 100 - 13215

  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/*

# infant warmer:

/Device:Model# RW82-1

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,"*

# Adverse Events With Infant Radiant Warmers and Neonatal Incubators

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/com 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,

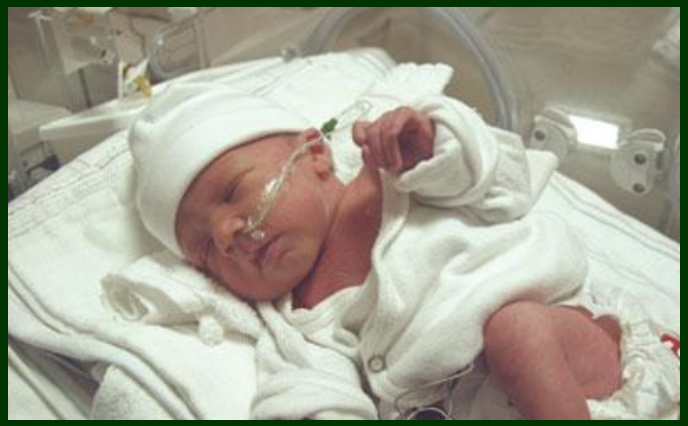
the bed was not put into Baby Mode.

-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

# respiration monitoring is still an imperfect science.


- SENSITIVITY
  ≤ 0.3 Ω at maximum,no breaths at 0 bpm)
- ECG FEATURES
- APNEA ALARM DELAY TIME (±20%)
- METER ACCURACY RATE (±10%)
- ALARM ACCURACY RATE

# 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/OCCLUSION ALARMS

# PUMP ACTIONS

# IN RESPONSE TO A HAZARDOUS EVENT

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

# External Defibrillator

Model# M-series

**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.***

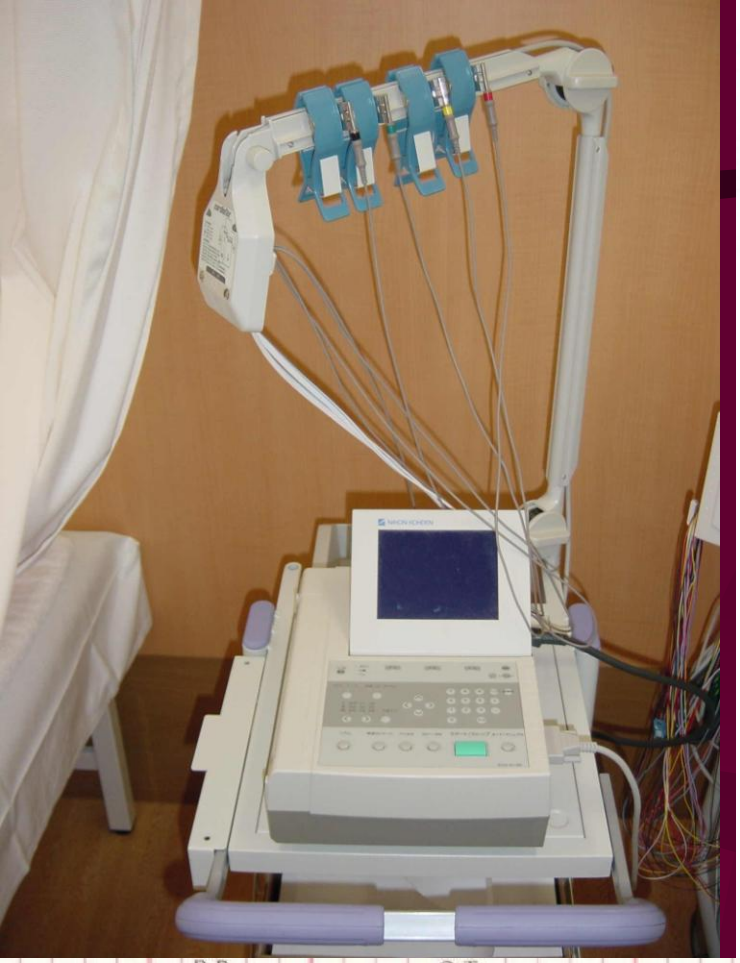
The team applied a different manufacturer's biphasic defibrillator that allows 360 joules defibrillation. The rhythm was captured and converted to normal sinus rhythm with a single biphasic shock at 360 joules

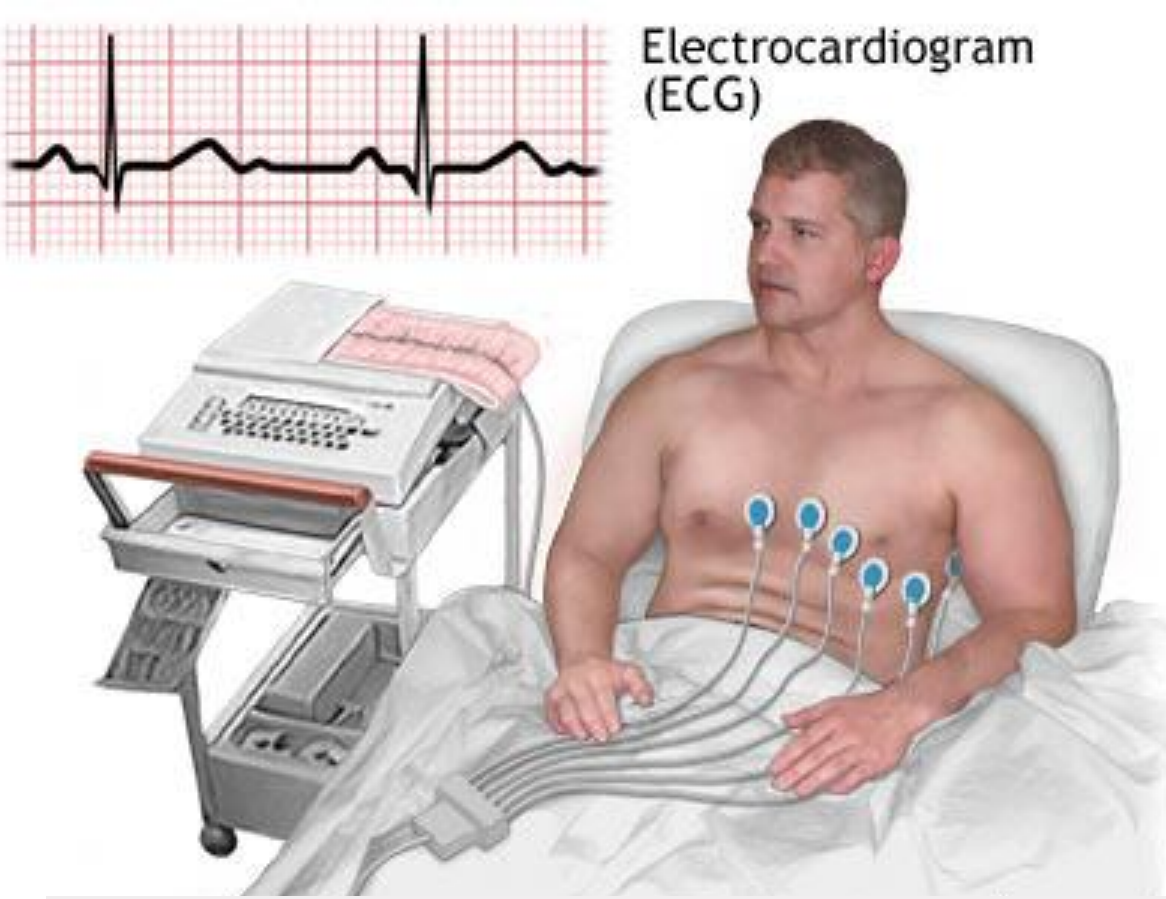
# DEFIBRILLATOR WITH ECG Monitor

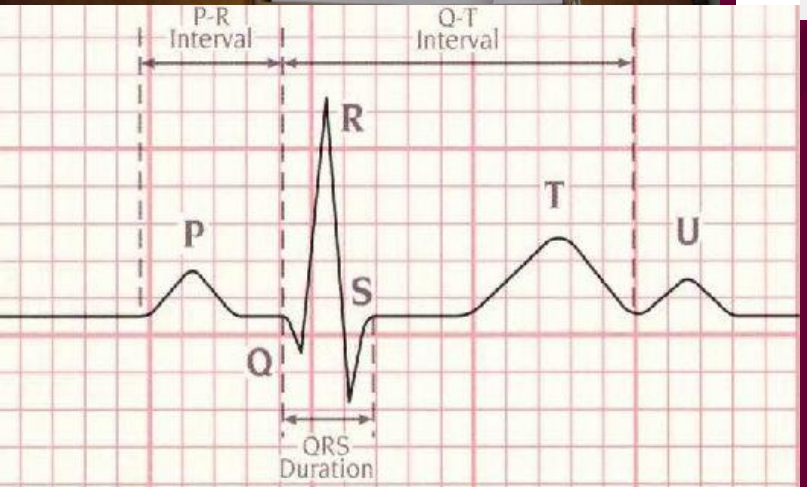
Review of 843 postimplant defibrillator tests from 31 centers.

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 1:1,1:1.5 (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%)**

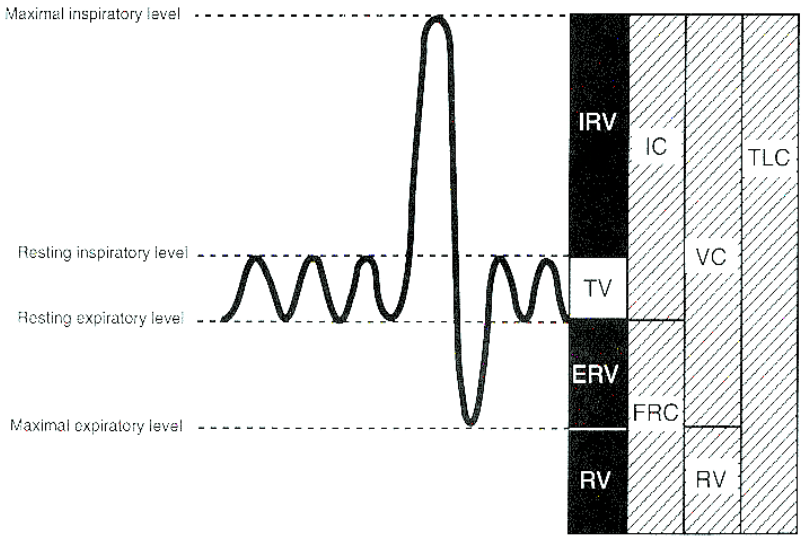
**2.10 OUTPUT CURRENT/POWER**

# การตรวจสมรรถภาพปอด
# Pulmonary Function Test

- 2 techniques

open and closed
circuit technique

**Evaluate the quality of test**
**Comparison with a set of published**





FVC(L)

: M -2.601+0.122A-0.00046$A^2$+0.00023$H^2$-0.00061AH

: F-5.914+ 0.088A-0.0003$A^2$ + 0.056H - 0.0005AH

FEV1(L)

: M -7.697+ 0.123A+0.067H - 0.00034$A^2$ - 0.0007AH

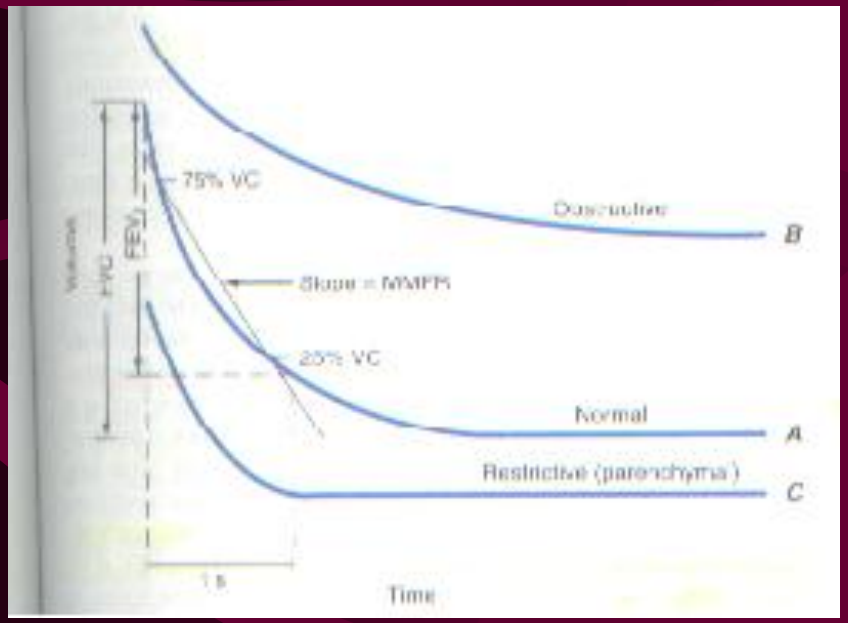
: F-10.603+ 0.085A-0.00019$A^2$ +0.12H -0.00022$H^2$

**FEV1/FVC(%)**

: M19.362+ 0.49A+0.829H - 0.0023$H^2$ - 0.0041AH

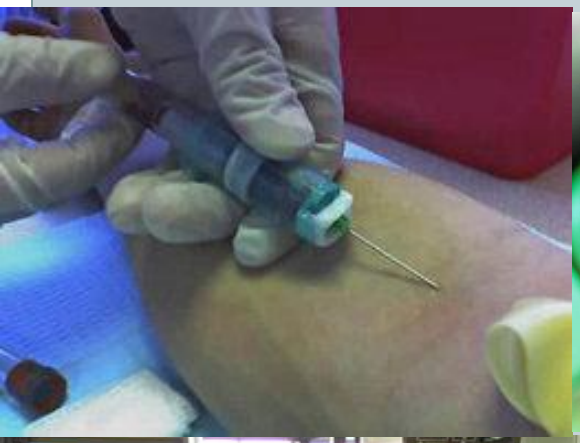
: F83.126+ 0.243A+0.002$A^2$ + 0.08H - 0.0036AH

# 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
  - doctor send a patient home with heart muscle damage, delay in treatment and potentially death
- Falsel high positive troponin result
  - 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.

| General Chemistry and Blood Gas | | | | |
|---|---|---|---|---|
| **TEST** | **Units** | **Low Value** | **High Value** | **Condition** |
| Ammonia | umol/L | N/A | >80 | 0-17 years old only |
| Bilirubin, Total | mg/dL | N/A | >15.0 | 0-30 days old only |
| BUN | mg/dL | N/A | > 90 | Called for selected patients -see below.* First Instance rule applies for inpatient results that are called. |
| Calcium | mg/dL | < 6.0 | > 12.0 | |
| Calcium, Ionized | mg/dL | < 3.00 | > 6.50 | |
| Carbon Monoxide | % | N/A | > 10 | |
| Glucose | mg/dL | < 40 | > 400 | Pediatric > 300 |
| Lactate | mmol/L | N/A | > 4.0 (ED)<br>> 10.0 (All Others) | |
| Magnesium | mg/dL | < 1.0 | > 5.0 | |
| Methemoglobin | % | N/A | > 3.0 | |
| pCO2 | mmHg | < 20 | > 70 | |
| pH | units | < 7.25 | > 7.65 | |
| pO2 | mmHg | < 55 | N/A | <55 Arterial, Capillary <40 mmHg |
| Potassium | mmol/L | < 3 .0 | > 6.0 | |
| Phosphate | mg/dL | < 1.0 | N/A | |
| Sodium | mmol/L | < 120 | > 165* | *First instance rule applies |
| Troponin | ng/mL | N/A | > 0.05 | Inpatients - First Instance rule applies<br>Outpatients - Called |

*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

| Toxicology and Immunosuppressants | | | | |
|---|---|---|---|---|
| **TEST** | **Units** | **Low Value** | **High Value** | **Condition** |
| Acetaminophen | mcg/mL | N/A | ≥ 150 | |
| Amikacin | mcg/mL | N/A | > 35.0 | |
| Amitriptyline | ng/mL | N/A | > 500 | Also called if total tricyclic is >500 |
| Caffeine | mcg/mL | N/A | > 40.0 | |
| Carbamazepine | mcg/mL | N/A | > 15.0 | |
| Carb. Metabolite | mcg/mL | N/A | > 3.7 | Also called if metabolite >50% of parent |
| Clomipramine | ng/mL | N/A | > 500 | Also called if total tricyclic is >500 |
| Cyclosporine | ng/mL | N/A | > 300 | Inpatients - Not called to B4/6 (Abd. TX)<br>Outpatients - Called |
| Desipramine | ng/mL | N/A | > 500 | Also called if total tricyclic is >500 |
| Digoxin | ng/mL | N/A | > 2.5 | |
| Doxepin | ng/mL | N/A | > 500 | Also called if total tricyclic is >500 |
| Ethosuximide | mcg/mL | N/A | > 150.0 | |
| Ethylene Glycol | mg/dL | All results | All results | |
| Everolimus | ng/mL | N/A | >15 | Inpatients - Not called to B4/6 (Abd. TX)<br>Outpatients - Called |
| Felbamate | mcg/mL | N/A | > 100 | |
| Gentamicin | mcg/mL | N/A | > 12.0 | |
| Imipramine | ng/mL | N/A | > 500 ng/mL | Also called if total tricyclic is >500 |
| Isopropanol | mg/dL | All results | All results | |
| Lamotrigine | mcg/mL | N/A | > 20.0 | |
| Lidocaine | mcg/mL | N/A | parent + metab. >8.0 | |
| Lithium | mmol/L | N/A | ≥ 1.50 | |
| Methanol | mg/dL | All results | All results | |
| Nortriptyline | ng/mL | N/A | > 500 | Also called if total tricyclic is >500 |
| Pentobarbital | mg/dL | N/A | > 3.0 | |
| Phenobarbital | mcg/mL | N/A | > 50.0 | |
| Phenytoin | mcg/mL | N/A | > 30.0 | |
| Phenytoin, Unbound | mcg/mL | N/A | > 3.0 | |
| Plasma HGB | mg/dL | N/A | > 100 | |
| Primidone | mcg/mL | N/A | > 15.0 | |
| Salicylate | mg/dL | N/A | > 50 | |
| Sirolimus | ng/mL | N/A | > 20 | Inpatients - Not called to B4/6 (Abd. TX)<br>Outpatients - Called |
| Tacrolimus | ng/mL | N/A | > 15 | Inpatients - Not called to B4/6 (Abd. TX)<br>Outpatients - Called |
| Theophylline | mcg/mL | N/A | > 20.0 | |
| Tobramycin | mcg/mL | N/A | > 12.0 | |
| Vancomycin | mcg/mL | N/A | > 30.0 | |
| Valproate | mcg/mL | N/A | > 150.0 | |

# 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)

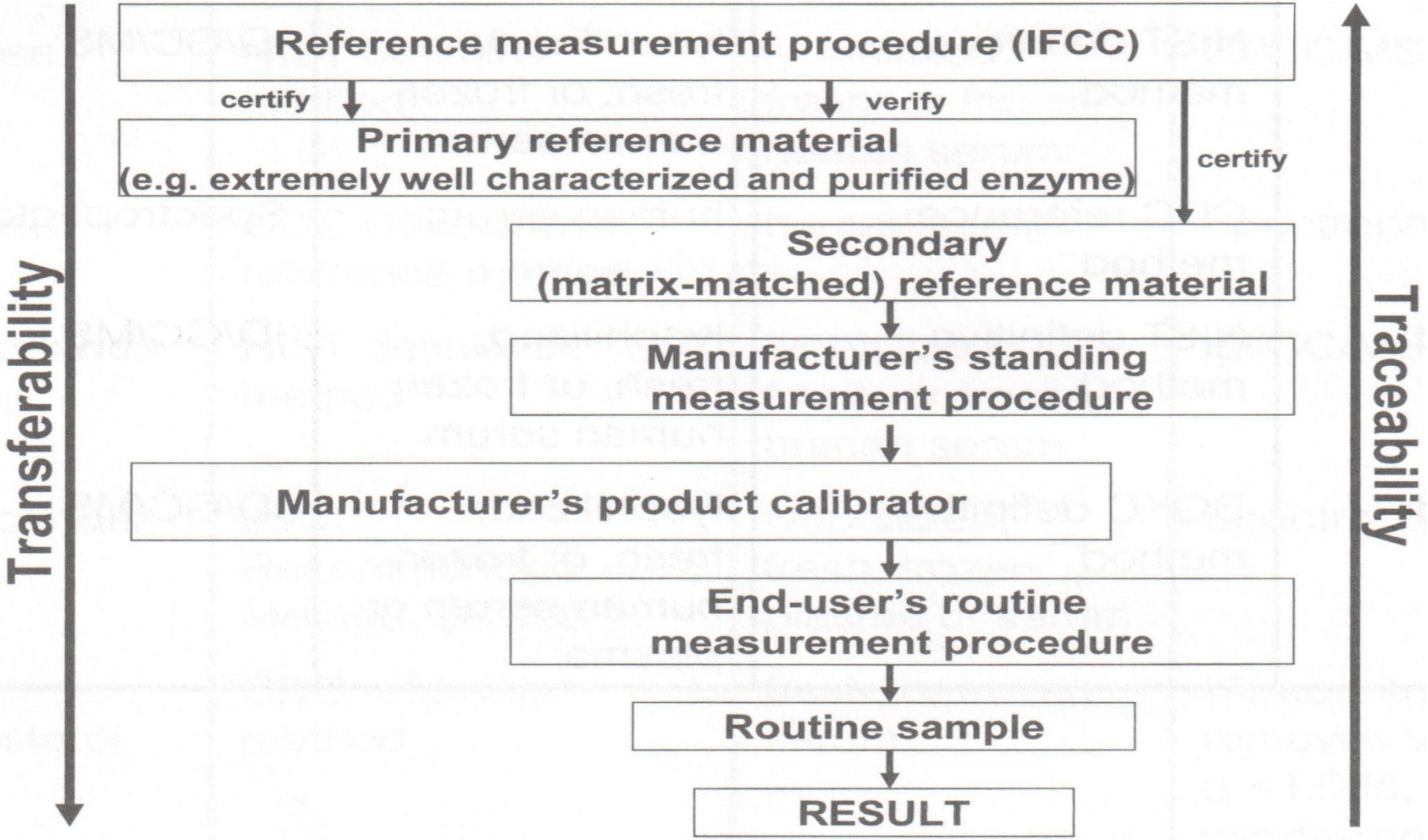
# The technics used involve one or more of

- 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

| Analytes | Reference method / procedures | Applicable matrices | Measurement principle/techniques |
|---|---|---|---|
| Bilirubin | DGKL reference method | lyophilized, fresh or frozen serum | Absorption spectrometry |
| Bilirubin | Doumas reference method for total bilirubin | lyophillized, fresh or frozen human serum | Spectrophotometry |
| Cholesterol | NIST definitive method | lyophilized, fresh, or frozen human serum | ID/GC/MS |
| Cholesterol | CDC Abell-Kendall method | lyophilized, fresh, or frozen human serum | Spectrophotometry |

# Reference system for Enzyme Analysis



# 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

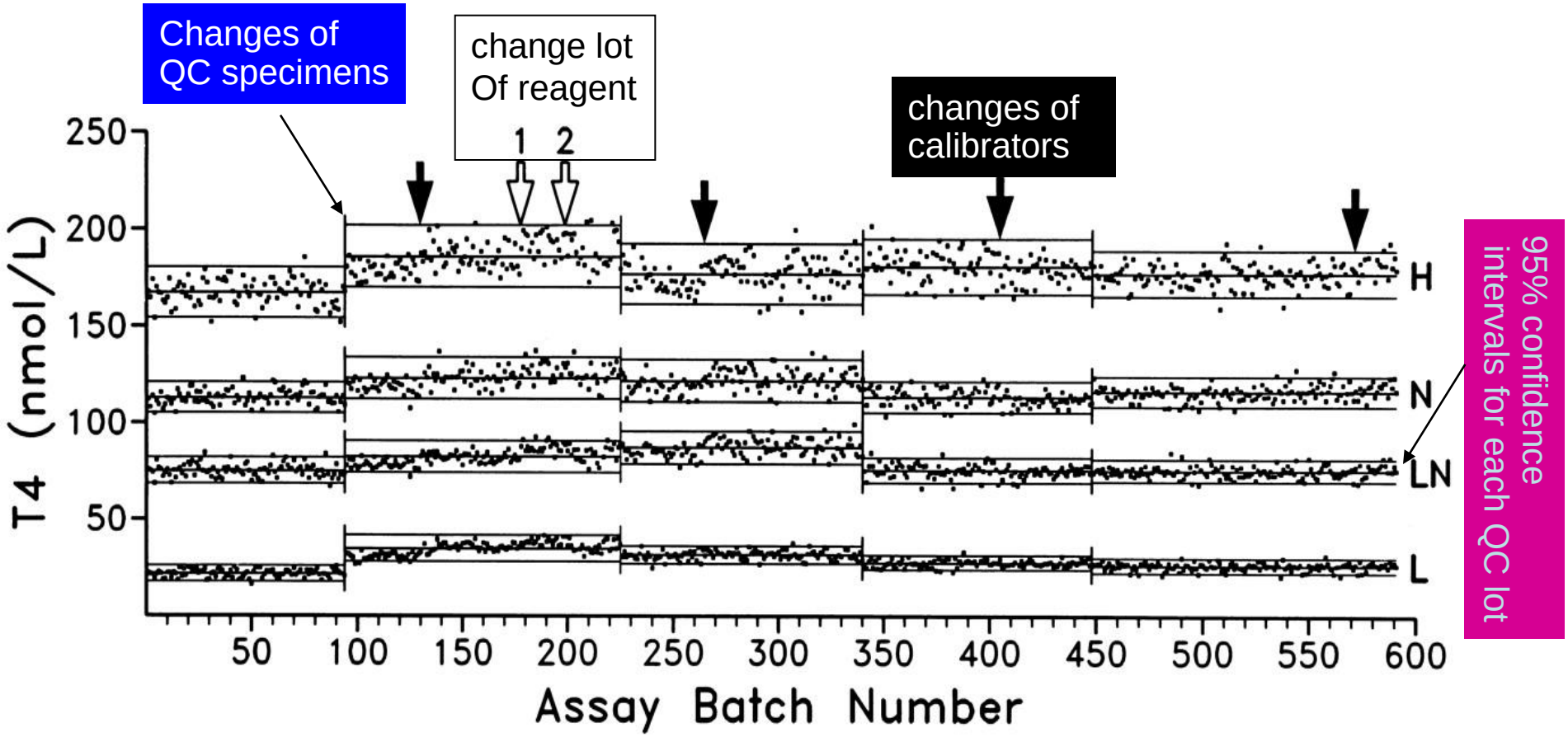
- should be performed at least once every 6 months and whenever the following occur:
- A complete change of reagents is introduced, unless it is demonstrated that control values are not affected
- There is major preventive maintenance or replacement of critical parts
- Control results indicate that there 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 $T_4$ 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 standars

***through an unbroken chain of comparisons***

all having stated uncertainties.

# IVD-Directive

## *Methodological Traceability*

For manufacturers
98/79/EC

*IVDD-requirement on Traceability:*

"The metrological traceability of values assigned to

- calibrators and controls must be assured through available
- reference materials and
- reference measurement procedures."

# IVD-Directive

## Methodological Traceability

### 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

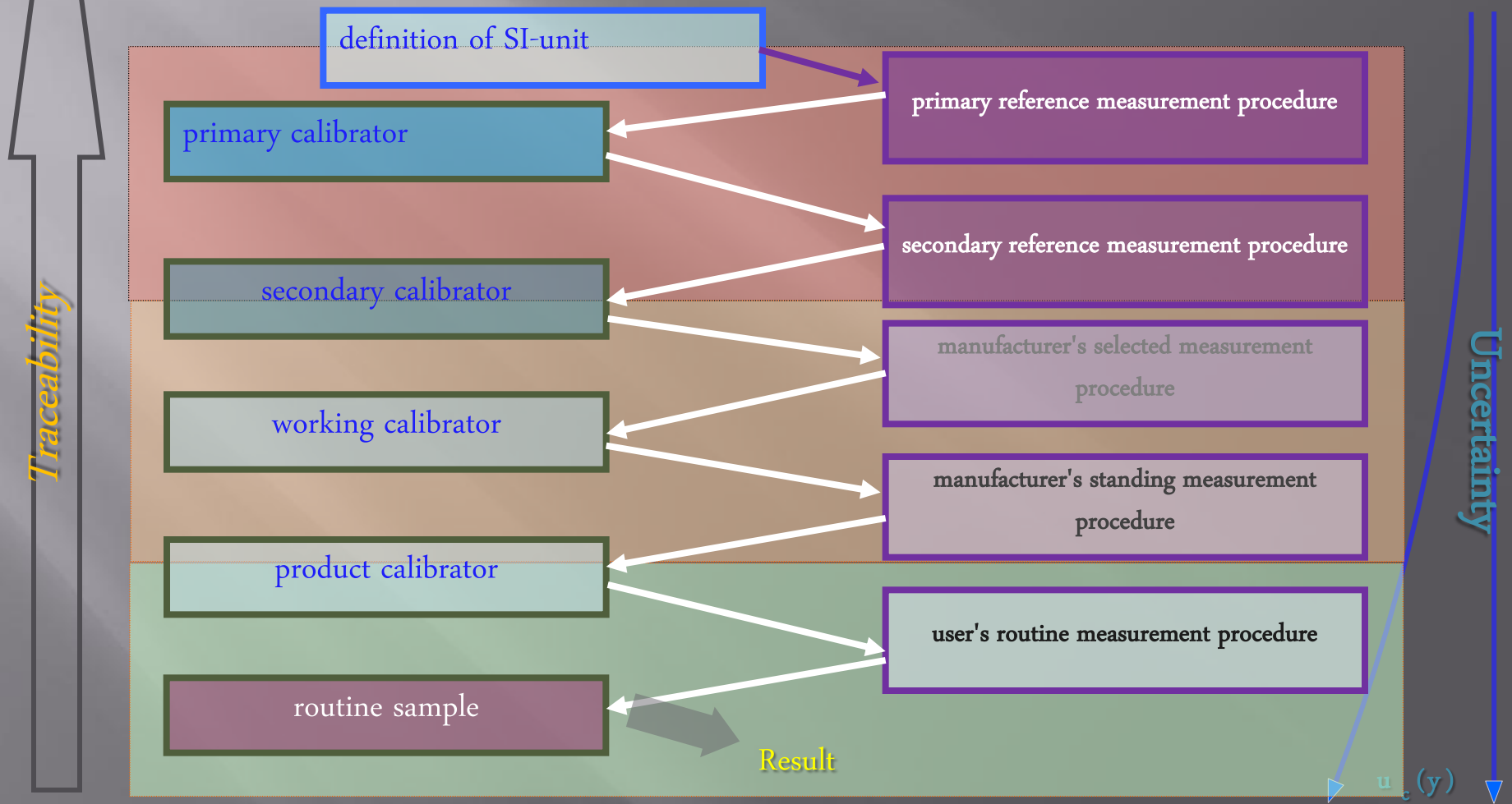
- ***ISO 15193 / EN 12286***
  Presentation of reference measurement procedures

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

- ***ISO 15195***
  Requirements for reference measurement laboratories

# ISO/FDIS 17511 and ISO/FDIS 18153

## *Metrological Traceability*



# 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)

Glucose+APT $\xrightarrow{\text{Hexokinnase}}$ Glucose-6-PO4+ADP

Glucose-6-PO4+NADP $\xrightarrow{\text{G-P dehydrogenase}}$ 6-Phosphogluconate+NADPH+$H^+$

**Glucose oxidase** (oxygen consumption indication)

Glucose + $O_2$ $\xrightarrow{\text{Glucose oxidase}}$ Gluconic acid + $H_2O_2$

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

$H_2O_2$ + pheol + 4-aminoantipyrine $\xrightarrow{\text{Peroxidase}}$ quinoneinine dye +2$H_2O$

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

**Glucose degydrogenase** (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).

***(Panuda,Bull Chiang Mai Assoc Med Sci)***

# Cholesterol in Blood and Plasma

determination on three different methods

Bias and precision at the

-highest level of traceability

Primary reference method

-Isotope dilution mass spectrometry

-measured cholesterol ONLY

(Expensive)

Secondary reference

-Abell-Kendall spectrophotometry

- measured Cholesterol & OTHER sterols (Inexpensive)

Bias and precision at the

End user routine methods

-lowest level of the tracability chain

-Multiple methods for same measurand

-Multiple instrument platforms

(indicator differences)

# Why Test & Calibration?

What you cannot measure
you cannot control

temperature
humidity
mechanical stress

components of
medical equipment

calibration

comparing
reference standard
within defined limits,
accuracies and
Uncertainties

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 & **A**vailable

- 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 IVDMDs*

- **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)

- EN 12286:1998+ 12286/A1:2000; ISO/FDIS 15193
- EN 12287:1999, ISO/FDIS 15194
- prENISO/FDIS 17511
- prENISO/FDIS 18153
- **reference measurement laboratories** prENISO/FDIS 15195