Inspection and Testing of Dialysis Machines

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Abstract Dialysis machines act as artificial kidney performing extracorporeal blood purification to remove excess water, detoxify the blood and balance the blood composition. The chapter presents development of dialysis from experiments to regular life-saving clinical practice, leading to modern dialysis machine organization and functionality. Function deterioration of a hemodialysis device, as a potential harm for a patient safety, is discussed. Further on, overview of standards related to hemodialysis machines safety and risk management is presented. The chapter concludes with a description of a procedure for safety performance inspection focused on key dialysis parameters: temperature and conductivity of dialysate, and blood pressure.

The dialysis machine is a therapeutic device aimed to provide hemodialysis treatment for patients with renal failure. Dialysis machines have central role as renal replacement therapy, with 2 million people in the world receive treatment either with dialysis or a kidney transplant. It is estimated that this number represent only 10% of people who need treatment to live [1].

In the course of the hemodialysis the blood is taken from the shunt between the veins and arteries of the patient forearm. The blood is circulated into the dialyzer for excess water and uremic toxins removal; and returned to the patient. Hemodialysis parameters as flow, temperature, blood pressure, blood leaks, etc. are monitored and controlled during the treatment.

The developments in design and construction of dialysis machines lead to contemporary devices (Fig. 1) equipped with controls, monitors, and alarms that provide for safe proportioning of dialysate.

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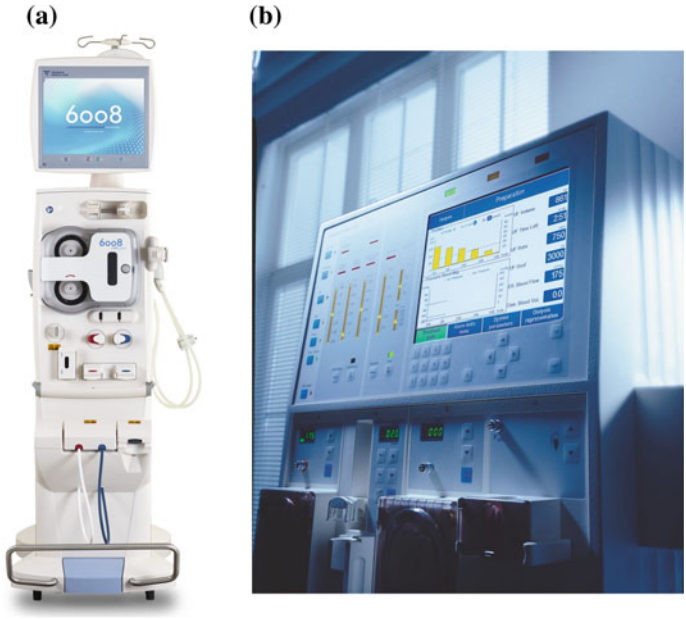

Fig. 1 Hemodialysis 6008 machine (**a**), and online clearance monitor for the 4008H/S (**b**), courtesy Fresenius Medical Care

1 History of Hemodialysis

The process of dialysis is based on principles of osmosis and diffusion. Thomas Graham (1805–1869), a chemist at the Glasgow University, conducted experiments on separating substances using a semi-permeable membrane made of bladders. Graham described the process in 1854 in his paper "Bakerian lecture on osmotic forces" [2]. He noticed the importance of controlling the rates of transfer through the membrane for successful removal of toxins from the blood, and repeated his experiments with different solutes to measure and compare the rates. Graham was the first to use parchment membrane, what he described in paper published in 1861 and he was the first to apply the term dialysis "*to the method of separation by diffusion through a septum of a gelatinous matter*" [3].

In 1855 Adolf Fick (1829–1901) provided mathematical description for selective transport processes through a semipermeable membrane caused by concentration gradients [4]. The description would became known as Fick's laws of diffusion. After Fick, who was the first to use collodion membranes, Schumacher in 1860 obtained excellent results with the skins from collodion, and afterwards with collodion tubes [5]. It was not until 1921 that Arnold Eggerth described standardized process for preparation of collodion membranes with controlled difference in water permeability [6].

The first dialysis device was developed in 1914 at Johns Hopkins University School of Medicine by John Abel (1857–1938) and his colleagues, and they named the device "artificial kidney" [5]. Their device used collodion tubes similar to present day hollow fiber dialyzers and was not used on humans, only for experiments on animals. The first hemodialysis device used to treat human patient was performed by George Haas in 1924 [7]. He developed a glass cylinder dialyzer with collodion tubes, and the first treatment lasted for 15 min. Hass performed several hemodialysis procedures in the following years and reported first clinical results. In his work for producing collodion membranes he followed the standards and procedures described by Eggerth [7].

The pioneer of artificial organs, Willem Kolff (1911–2009) from Netherlands, built in 1943 the rotating drum hemodialysis device using cellophane membranes. Kolff was treating patients with the acute renal failure in the following years, and after the series of unsuccessful treatments, in 1945 his hemodialysis treatment saved a patient's life. Kolff continued his work in the USA and he was influential in developing hemodialysis from experimental into standard clinical therapy.

In 1947 Swedish scientist Nils Alwill (1904–1986) described his apparatus for dialysis with improved function for removal of excess water, based on combination of dialysis and ultrafiltration. Alwill was using cellophane membrane with tight fitting container enabling better control of extracorporeal blood volume [7].

Hemodialysis was not seen as a solution for end-stage chronic renal failure, since dialysis treatment damaged patients' veins and arteries. Typical patient with chronic renal failure would need dialysis treatment three times a week, with sessions lasting several hours, so the next important challenge for hemodialysis treatment was development of a suitable vascular access. Scribner and colleagues created in 1960 a shunt between the radial artery and the cephalic vein using an external silicon device [8]. This solution enabled hemodialysis treatments for patients with end-stage renal failure and marked inception of dialysis as a standard clinical treatment. In 1966 Breschia and Cimino proposed a surgical arteriovenous (AV) fistula as a solution to eliminate the external shunt prone to bleeding and infection. AV fistula demonstrated as safe and long-lasting vascular access [8].

The hemodialysis developed significantly since 1960 with modern dialysis machines with improved dialyzer design, volumetric control, embedded monitoring and alarming systems, high flux membranes. In order to ensure no chemical or bacterial contamination in dialysate, important requirement for dialysis membrane is adsorption capability for bacterial and organic contaminants and inflammatory mediators. In addition, membrane interaction with blood requires blood compatibility and biocompatibility [9]. Significant developments over the recent years are online dialysis monitoring devices and continuous therapy. The modern hemodialysis devices continually measure and record values allowing features as: sodium profiling, ultrafiltration variation based on blood pressure measurement, urea kinetics, etc. [10].

Although dialysis devices are still limited in their functions compared with the complex physiological tasks of the natural kidneys, improvement trends are focused

on: maximum removal of uremic retention substances combined with reduced patient exposure to influence of inflammatory stimuli [9].

2 Dialysis Machine Organization and Functionality

The major components of the hemodialysis machine are: (a) extracorporeal blood circuit, (b) dialysate circuit, and (c) dialyzer. The hemodialysis machine provide monitoring and control functions in order to provide safe, efficient and accurate treatment. The basic schematic diagram of the dialysis machine with the relevant parts is presented in Fig. 2.

Basic functions of dialysis machine are: dialysate preparation, dialysate heating to physiological range, monitoring of conductivity and pH, controlling fluid removal, pumping blood and anticoagulant at determined rates, and monitoring pressure in the extracorporeal blood circuit.

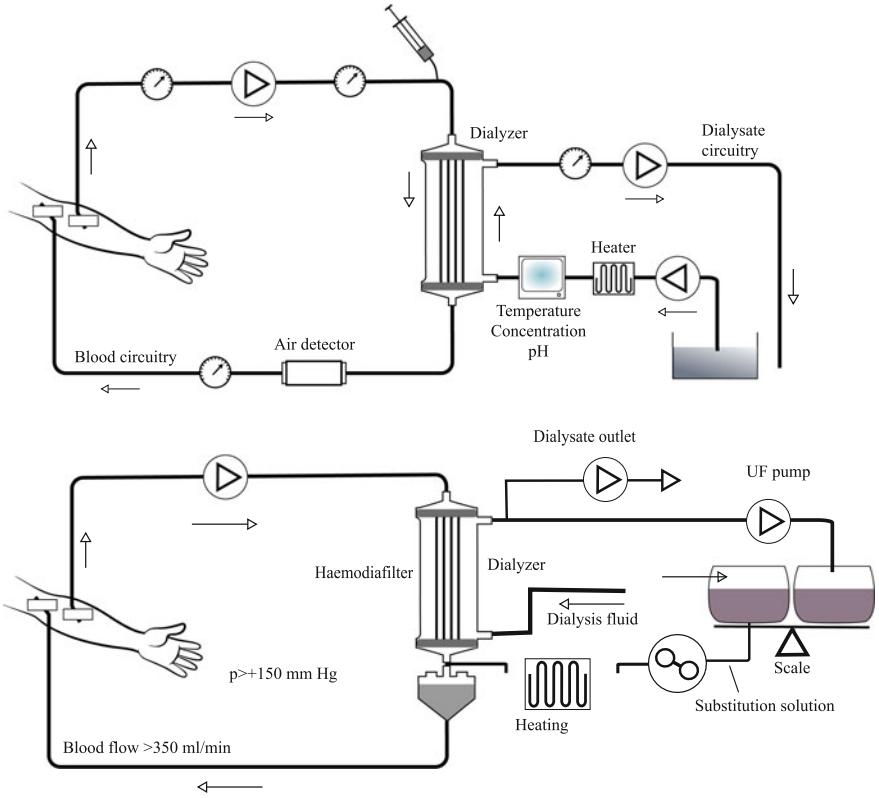

Fig. 2 Dialysis machine—schematic diagram

The *extracorporeal blood circuit* main function is to provide the continuous blood circulation from the patient through a dialyzer, where waste is removed through a semi-permeable membrane, and returned to the patient. The hemodialysis machine administer anticoagulant (heparin) throughout the treatment. The parameters monitored in the blood circuitry are venous and arterial blood pressures, and additional control is air presence detection.

The *dialysate circuitry* is responsible to deliver dialysate fluid and maintain its appropriate temperature, pressure and concentration. Main components of dialysate circuitry are: heating, deaeration, proportioning, ultrafiltration, and monitoring. Monitoring is used for continual verification of the composition of the dialysate and to detect any abnormal occurrence as blood leak in dialysate circuit.

The blood purification takes place in the *dialyzer*, as presented in Fig. 3. Dialyzer contains about 20,000 hollow membranes imitating the filtering function of the natural kidney unit: the glomerulus. The capillary membranes have an inner diameter of 200 μm. The wall of the capillaries consist of membranes with a thickness of about 40 μm through which material exchange takes place [9].

The space between the capillary membranes are perfused with a dialysis fluid or dialysate in opposite flow to the direction of blood flow. This creates a concentration gradient and various uremic toxins are transferred out of the blood into the dialysate as filtrate, by means of the concentration gradients across the semipermeable capillary membranes. The mass transfer of the solutes is based on principles of diffusion (conduction transfer) and ultrafiltration (convection transfer) [11]. A measure for the efficiency of dialysis is clearance, defined as amount of substance removed from blood over a unit of time, divided by the respective concentration in the blood of a patient [9]. Clearance is calculated as a sum of diffusive and convective portion.

Monitoring devices are responsible to detect and identify hazardous events potentially harmful to patients such as: blood leaks, incorrectly dialysate pressures or temperature, and air in the blood. After detecting adverse event device should trigger an alarm and stop circulation in the blood and/or the dialysate circuitry.

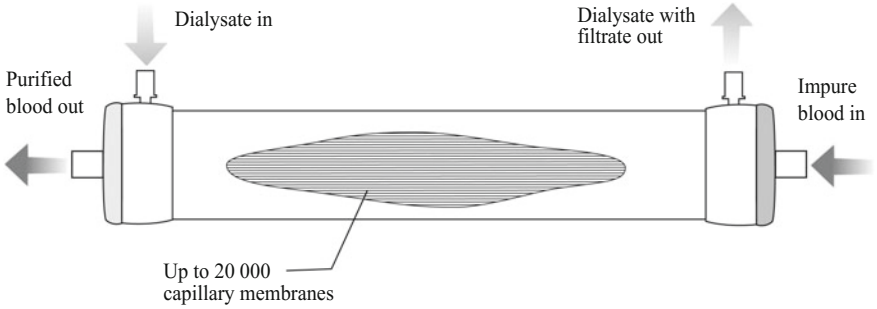

Fig. 3 Dialyzer

Control of the blood pump in the blood circuitry is related to the following:

- Monitor for continual measuring of the blood pressure in the extracorporeal blood circuit in the venous segment.
- Air detection in the venous segment before blood is returned into vein.
- Blood leak monitoring by method of detecting hemoglobin in the dialysate circuitry.

Control of the dialysate circuitry is related to monitoring the following parameters:

- Temperature sensor provides a short feedback to heater to maintain body temperature (35–39) °C; low temperatures can cause shivering and high temperatures can cause protein denaturing or hemolysis.
- Conductivity monitor checks the electrolyte concentrations and prevents any adverse events caused by incorrect dialysate proportioning.
- Measuring pH value, as useful additional parameter for the dialysate proportioning monitoring.

If the concentration of electrolytes changes, the voltage will change, thus increase in electrolytes shall increase the conductivity of the dialysate. Conductivity reflects electrolyte concentration of dialysate and provides for real-time estimate of concentration [12, 13]. This feature of modern dialysis machines support comparison with other important physiological parameters and can help in deciding on appropriate composition of the dialysate what has been one of the central topics in the delivery of dialysis treatment [14]. Alarm limits for conductivity can be adjusted based on set-up concentrate composition and for standard temperature. Conductivity measurements are temperature compensated. Although monitoring display range can be as 10–17 mS/cm, devices have predefined safety alarm limits, as e.g. 12–16.5 mS/cm [15]. Conductivity is also used for modelling sodium mass transfer; calculating differences in conductivity values measured pre and post dialyzer, and conductivity can be used as a surrogate for sodium concentration with one mS/cm conductivity equivalent to 10 meq/L sodium [12].

During the design of a medical device, potential risks and hazards should be identified, and monitoring, control and alerting functions foreseen in order to reduce probability of occurrence of any harm to patient health to a minimum level.

3 Potential Safety Hazards in Dialysis

Safety of a patient is the most important requirement for medical device design and operation. Erroneous hemodialysis device or improper clinical application may cause different serious adverse effects as hemorrhage, low blood pressure, uremia, and etc. [16–19].

A multidisciplinary task force composed by engineers representing manufacturers of dialysis machines, nephrology clinicians, and dialysis experts published their thorough analysis of hazards and harms related to hemodialysis devices [20].

Based on reviewing adverse events databases, literature and clinical experience, the task force identified and described more than 50 different harms related to a hemodialysis device. The harms are classified in five levels of severity and linked to underlying hazards. The hazards are classified as: biocompatibility, biological, chemical, electromagnetic, mechanical, function deterioration, use error and labelling. Further on hazards are related to physical quantities if adverse event is caused by fault measurement.

Medical device inspections are aimed to prevent device function deterioration as a potential cause of adverse events and harm to a patient. Subset of harms identified in [20] is presented in Table 1, with a following selection criteria: hazards of a type function deterioration, including only hazards related to measurable quantity. With exception of Under dialysis, selected harms are classified with a highest level of severity (5 and 4).

Analyzing quantities in the Table 1, and knowing that conductivity reflects electrolyte concentration, it is possible to conclude that the key parameters for a patient safety are: dialysate temperature, dialysate concentration and extracorporeal blood pressure.

Table 1 Hemodialysis device hazards related to function deterioration

Harm	Hazardous situation	Related quantity	Severity (min = 1, max = 5)
Acid-base imbalance	High/low bicarbonate in dialysate/substitution fluid	Bicarbonate in dialysate (mmol/L)	4
Hemolysis	Reduced dialysate tonicity	Dialysate conductivity (mS/cm)	5
Hemolysis	Blood exposed to high temperature	Dialysate temperature (°C)	5
Hemolysis	Mechanical stress to red cells as a result of extracorporeal circulation	Extracorporeal BP (negative and positive; mmHg)	5
Hyperthermia	Extracorporeal blood exposed to high temperature	Dialysate temperature (°C)	5
Hypothermia	Extracorporeal blood exposed to low temperature	Dialysate temperature (°C)	5
Plasma electrolyte imbalance	High/low sodium in dialysate/substitution fluid	Sodium in dialysate (mmol/L)	5
Plasma electrolyte imbalance	High/low potassium in dialysate/substitution fluid	Potassium in dialysate (mmol/L)	5
Plasma electrolyte imbalance	High/low calcium in dialysate/substitution fluid	Calcium in dialysate (mmol/L)	5
Underdialysis	Reduced dialysis effectiveness (i.e., inadequate urea removal)	Kt/V	2

4 Standards and Regulations for Dialysis Machines

With an objective to protect hemodialysis patients from adverse effects, responsible international and national organizations provide standards, regulations and guidelines to the medical equipment manufacturers, and to the medical professionals for the use, care, and/or processing of a medical device or system.

4.1 Standards

The International Electrotechnical Commission (IEC) has provided the standard IEC 60601-1:2005 (Medical electrical equipment—Part 1) specifying general requirements for basic safety and essential performance of medical devices [21].

IEC 60601 is a series of technical standards for the safety and essential performance of medical electrical (ME) equipment. The consolidated version is the third edition IEC 60601-1 from 2005 with its amendment 1 from 2012. These general requirements are supplemented by the special requirements of collateral and particular standards.

IEC 60601-2-16:2012 is particular standard for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment. This particular standard takes into consideration the specific safety requirements concerning electrical safety and patient safety, and does not take into consideration the dialysis fluid control system of hemodialysis equipment using regeneration of dialysis fluid and central delivery systems [22].

The general standard, IEC 60601 Part 1 is adopted in many countries by their regulatory bodies and recognized as requirement for the commercialization of medical equipment. Some countries also adopted standards or guidelines for further safety testing, inspection and calibration of medical equipment specific for different phases of the medical equipment life cycle. Some examples are: acceptance test, inspections performed in regular intervals, and/or directly following service or repair.

Regulations stipulating technical and measurement requirements for medical equipment include following chapters: terms and definitions, general technical requirements, measurement requirements, identification, marking and documents.

The IEC 60601 defines that ME equipment shall be marked with the information on supply voltage(s) or voltage range(s) to which it may be connected. ME equipment shall be accompanied by documents containing the instructions for use and a technical description, and also all data that is essential for safe operation, transport and storage, and measures or conditions necessary for installing the ME equipment, and preparing it for use.

It is a common practice that the IEC 60601 standard has been adapted into local national standard for use in specific country. In such cases national standards can

introduce additional requirements specific for that environment, such as voltage to which the ME equipment may be connected.

Standard documents provide applicable terms and definitions. Dialysis machine is considered as ME equipment or ME system used to perform hemodialysis, hemofiltration and/or hemodiafiltration.

The IEC 60601-2-16 provide following definitions:

Hemodialysis (HD) is defined as "process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient with renal insufficiency are corrected by bidirectional diffusive transport and ultrafiltration across a semi-permeable membrane separating the blood from the dialyzing fluid."

Hemofiltration (HF) is defined as "process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient with renal insufficiency are corrected by unidirectional convective transport via ultrafiltration across a semi-permeable membrane separating the blood from the dialyzing fluid. Ultrafiltrate is simultaneously replaced by an approximately isoosmolar substitution fluid at a rate such that the difference between the ultrafiltration rate and the rate of substitution fluid addition will lead to removal of the excess fluid over the course of the treatment."

Hemodiafiltration (HDF) is defined as "process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient with renal insufficiency are corrected by simultaneous combination of HD and HF."

The scope of the IEC 60601-2-16 states that the particular requirements in that standard do not apply to: extracorporeal circuits, dialyzers, dialysis fluid concentrates, water treatment equipment, and equipment used to perform peritoneal dialysis.

International Standard Organization (ISO) provided several standards related to specific aspect of hemodialysis:

- ISO 8637:2010 Cardiovascular implants and extracorporeal systems—Hemodialysers, hemodiafilters and hemoconcentrators
- ISO 8638:2010 Cardiovascular implants and extracorporeal systems—Extracorporeal blood circuit for hemodialysers, hemodiafilters and hemofilters
- ISO 11663:2014 Quality of dialysis fluid for hemodialysis and related therapies
- ISO 13958:2014 Concentrates for hemodialysis and related therapies
- ISO 13959:2014 Water for hemodialysis and related therapies
- ISO 23500:2014 Guidance for the preparation and quality management of fluids for hemodialysis and related therapies
- ISO 26722:2014 Water treatment equipment for hemodialysis applications and related therapies

The following sections cite Abstracts of these standards:

- "ISO 8637:2010 specifies requirements for hemodialysers, hemodiafilters, hemofilters and hemoconcentrators for use in humans" [23].

- "ISO 8638:2010 specifies requirements for hemodialysers, hemodiafilters, hemofilters and hemoconcentrators and (integral and non-integral) transducer protectors which are intended for use in hemodialysis, hemodiafiltration and hemofiltration" [24].
- "ISO 11663:2014 specifies minimum quality requirements for dialysis fluids used in hemodialysis and hemodiafiltration, including substitution fluid for hemodiafiltration and hemofiltration" [25].
- "ISO 13958:2014 specifies minimum requirements for concentrates used for hemodialysis and related therapies. For the purpose of ISO 13958:2014, "concentrates" are a mixture of chemicals and water, or chemicals in the form of dry powder or other highly concentrated media that are delivered to the end user to make dialysis fluid used to perform hemodialysis and related therapies. ISO 13958:2014 is addressed to the manufacturer of such concentrates. ISO 13958:2014 includes concentrates in both liquid and powder forms. Also included are additives, also called spikes, which are chemicals that may be added to the concentrate to increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid. ISO 13958:2014 also gives requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility" [26].
- "ISO 13959:2014 specifies minimum requirements for water to be used in haemodialysis and related therapies. ISO 13959:2014 includes water to be used in the preparation of concentrates, dialysis fluids for hemodialysis, hemodiafiltration and hemofiltration, and for the reprocessing of hemodialysers" [27].
- "ISO 23500:2014 provides dialysis practitioners with guidance on the preparation of dialysis fluid for hemodialysis and related therapies and substitution fluid for use in online therapies, such as hemodiafiltration and hemofiltration. ISO 23500:2014 functions as a recommended practice. ISO 23500:2014 addresses the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. For the purposes of ISO 23500:2014, the dialysis fluid includes dialysis water used for the preparation of dialysis fluid and substitution fluid, dialysis water used for the preparation of concentrates at the user's facility, as well as concentrates and the final dialysis fluid and substitution fluid" [28].
- "ISO 26722:2014 is addressed to the manufacturer and/or supplier of water treatment systems and/or devices used for the express purpose of providing water for haemodialysis or related therapies. ISO 26722:2014 covers devices used to treat water intended for use in the delivery of haemodialysis and related therapies, including water used for: (1) the preparation of concentrates from powder or other highly concentrated media at a dialysis facility; (2) the preparation of dialysis fluid, including dialysis fluid that can be used for the preparation of substitution fluid; (3) the reprocessing of dialysers for multiple uses. Included within the scope of ISO 26722:2014 are all devices, piping and fittings between the point at which potable water is delivered to the water treatment system, and the point of use of the dialysis water. Examples of devices included within the scope of ISO 26722:2014 are water purification devices,

online water quality monitors (such as conductivity monitors), and piping systems for the distribution of dialysis water" [29].

Other relevant ISO standards are:

- "ISO 13485:2016 specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements" [30].
- "ISO 14971:2007 specifies a process for a manufacturer to identify the hazards associated with medical devices, including in vitro diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. The requirements of ISO 14971:2007 are applicable to all stages of the life-cycle of a medical device" [31].

4.2 Conformity Assessment

Conformity or compliance assessment involves a set of processes that show medical equipment meets the requirements set forth in the standards related to device type. The main forms of conformity assessment are testing, certification, and inspection. In addition to standards and regulations against which products are assessed, regulatory bodies adopt procedures for specific assessment methods as acceptance test procedure, procedure for regular inspections.

The necessary content of a technical documentation for compliance assessment according to the IEC 60601 is as follows:

- A general description of the device/device family, including any variants planned,
- Design and specifications,
- Label and instructions for use,
- Reference to applicable harmonized standards,
- Results of risk analysis,
- Evidence that the essential requirements have been met.

Dialysis machine design and construction, under referential operating conditions, shall provide for protection against electrical hazard, excessive temperature, and intrusion of fire, dust or water in the device housing. Identification requirements define that dialysis machines shall be marked with the name and trademark of manufacturer, serial number, production year, and model or type reference.

Risk analysis is important for deciding which aspects of a medical device's performance are essential. If variation in a performance may result in injury, then it is considered essential performance. Defining essential performance associated with risk management is crucial for compliance with the IEC 60601. Maintaining risk at

acceptable levels is responsibility of the alarming functions of medical device, and alarming functions are built upon accuracy and reliability of the key performance parameters measurement.

Within the European Union medical devices conformity assessment is defined with the essential requirements of the Medical Device Directive (MDD) 2007/47/EC amending the MDD 93/42/EEC [32]. The MDD 93/42/EEC has introduced medical device classification system in order to apply gradual and appropriate conformity assessment procedure. According to the MDD 93/42/EEC dialysis machines are devices with measuring function. With respective to additional rules as duration of contact with the body, degree of invasiveness, and local or systemic effect; dialysis machines are classified as Class IIb medical devices [33] and should follow the procedures referred to in Annex IV, V or VI of the MDD 93/42/EEC, for the "aspects of manufacture concerned with the conformity of the products with the metrological requirements" [34].

5 Dialysis Machine as a Measuring Device

At a national level there are national institutes of metrology (NMIs) responsible to establish and maintain reference standards for these metrological requirements, more specific for the following metrology areas: (1) *scientific metrology* through traceability to the International System of Units, or SI; (2) *legal metrology* through regulated measurements and measuring instruments, and (3) *industrial metrology* through confidence in testing and measurement results via certification, standardization, accreditation and calibration. In case of pending national regulations, directive MDD 93/42/EEC, also IEC 60601 and ISO 62353 refer to standardized safety tests and measurement of output parameters of medical devices related directly to patient.

The IEC 60601 addresses risk management stating: "that the technical description provided by the manufacturer shall include characteristics of the ME equipment, including range, accuracy, and precision of the displayed values." Further on it is defined: "that the instructions for use shall identify the parts on which *preventive inspection and maintenance* shall be performed, by service personnel, including the periods to be applied."

Within the scope of patient safety and risk management the *safety performance inspections* of medical devices and corresponding metrological regulations gain importance. The accuracy and reliability of medical measurements are of direct consequences for the health of a patient, and quality assurance of measurement should be ensured by metrological tools, as calibrations, legal metrological inspections and reference measurement methods [35].

The inspection process should be conducted by a medical device inspection laboratory accredited to ISO 17020 with the objective to determine if specified safety requirements and manufacturer specifications are met. The inspection process procedure should be defined with: purpose and scope, frequency, respective

standards, required equipment, permissible error range, assessment process description, remedial action, and required documents. The inspection should be documented by an Inspection Report issued by the accredited laboratory and should comprise Work Order, Measurement Report, Calculation of absolute and relative error of device, and Inspection Certificate [36–40].

In the Sect. 3 the key parameters for a patient safety are identified as: dialysate temperature, dialysate concentration and extracorporeal blood pressure. The measurement components for these parameters require periodic inspections to maintain safe and effective hemodialysis systems.

Measurement range for dialysis machine measurements as defined in respective manufacturer technical documentation [15] are:

- Conductivity (10–17) mS/cm
- Temperature (35–39) °C
- Pressure (−300 to 500) mmHg

Measurement requirements define maximum permissible measurement error as defined in respective manufacturer technical documentation [15] are:

- Conductivity ±1.5% (average)
- Temperature ±3 °C (calibration conditions for dialysate flow of 500 mL/min)
- Pressure ±20 mmHg or ±10% of measurement reading, whichever is greater

6 Dialysis Machine Inspection Procedure

Dialysis machine inspection procedure includes (a) visual inspection and (b) verification of measurement error.

Visual inspection, although not defined in the IEC 60601, are important step for the safety inspections. Visual inspection is a simple procedure confirming that medical device is still in compliance with the manufacturer specifications. Visual inspection include:

- Contamination inspection
- Integrity and functionality inspection
- Markings and labelling inspection

Integrity inspection is visual examination of device and its mechanical parts including: connectors, tubes, cables, sensors, etc. The examiner shall look for cracks, obstructions and other damages.

Functionality inspection is testing of all device functions performance and visual examination of their status on device monitor. Functional inspection includes testing of the alarm system. If the device is damaged or if it fails to perform the functions, the inspection shall be temporary interrupted, and device shall be sent for repair. This remedy action shall be taken with the consent of the institution under

the inspection. After repair is performed, depending on the result of the repair, inspection is either continued, or if the device is considered defective or malfunctioning, the device shall be taken out of usage and sent for further remedy action.

Device measurement error verification objective is to confirm that the measurement error is smaller than specified maximum permissible error.

Modern instrumentation systems used for hemodialysis device verification are portable and modular. Dialysis meters are composed of the main display module and sensor modules for measuring specific parameter as: conductivity, pH, temperature and pressure (Fig. 4) of the dialysate fluids supplied by hemodialysis delivery systems. These physical values are primary parameters indicating safe and accurate operation of hemodialysis systems.

In case the dialyses meter is accompanied with the specific software application, during the inspection process the meter shall be connected to the computer running licensed software application for data upload and processing.

Verification is performed to establish indication error for the key dialysis parameters, and verification method shall include range, number of required observations, error type to be calculated, and number of points in calibration curve. Example verification method for the key physical quantities:

- Conductivity: single measurement (10–17 mS/mm), determining relative error,
- Temperature: single measurement (35–39 °C), determining absolute error,
- Pressure: six measurements (−300 mmHg, −150 mmHg, 0 mmHg, 150 mmHg, 350 mmHg, 500 mmHg), determining relative error.

Verification process for pressure sensor linearity is in accordance with the measurement experience of collecting measurement data at six points, at equal intervals along the measurement scale.

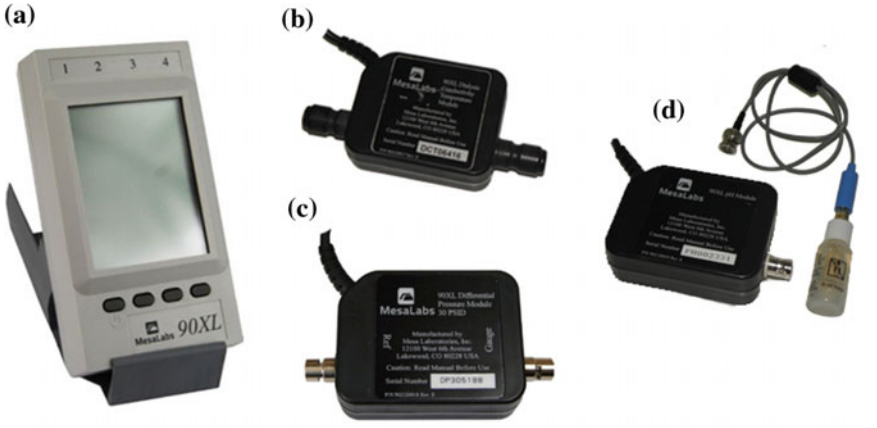

Fig. 4 90XL™ meter (**a**), with conductivity and temperature (**b**), pressure (**c**), and pH module (**d**)

Maximum permissible measurement error pending relevant international regulations, as defined in respective manufacturer technical documentation [15]:

- Conductivity ±1.5% (average)
- Temperature ±3 °C (calibration conditions for dialysate flow of 500 mL/min)
- Pressure ±20 mmHg or ±10% of measurement reading, whichever is greater.

Verification process is described as follows:

Dialysis machine and dialyses meter shall be connected to power supply as marked on the device. If the dialyses meter is battery powered, the batteries should be recharged prior to verification. The sensor modules needed for the verification shall be attach to the meter device with cables that plug into connectors on the meter.

Conductivity and temperature measurements are taken as the dialysis fluid flows through the dialysate circuitry. If performing sample based measurement the sensor end of the conductivity/temperature sensor module is inserted into the container of test solution. Sample solution steadily flow through the sensor module, and when the display is stable, measurement may be taken. For in-line measurement method, conductivity/temperature sensor module is connected directly to the dialysate delivery system. After the flow is re-established through the sensor module measurement may be taken when the display is stable.

Pressure measurement is performed only after one hour post to attaching a pressure sensor module to the meter device. The pressure sensor module may be used for verification of arterial, venous, negative and differential pressure of the delivery system fluid. Intrusion of fluids into the pressure sensor module is prevented with transducer protectors.

Hemodialysis machine verification include inspection of measurement range and permissible measurement error for defined measurement values. If permissible measurement error is larger than stipulated maximum permissible error dialysis machine shall be ordered for service and verification shall be reiterated. Upon completed inspection procedure the inspection officer shall draft inspection results report and mark the device with the appropriate label.

Legal metrology should provide the necessary infrastructure for the traceability of regulated measurements and measuring instruments to SI or national standard, through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty [41]. For medical devices that are applied in the EU but which are not covered by legal metrology in some countries calibration process has to be ensured with an adequate traceability chain.

If medical devices are not covered by legal metrology traceability of results is ensured through calibration procedures with an adequate traceability chain pertaining to the accuracy and correctness of measurement methods. Accordingly, it is necessary to establish adequate traceability chain for measurement results of dialysis machines as medical devices with the measuring function.

For that reason, dialysis meter and verifying sensor modules should be calibrated, according to the ISO 17025 standard, and the results of conductivity,

pressure, and temperature measurements can be related to national or international standards, through an unbroken chain of comparisons all having stated uncertainties. Therefore, manufacturers in their specifications and manuals for dialysis meters recommend calibration using traceable reference standards before use or whenever inaccurate readings are suspected [42].

Example of inclusion of dialysis machines in national legal metrology system is Bosnia and Herzegovina. Institute of Metrology of Bosnia and Herzegovina (IMBIH) adopted in 2014 the Measurement and Technical Requirements Rule Book for Dialysis Machines, that establish the metrological characteristics, required of dialysis machines, and which specify methods and equipment for checking their conformity [43].

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