Chapter 15
Biomedical Metrology: Role in Nation’s Healthcare Sector

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Abstract Metrological assurance is decisive in medical equipment calibration and is indispensable in quality control and assurance, risk assessment, monitoring of the patients, diagnosis and treatment of patients. As a part of health care regulations, the biomedical equipment must demonstrate compliance with metrological traceability to SI unit chain through a chain of calibration, verification and certification on the performance of the equipment. In this context, CSIR-NPL is serving the country by providing calibration facilities traceable to SI units to support the quality regulation of Medical equipment. The Biomedical Metrology program at CSIR-NPL contributes enormously to the economic development and healthcare sector of the country by way of providing calibration and consultancy services to healthcare sector that includes accredited laboratories, regulatory bodies, hospitals and testing laboratories, etc. In this chapter, we have elaborated the role of regulatory bodies of India and National Metrology Institute, CSIR-NPL in context of the “New Medical Device Rule”. We also critically analyse the importance and implementation of Medical Device policy and Metrology, its significance on healthcare sector and the quality infrastructure of Medical devices. The contribution of CSIR, NPL in strengthening and supporting the medical device policy, as well as the establishment of medical device calibration facilities and the development of diagnostic devices through R & D are highlighted and discussed briefly.

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– Walter Fletcher (1892-1956)
15.1 Introduction to Biomedical Metrology

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Implementation of Quality infrastructure boosts the healthy competition in the industrial sector and ensures the safety of the products, which facilitates the ease in international trade and the protection of consumers. Accuracy and precision in the functioning of medical devices used for diagnostic and treatment in the medical area are of paramount importance as the quality and maintenance of the biomedical devices are directly linked to the health care system of a Nation. The calibration for the medical devices used in the healthcare sector, where the measurement results are traceable to SI units are vital for the maintenance of proper healthcare system, prevention and control of health ailments and diseases. Calibration and metrology in this area result in reliable measurements and thus have innumerable benefits in the health sector. Therefore, the efficacy of quality control steps depends directly on the accuracy and precision of the testing and measurement procedure, the quality control and periodic calibration and testing of the measuring equipment. To prevent Medical device errors, it is essential to assess the performance of the equipment and get reliable measurements. In present times, a large portion of the global economy and health care sector depends on accurate and precise measurements and tests with stated uncertainty, which is trusted and accepted internationally [1]. The business and the national economy depend on the manufacturing and production of the quality-controlled products in the health sector such as medical electronics through sustained innovation, calibration, testing and accreditation traceable to international technical standards. Metrological assurance is very crucial in medical equipment calibration and is indispensable in quality control and assurance, risk assessment, monitoring of the patients, diagnosis and treatment of patients. As a part of health care regulations, the biomedical equipment must demonstrate compliance with metrological traceability chain through the calibration and certification of the performance of the equipment. These certificates will be valid if issued by a laboratory accredited for the activities concerned traceable to the SI units. In this context, the development of biomedical equipment standards supports the National economy by strengthening the quality infrastructure and thereby minimizing the dependence on other International NMIs for Quality assurance.

Indian Medical Device Industry sector is growing fast and its current market size is at least $11 billion. The sector growing rapidly at an unprecedented scale and the statistical estimates indicate that the market size is expected to reach $280 billion by 2025 mainly due to the building up of quality infrastructure in the nation [2]. In 2015, India permitted 100 percent FDI through automatic route in Medical device sector. This step resulted in the steep increase in the FDI to 430 million dollars in 2016. A total of USD 2.1 billion foreign direct investment (FDI) has come to India in the medical device sector during the last ten years [3]. The significant growth in FDI
inflow in the recent past is certainly helping and encouraging new R&D activities, start-ups and manufacturing innovations, in the area of medical electronic products. The development of new advancements in the medical device technologies and their product quality implementation has led to the enhancement in the Indian medical tourism. During the last few years, there is significant acceleration in International patients travelling to India to avail the cost-effective and quality health care facilities. The accreditations to hospitals and clinics are provided by Joint Commission International (JCI) and National Accreditation Board of Hospitals (NABH) to maintain the quality healthcare structure and to achieve a safe environment for patients, staff and visitors.

Accreditation for medical electronics and clinical diagnostics is a boon and highly beneficial for hospitals in achieving their desired quality standards. Indian Health ministry has published New Medical Device Rule 2017 with effective medical equipment regulations on 31.01.2017 under Drugs and Cosmetics Act, which are being implemented with effect from January 1, 2018.

These regulations emphasize the critical requirement of quality control and periodic calibration checks of medical equipment [4]. In this context, CSIR-NPL, National Metrology Institute is serving the country by providing calibration facilities traceable to National standards to support the quality regulation of Medical equipment.

15.2 Medical Device Policy and Metrology

In India, various acts have been formulated time to time to strengthen the National quality infrastructure in healthcare sector and a few among them are Legal metrology act 2009, New Drugs and Clinical Trials Rules, 2019, Food Safety and Standards Rules, 2011, Food Safety and Standards Act, 2006 (Act 34 of 2006), etc. All these have served the very purpose for which they were formulated. However, in recent years, world has seen changes to meet their national requirements. India imports almost 80% of its medical instruments every year, and one of the reasons is the lack of quality infrastructure in medical sector.

In spite of above-said acts, the quality of imported equipment was not regulated and this resulted in a much-needed act on the regulation of medical devices. Development of medical device policy has been the most critical and challenging task, not just for our country but across the globe. As per the survey of WHO in the year 2010, among the low-income countries, 33% had a national policy for health technology, leaving out 67% of countries having no defined policy. Whereas, around 55% of the countries have a notified health regulation authority for the enforcement and implementation of medical device regulations and 85% of the countries have a designated unit within the health ministry which is responsible for managing the technical and quality issues of the medical devices [5]. One of the major challenges in formulating policy was that the medical device ranges from very sophisticated equipment to ordinary medimeter/ruler as measuring tool. Some are life-saving, while some have an
indispensable role in operations. Till date, variety of different international classification systems is being followed for medical devices in the world. This irregular classification of devices is one of the prime reasons for not having a uniform defined policy globally. Indian medical device policy classifies them in four major categories, on the basis of their risk assessment and a detailed classification is discussed in section ‘Role of Legal Metrology in Medical Device Sector’. However, this qualification is as per their intended use and not the technology involved in manufacturing, operation or calibration. Every country has its own norms for classification and challenges and required various degrees of skills for operation and even maintenance. However, considering its relevance in patient safety it is vital to achieve harmonization in the nomenclature of medical devices.

Proper functioning and calibration of the medical devices over time is another major challenge, where the metrological assurance plays its critical role. The functioning of healthcare quality infrastructure is represented in Fig. 15.1 showing the government policies such as the medical device rule 2017, which defines the role of primary service providers of quality infrastructures whose services are utilized by the industries and private labs to support quality health structure of the Nation. It is the unbroken chain of quality assurance that ultimately governs the quality of life. Thus, metrological traceability of medical device is an essential component that ensures the functioning of the device, and therefore has been given utmost importance in Medical device policy 2017.

Fig. 15.1 Schematic of India’s quality infrastructure in health sector demonstrating the impact of policies such as medical device rule 2017 on quality of life
15.2.1 Medical Device Quality Infrastructure

Keeping in view of rapid growth in Indian economy, its size and significance in global trade, it is highly desirable to establish a robust ‘Quality Infrastructure’ in India. This would stimulate the economic growth and boost the ‘Made in India’ program. The “standards” are considered as catalysts for technological development, industrial growth and well-being of the society. The role of standards and regulations have been well recognized in global trade through international agreements like World Trade Organization (WTO). In India, strategies have been formulated to coordinate the standardization work with technological, societal, and economic development at the national level and efforts are being made for global standardization through various regulatory bodies as discussed below.

15.2.1.1 Regulatory Bodies

The Indian medical equipment and medical electronics sector is regulated by four regulatory bodies (i) Ministry of Health and Family Welfare, (ii) Drug Controller General India (DCGI), (iii) Bureau of Indian Standards (BIS) and (iv) Atomic Energy Regulatory Board (AERB). However, In India, “Medical Devices” have no separate regulatory status and are under the Drugs and Cosmetics Act, 1940, and Central Drugs Standard Control Organization (CDSCO) is responsible for its regulation in coordination with Department of Consumer Affairs for labeling and declaration requirements for notified medical devices under the Legal Metrology Act, 2009 [6] and the Legal Metrology Rule (Packaged Commodities) Rules, 2011 and consequent legal metrology rule 2019 [7].

Role of CDSCO and Medical Device Rule 2017

Indian Medical Device sector is regulated by The Drugs and Cosmetics Act, 1940 (“DCA/Act”) and its enforcement is the responsibility of the Central and the state Governments. Drugs Controller General of India (“DCGI”) of “CDSCO” ascertains the formulation of policies and implementation of the act throughout the country by coordinating with State Drugs Licensing Authorities.

Prior to year 2006, the manufacturers from India and abroad could sell the medical devices in Indian market without any restrictions, due to the absence of necessary regulation. However, since 2006, as per the regulations of CDSCO, before marketing the notified medical equipment must comply with the Indian Medical Device Regulation described by CDSCO. This organization handles regulation and approval of new drugs, clinical trials, quality control of the drugs, coordinating with state drug control organizations by providing expert opinion about the uniformity and enforcement of Drugs and cosmetic act.
As per the CDSCO guidelines, the conformity assessment should be done and the guidelines are different for different classes of devices as per the classification. For Class A (low risk) and B devices (low moderate risk), the medical equipment manufacturers are permitted to perform their own conformity assessment procedures, whereas for other classes (Class C, moderate high risk and D devices, high risk), central licensing approval authority in consultation with the BIS notified the approved list of authorized laboratories or bodies to perform conformity assessment. There is a need to submit an application for the assessment of class C and D devices by the medical device manufactures to any of these authorized notified laboratories [8].

Since Medical Devices are high on innovation, India is becoming the world’s preferred medical tourism place, therefore, defining an appropriate framework for standards and calibration of medical instruments becomes imperative. This has to lead the center to unveiled a Medical Device Rule 2017, which came in to force with effect from January 2018, for regulating manufacturing/Import/sale/Clinical investigation (Rule-19 in chapter-III, of Medical Device Rule, 2017, prescribes that no Medical device Testing laboratory, shall be so designated unless it has been duly accredited by NABL or any other similar body) and other related issues concerning Medical devices. CDSCO has introduced risk based classification of various medical devices as Class A, Class B, Class C and Class D and defined the product standards. Besides this, the organization has introduced single-window clearance and defined the timelines for issuing licenses to the Medical device companies and industries to facilitate the high-quality end products and accelerate “Make in India” Program. In addition, it also consolidated the requirement of obtaining import license and registration certificate into a single license for foreign manufacturers [4]. CDSCO has amended Medical Device rules to simplify the rules for easy regulation of Medical devices to obtain licensing and registration thereby accelerating the manufacture and export of indigenously made medical devices from India. On February 11, 2020, the Ministry of Health and Family Welfare (MoH and FW) issued two notifications in the Indian Gazette [9, 10] on registration rules of medical devices and new description of medical devices. The Medical Devices (Amendment) Rules, 2020, the latter amends the Medical Devices Rules, 2017, and has been effective from April 1, 2020. The Ministry after consultation with Drugs Technical Advisory Board (DTAB) has intended for a cumulative effect of both these notifications to ensure that all medical devices must meet certain standards, safety measures and quality and for mandatory registration of all medical devices as per the CDSCO enacted act 1940. Until February 11, 2020, only 37 medical devices have been notified as drugs by CDSCO [4], which are shown listed in Table 15.1. CSIR-NPL provides measurement traceability for physical and electrical parameters to some of the medical devices listed in the table are traceable to primary standards maintained at CSIR, NPL like disposable hypodermic syringes, blood monitoring devices, digital thermometers, defibrillators, MRI equipment and ultrasound equipment, whereas the measurement traceability to X-Ray machine are being provided by Atomic Energy Regulatory Board (AERB).

As per the new Medical device rule, Medical devices which come under the following classification (Fig. 15.2) will be regulated as ‘drug’ under the DCA and MDR.
### Table 15.1 A list of 37 notified medical devices before 11th February, 2020

| S. No. | Medical devices                                                                 |
|--------|---------------------------------------------------------------------------------|
| 1      | Disposable hypodermic syringes                                                  |
| 2      | Disposable hypodermic needles                                                   |
| 3      | Disposable perfusion sets                                                       |
| 4      | Substances used for in vitro diagnosis including blood grouping sera             |
| 5      | Cardiac stents                                                                  |
| 6      | Drug-eluting stents                                                             |
| 7      | Catheters                                                                       |
| 8      | Intra ocular lenses                                                             |
| 9      | I.V. Cannulae                                                                   |
| 10     | Bone cements                                                                    |
| 11     | Heart valves                                                                    |
| 12     | Scalp vein set                                                                  |
| 13     | Orthopedic implants                                                             |
| 14     | Internal prosthetic replacements                                                |
| 15     | Ablation devices                                                                |
| 16     | Ligatures, sutures and staplers                                                  |
| 17     | Intra uterine devices (Cu-T)                                                     |
| 18     | Tubal rings                                                                     |
| 19     | Condoms                                                                         |
| 20     | Surgical dressings                                                              |
| 21     | Umbilical tapes                                                                 |
| 22     | Blood/blood component bags                                                      |
| 23     | Organ preservative solution                                                      |
| 24     | Nebulizer                                                                       |
| 25     | Blood pressure monitoring device                                                 |
| 26     | Glucometer                                                                       |
| 27     | Digital thermometer                                                             |
| 28     | All implantable medical devices equipment                                       |
| 29     | CT scan equipment                                                               |
| 30     | MRI equipment                                                                    |
| 31     | Defibrillators                                                                  |
| 32     | PET equipment                                                                    |
| 33     | X-ray machine                                                                    |
| 34     | Dialysis machine                                                                |
| 35     | Bone marrow cell separator                                                      |
| 36     | Disinfectants and insecticide                                                   |
| 37     | Ultrasound equipment                                                            |
All the medical devices other than 37 will now be referred as “Newly Notified Medical Devices” under the new definition of medical devices. “The new medical device Rules 2020 has been introduced by CDSCO to implement quality healthcare structure in India to ensure that every medical device either manufactured in India or imported, have quality assurance before marketing. According to newly notified medical device rule, all the medical device manufacturers, whether indigenous or imported must mandatorily register for the certificate of compliance as per the ISO-13,485 guidelines. The Medical devices and Quality Management Systems and their Requirements for Regulatory Purposes are to be compliant with ISO 13,485 guidelines. The registered company or the manufacturers mandatorily require to maintain and implement the quality management system by proper documentation according to ISO 13,485 guidelines and by conducting periodic auditing.

For the licensing and registration, medical devices are categorized on the basis of the prescribed risk. The suitable timeline for the registration as per the risk-based category shall serve as a breather for pharmaceutical companies. It opens a wider scope to test and modify such devices, which fall under the ambit of the new definition, post-introduction upon the relevant market. Under section 3 of the BIS Act, 1985 (63 of 1985) [11], the quality guidelines indicate that all the medical devices shall be in conformity with BIS standards. However, in case of non-availability of any such standards, the medical devices shall conform to the International standards laid down by ISO and IEC [12] or any other pharmacopeia standards. The Act further mentioned that in absentia of written standards by international or national organizations, it must conform to the validated manufacturer’s standards.

The overall objective of Drugs and Cosmetics Act, 1940 (DCA), and Medical Device Rules, 2017 (MDR) is to:

1. Regulate the manufacture, distribution and sale including import of notified medical devices.
2. Ascertained the availability of notified medical devices with standard quality to the end user.
The Medical Device Rules, 2017 under the Drug Control Authority, regulate the following categories of Medical devices:

(i) Notified Medical Devices are defined as those which are intended to use for the prevention of mitigation, diagnosis and treatment of diseases or disorders in human beings or animals. Under the DCA, these medical devices are notified by the government from time to time.

(ii) Devices intended to functioning or structure of the human body such as Mechanical contraceptives insecticides and disinfectants, etc.

(iii) Surgical Devices used for surgical applications such as staples, sutures, dressings, bandages, ligatures, blood and blood component collection bags, etc.

(iv) Medical Devices used for in vitro diagnosis.

Role of Legal Metrology in Medical Device Sector

The Legal Metrology (Packaged Commodity) Rules, 2011, notified under the Legal Metrology Act, 2009, regulates the packaging and labelling of pre-packed commodities. The notified medical devices are required to declare the particulars like the name of the country of origin or manufacture or assembly on the package with effect from 1st January 2018. National Pharmaceutical Pricing Authority (NPPA), a drug price regulator, notified 22 medical devices as ‘drugs’ that must carry MRP on packs. These devices included surgical dressings, heart valves, stents, disposable hypodermic syringes, condoms, orthopaedic implants, etc.

15.2.1.2 Role of Bureau of Indian Standard in Medical Metrology

BIS is the Indian counterpart of ISO and works in the documentation of quality standards as per the country requirements. BIS has dedicated division dealing with medical devices under the name “Medical Equipment and Hospital Planning (MHD)”. At present, 20 committees as shown in Table 15.2 are operating under MHD and have published 1731 standards in this area till July 18, 2020 [13].

MHD mainly focuses on making written standards in diversified areas such as equipment relating to rehabilitation, diagnosis, dental implants, surgery, etc. Besides this, the organization also contributes to written standards in Bio-medical Waste Management and Infection Control in Hospital management, Medical Biotechnology and Nanotechnology, etc. Scientists working on biomedical metrology at CSIR-NPL are members of BIS committees of MHD and are contributing their expertise in formulating the written standards for various medical devices. To make the conformity assessment in actual practice as per the BIS standards, it has introduced a “Laboratory Recognition Scheme” with laboratories in India and abroad to cater to the needs of medical device manufacturers. The product certification scheme is also executed by BIS for ensuring conformity with Indian Standard. The manufactured quality of the Indian Products is certified with ISI mark by BIS to comply with its
Table 15.2 A list of total number of committees under MHD and standard published [13]

| S. No. | Committee number | Committee name                                                                 | Published standards |
|--------|------------------|--------------------------------------------------------------------------------|---------------------|
| 1      | MHD 1            | Surgical instruments                                                           | 115                 |
| 2      | MHD 2            | Orthopaedic Instruments, Implants and accessories                               | 130                 |
| 3      | MHD 3            | Obstetric and gynaecological instruments and appliances                         | 64                  |
| 4      | MHD 4            | Ear, nose and throat surgery instruments                                         | 82                  |
| 5      | MHD 5            | Ophthalmic instruments and appliances                                           | 91                  |
| 6      | MHD 6            | Thoracic and cardiovascular surgery instruments                                 | 53                  |
| 7      | MHD 7            | Neurosurgery instruments Implants and accessories                                | 46                  |
| 8      | MHD 8            | Dentistry                                                                      | 174                 |
| 9      | MHD 9            | Artificial limbs, Rehabilitation appliances and equipment for the disabled      | 116                 |
| 10     | MHD 10           | Medical laboratory instruments                                                  | 32                  |
| 11     | MHD 11           | Anaesthetic, resuscitation and allied equipment                                  | 58                  |
| 12     | MHD 12           | Hospital equipment and surgical disposal                                        | 137                 |
| 13     | MHD 13           | Veterinary hospital planning and surgical instruments                           | 17                  |
| 14     | MHD 14           | Hospital planning                                                               | 42                  |
| 15     | MHD 15           | Electromedical diagnostic imaging and radiotherapy equipment                    | 92                  |
| 16     | MHD 17           | Health informatics                                                              | 88                  |
| 17     | MHD 19           | Immuno-biological diagnostic kits                                               | 34                  |
| 18     | MHD 20           | Medical biotechnology and nanotechnology                                        | 2                   |
| 19     | MHD 21           | Hospital biomedical waste management and infection control                       | 0                   |
| 20     | MHD 23           | Anatomy and forensic sciences equipment                                          | 0                   |
|        |                  | Total no of published standards as on 18th July 2020                            | 1373                |

standard. The compliance of several products with Indian standards is mandatory as per the Indian Government guidelines under various statues in the public interest.

Medical device rules, under chapter III, section 11, clearly state that national accreditation body shall not act as a notified body. The notified body herein refers to a body corporate or other legal entity, registered under rule 13, as a body competent to carry out audit of the manufacturing site, assessment, and verifications of specified category of medical devices for establishing conformity with standards. At present, various quality implementing and regulatory bodies have overlapping
roles in the quality infrastructure pertaining to medical devices and therefore, they need to interact periodically to avoid the overlapping mandates by actively involving CSIR-NPL (the NMI of India) for the improvement and advancements in the quality infrastructure.

### 15.2.1.3 Role of Quality Council of India in Health Sector

QCI is a registered non-profit society and is responsible for the establishment, operation and promotion of national accreditation structure under the ministry of commerce and Industry. QCI was established in 1977 jointly by the Government of India, Confederation of Indian Industry (CII), Federation of Indian Chambers of Commerce and Industry (FICCI) and Associated Chambers of Commerce and Industry of India (ASSOCHAM). QCI is administrated by a Council of 38 members with equal representations of industry, government, and consumers [14]. The QCI accreditation structure is depicted in Fig. 15.3, wherein the organization functions through the executive boards in the specific areas, i.e., accreditation for:

1. Healthcare Establishments
2. Conformity Assessment Bodies
3. Education and Vocational Training Providers.

### Role of NABL in Medical Metrology

In India, NABL adopts the responsibility of assessment and accreditation of Testing and Calibration Laboratories for biomedical equipment as per the international standard ISO/IEC 17,025 and ISO 15,189 guidelines. Till March 2020, NABL has provided accreditation to 1206 biomedical equipment calibration laboratories based on the quality assessment as per the ISO guidelines of medical equipment [15].

![Accreditation boards under quality control of India](Fig. 15.3)
NABL lays down specific criterion for the laboratories to operate and demonstrate its competency to carry out calibration of medical devices in accordance with ISO/IEC 17,025:2005, ISO 13,485, IEC 60,601, IEC 62,353 [16]. The purpose of these general requirements are (i) to have a uniformity between the laboratories, assessors and assessment process in terms of maximum permissible error, calibration and measurement capability, measurement uncertainty, etc. in accordance with national/international standards; (ii) To achieve uniformity in selection of equipment, calibration methods, maintaining required environmental conditions and personnel with relevant qualification and experience.

Role of NABH

NABH provides accreditation to hospitals and sectors specific to healthcare on similar lines as NABL provides accreditation at laboratory level and relies on the competency of calibration and testing laboratories. NABH is also a constituent board of QCI. It was set up in the year 2006 to establish and operate accreditation program for healthcare organizations on the lines of International Accreditation Standards like JCI of USA and ACHS of Australia. These accreditations bodies are members of International Society for Quality in Health Care (ISQua) that grants approval to Accreditation Bodies in the area of healthcare as the mark of equivalence of accreditation program of member countries. NABH is a founder member of the Asian Society for Quality in Healthcare (ASQua), which is a sub-continent body of ISQua. It can be seen as a chain of accreditation bodies, ensuring uniform protocols across the globe. To cater to the needs of the consumers, the above bodies have been structured to set criterion for the growth of health care industry [17]. NABH in India is known for maintaining the highest benchmark standard for hospital quality infrastructure in the country. The various activities of NABH are to provide accreditation and quality promotion in healthcare facilities through offering healthcare quality courses, workshops and trainings in patient safety, as represented schematically in Fig. 15.4.

NABH is a designed accreditation board in the medical field and it highly focuses on quality medical care and safety, and quality in diagnosis. NABH accreditation ensures regular training, qualification and expertise of the hospital staff for patient safety and quality. Additionally, NABH insures improved quality of additional services provided by hospitals such as empanelment of Insurance and third-party administrator. It also stimulates continuous improvement and commitment to quality care. There are different levels of accreditation for hospitals like pre-entry level, surveillance or re-assessment, 3rd edition standard level and 4th edition standards. The accreditation for pre-entry level is valid for three years, but the surveillance should be done after two years or 18 months of pre-entry level accreditation. It is different from NABL as a formal recognition of the competency of a lab-based on Third-party assessment following international guidelines. At present NABH claims to have 102 standards with 636 objective elements grouped in ten main chapters. For any hospital to obtain NABH accreditation, it must ensure the implementation of
above-said standards in their setup. As per NABH records currently over 350 hospitals in India are accredited and according to a report of “centre for disease dynamics, economics and policy” published on 20th April 2020 [18], around 70,000 hospitals in the country are NABH accredited, which is still an insignificant number considering the size of the Nation and population.

### 15.2.2 Role of National Metrology Institute (NMI)

NMIs occupy the top level of the calibration hierarchy and are officially entrusted with calibrations, and are responsible for the implementation and maintenance of the National metrology infrastructure. CSIR-NPL is designated National Metrological Institute of India, which has taken initiatives in establishing a biomedical metrology facility to cater to the need of medical device sector. To achieve its designated mandate in medical metrology, the laboratory has actively participated in Asia Pacific Metrology Program (APMP) by becoming a member of a dedicated medical metrology focus group with the primary scope as defined and represented schematically in Fig. 15.5.

APMP medical focus group formed with collaboration among NMI’s of Asia pacific region has the following objectives:
Fig. 15.5 Significant activities of APMP medical focus group

(i) Establishment of collaborations on progress of medical metrology techniques, instrumentation and facilities, etc.
(ii) Development and validation of calibration procedures for medical devices.

15.3 Biomedical Metrology and Instrumentation at CSIR-NPL

The economic development has created vast commercial opportunities in India in the area of medical sciences for various industries and other stakeholders. The medical devices in the country are getting measurement traceability from other NMIs abroad and therefore are shipped abroad every year for calibration. National Measurement Institutes (NMIs) from other countries are capturing Indian market and a huge amount of money is going abroad for the same. As NMI’s of other countries have well established biomedical metrology group, the same is required in our country too to support the medical device sector, especially in the context of newly enacted ‘Medical Device Rule 2017’ which oversee the quality and condition of the medical devices used in the healthcare sector. It highlights the requirement of establishing Calibration and Testing centres for medical devices, thereby providing quality control regulation in health sectors. CSIR-NPL is uniquely positioned to cater to emerging needs of
calibration in medical devices because of the availability of relevant expertise and mandate of the laboratory.

CSIR-NPL is promoting the quality measurements in the domains of biomedical metrology under its mission project through working with different stakeholders, for fulfilling the societal needs of the nation in healthcare sector with the following objectives:

(i) To establish and realize National Standards of measurements compatible to International standards in biomedical instrumentation through continuous research and development.
(ii) To provide Apex level calibration and dissemination of standards in the area of biomedical instruments as per ISO17025:2017 at one place.
(iii) Establishment of medical equipment standards in India.
(iv) Calibration and testing.
(v) Research and development.
(vi) To provide the above facility to various hospitals, clinical labs, industries, institutes and other stake holders.
(vii) Training on biomedical calibration and testing.
(viii) Preparation of standard documents to be used by regulatory bodies such as care NABH, NABL, CDSCO and BIS at National level.
(ix) Promote importance of standards in health care.

This activity could be further elaborated with a flow diagram as shown in Fig. 15.6. The activity is mainly focused on the establishment of a calibration facility for medical devices with an unbroken chain of measurement tractability to national/international standards, which in turn supports the accreditation bodies like NABL, NABH, NACB and BIS in implementing the medical device regulations. The metrological program is also providing training to healthcare personnel and supporting the other calibration laboratories, manufacturers and end users by providing calibration services to promote the quality infrastructure in Indian medical device sector.

The outcome of such an establishment would support the country healthcare sector in the following way:

(i) Excellence, accountability and uniformity in medical facilities throughout the country.
(ii) Trust building on medical health-care industry, resulting in India as major hub in international market for medical tourism.
(iii) Restriction on non-quality controlled equipments from grey market.
(iv) Such establishment would improve the health of public, support Indian industries to export their equipment with globally accepted norms, creation of jobs and start-ups.
(v) Providing high-quality control regulation through standardization
(vi) Biomedical equipments in health sectors, which in turn would contribute to healthy, risk-free and dispute free treatments to society.
Taking concern of public health in our country, the scientists associated with biomedical metrology activity are also engaged in the R&D of fabricating indigenous point-of-care devices using novel biocompatible sensing materials for the diagnosis of chronic disease viz. renal dysfunction and heart disease by quantifying their markers and constantly working towards improved diagnostic systems.

### 15.3.1 Calibration services

Biomedical metrology program at CSIR-NPL is committed towards establishment and realization of National Standards for biomedical metrology. The Institute is developing measurements compatible to International standards in biomedical instrumentation through continuous research and development. So far the institute has developed national standard for medical devices such as defibrillator, blood pressure, clinical thermometer, magnetic resonance imaging devices and disseminating its services to nation through calibration.

In order to protect the traceable calibration certificate issued by the CSIR-NPL from being misused or copied by unethical means for unwanted reasons and to protect its genuineness and originality, a trademark as shown in Fig. 15.7, is secured for the above said calibration services.
15.3.1.1 Calibration Setup of Defibrillator Analyzer/Defibrillator

With the onset of new medical device rule in 2017, CSIR-NPL had initiated establishments of much-required standards as per the policy. In this regard, we have established an apex level calibration facility for defibrillator analyzer by installing a set-up of a primary standard of defibrillator with its physical parameters traceable to national standards [19]. This facility is the “first-of-its-kind” in India to cater the needs of quality assurance in the area of healthcare. Defibrillator analyzer is used for the calibration of the defibrillators. Defibrillator is the most critical life-saving biomedical equipment used to restore the normal heart rhythm of a patient by applying an energy pulse during sudden cardiac arrest and for this reason it is mandatory to have defibrillator installed at public places, offices, airports, railway stations, ambulances, hospitals, etc. Defibrillator works by supply monobasic/biphasic pulse to patient with energy levels in range of 50–360 J. It is critical to supply defined energy to patient as per physiological conditions; else the treatment will not be effective and may cause death. Thus, it is extremely essential to have defibrillator analyzer calibrated and in turn the defibrillator with high precision, in stipulated time periodically, as per the accuracy requirement of the energy function, specified in the international standard (IEC 60,601-2-4) for medical electrical equipment. Traceability of the measurement result is linked with calibrated standards (voltage, resistance and time) used for the calibration of Defibrillator Analyzer (DA). A schematic setup of the calibration facility is shown in Fig. 15.8, wherein a defibrillator is used as an energy source which discharges a pulse of required energy to the defibrillator analyzer (unit under test). A specially designed high voltage divider is used to steps down the discharged

Fig. 15.7 A composite trademark for the scientific and technological services provided for the calibration of biomedical equipment
Fig. 15.8 A setup of calibration facility for Defibrillator analyzer and defibrillator

voltage in 1000:1 (V/V) ratio for calculating the energy through a high-speed digital storage oscilloscope (DSO).

The energy contained in a pulse of arbitrary wave shape, such as the biphasic waveform, is area drawn by biphasic curve, thus total energy is a sum of these two arbitrary shaped areas (A1 and A2) as shown in Fig. 15.8, and can be calculated [20] using Eq. 15.1.

\[ E = \int_{0}^{T} v(t) \cdot i(t) \, dt \quad (15.1) \]

where

- \( E \) is the energy of the discharge pulse (J).
- \( v(t) \) is the voltage as a function of time.
- \( i(t) \) is the current as a function of time.
- \( T \) is the time duration of the pulse.

The current in Eq. 15.1 is replaced with voltage according to ohm’s law, wherein the energy dissipated through pulse across a physiological resistance (~50 Ω) is determined by using Eq. 15.2.
\[ E = \int_{0}^{T} [v(t)]^2 \cdot dt / R_L \]  

(15.2)

The reference energy (source) is calculated by Eq. 15.3

\[ E_{\text{calculated}} = \sum \left[ (\text{data}(i) + V_c) \times V_r \right]^2 / R_L \times t_{\text{sampling}} \]  

(15.3)

The corrections in the DA reading is estimated with respect to reference (source) energy by using Eq. 15.4

\[ E_c = E_{\text{calculated}} - E_{\text{reading}} \]  

(15.4)

where
- \( E_c \) is the correction in UUT (DA) energy;
- \( E_{\text{calculated}} \) is the reference (source) calculated energy;
- \( E_{\text{reading}} \) is the mean reading of UUT (DA);
- Data \((i)\) is the \(i\)th reading of the DSO (V);
- \( V_c \) is the correction in DSO (V);
- \( V_r \) is the ratio of the high voltage divider;
- \( R \) is the internal resistance of UUT (DA) (\(\Omega\));
- \( t_{\text{sampling}} \) is the sampling time of the DSO (s);

The actual set up of configuration for the above-said facility is shown in Fig. 15.9 for the accurate measurement of energy with a standard uncertainty \(u(x) \approx 0.64\) J.

The combined uncertainty is calculated by taking into account the individual measurement uncertainty associated with all the possible sources (voltage, resistance and time) as envisaged by a fish bone diagram given in Fig. 15.10.

A flow chart to demonstrate the measurement traceability is shown in Fig. 15.11, wherein the physical parameters involved in the measurement are traceable to national
standards viz. voltage, resistance and time, maintained at CSIR-NPL, as described in Chaps. 3 and 5, through which a derived unit of energy (J) is assigned to the primary source (defibrillator).

This calibration facility is providing services to various stakeholders with effect from 1st September 2018. The recent beneficiaries of this service are the testing and calibration laboratories viz. Lawkim Motors Group (Godrej), Mumbai; Tektronix, Mumbai, TransCal Pvt. Ltd., Bangalore; APEX Laboratories, Jaipur, Rajasthan, Life-Force Pvt. Ltd. Faridabad, Haryana, Kirloskar Group, Bangalore, Inspire Biomed, Calcutta, West Bengal, KIMS Healthcare Management Ltd., Thiruvananthapuram, Kerala, etc.
15.3.1.2 Calibration of Syringe Pump and Infusion Pump Analyzer

A syringe pump is extensively used biomedical equipment. The prime application of the syringe pump is the accurate and precise delivery of drugs, blood and even nutrition, as volume (mass) is the most critical parameter in medical treatment. It also has wide applications in microfluidic-based biomedical devices and thus its traceable calibration is crucial for accurate measurements. Gravimetric method is the most preferred primary calibration method for infusion pump and syringe pump. A calibration setup of syringe pump based on Gravimetric method is shown in Fig. 15.12. Gravimetric principle relates the flow of a liquid to its volume delivered in the specified time. Further, the volume and density of the known liquid, at a given temperature, is directly associated with the weight of the liquid, which is measured using high precision balance, and thus obtained its traceability from mass. Though gravitation method, being a primary method, is mostly used by NMI’s for the calibration of syringe and infusion pumps, the hospitals and secondary laboratories instead use infusion pump analyzer to disseminate the traceability of flow in infusion pumps with incremental uncertainty.

The schematic of the Infusion pump analyzer (IPA) calibration set up under development at CSIR-NPL with traceability chain is depicted in Figs. 15.13 and 15.14, respectively.

The calibration setup is designed with the following accessories: (i) a storage tank for water, (ii) infusion pump as a source of pressurized flow, (iii) standard pressure gauge, (iv) infusion pump analyzer, as a device under test and (v) standard high precision balance. The above individual parts are connected with 1/4” diameter tube for maintaining a consistent flow throughout the measurement.

In a typical procedure [21], the volumetric flow rate is calculated by directly converting the mass into volume \(V_0\) with respect to a reference temperature normally at 20 °C using Eq. 15.5, as per ISO/TR 20,461 (“Determination of uncertainty for volume measurements by gravimetric method”). However, IS 13,450 (Part 2/Sec 24): 2009 equivalent to IEC 60,601-2-24 describes a calibration procedure particularly for the medical electrical infusion pump device.

![Fig. 15.12](image)

**Fig. 15.12** a Calibration set up of syringe pump at CSIR-NPL; b schematic of primary gravimetric method of syringe pump
Fig. 15.13 Schematic of Infusion pump analyzer calibration set up at CSIR-NPL

\[ V_0 = m \times Z \times Y \]  \hspace{1cm} (15.5)

where,

- \( m \) is the balance reading of delivered water;
- \( Z \) is the combined factor for buoyancy correction and conversion from mass to volume;
- \( Y \) is the thermal expansion correction factor of the delivering device.
By using Eqs. 15.6 and 15.7, the buoyancy corrections and thermal expansion in volume is applied to obtain the measured volume \((V_o)\), at a given temperature, as given in Eq. 15.8.

\[
Z = \left[ \frac{1}{\rho_w - \rho_a} \right] \times \left( 1 - \frac{\rho_a}{\rho_b} \right) \tag{15.6}
\]

\[
Y = 1 - \alpha_c (t_d - t_0) \tag{15.7}
\]

\[
V_0 = (I_L - I_E) \times \left[ \frac{1}{\rho_w - \rho_a} \times \left( 1 - \frac{\rho_a}{\rho_b} \right) \right] \times \left[ 1 - \alpha_c (t_d - t_0) \right] \tag{15.8}
\]

wherein,

- \(I_L\) is the balance reading of vessel with water, in grams;
- \(I_E\) is the balance reading of empty vessel, in grams;
- \(\rho_w\) is the density of water, at \(t_d\) °C, in grams per mL;
- \(\rho_a\) is the density of air, in grams per mL;
- \(\rho_b\) is the density of the standard weight used to calibrate the balance, in grams per mL;
- \(\alpha_c\) is the coefficient of cubical thermal expansion of the test material in reciprocal degrees Celsius;
- \(t_d\) is the temperature of water used in testing, in degrees Celsius;
- \(t_0\) is the reference temperature (normally at 20 °C).

Volumetric flow \((Q)\) of the test device can be obtained from Eq. 15.9 by taking difference between the volume at two instances \((t_{initial}, t_{final})\) using Eq. 15.8.

\[
Q = \frac{1}{(t_f - t_i)} \left[ I_f \times \left( 1 - \frac{\rho_a}{\rho_b} \right) \frac{\left[ 1 - \alpha_c (t_d - t_0) \right]}{(\rho_w - \rho_b)} \right] - I_i \times \left( 1 - \frac{\rho_a}{\rho_b} \right) \frac{\left[ 1 - \alpha_c (t_d - t_0) \right]}{(\rho_w - \rho_a)} \delta V_{evap} \tag{15.9}
\]

wherein, an additional compensatory term \(\delta V_{evap}\) has been added to overcome the uncertainties arises due to evaporation.

Figure 15.14 represented a traceability chart of a typical flow of uncertainties associated with the potential sources viz. mass, temperature, time and density and pressure, which are traceable to national standards maintained at CSIR-NPL, as described in Chaps. 3 and 4. However, the present setup is being tested and any further improvement in the setup may lead to modification in the traceability chart.
15.3.1.3 Calibration Set Up for Blood Penetration Test on Personal Protection Equipment

CSIR-NPL has setup testing of personal protective equipment in the time of pandemic due to COVID 19 virus, which included blood penetration setup as per international protocols and the schematic of the fabricated set up is represented in Fig. 15.16. As per Indian standard (BIS 16,546:2016) a material used in PPE kits is placed in contact with pressurized synthetic blood, and the resistance offered by test specimen to synthetic blood at varying pressure is tested. A dedicated test setup as per ASTM 903 standard has been fabricated at NPL workshop. In the typical procedure, a test specimen (Fig. 15.15a) is placed in a leakage-proof cell assembly (Fig. 15.15b). Further, artificial blood is subjected to the cell backed with regulated air pressure (Fig. 15.15d) measured using a calibrated gauge (Fig. 15.15c). The pressure gauge gets its traceability from national standard, as described in Chap. 4.

15.3.1.4 Bharatiya Nirdeshak Dravya; BND (Indian Reference Material) of Artificial Blood

The resistance offered by PPE to artificial blood is considered as an acid test for their utility in pandemic situations like the worldwide spread of COVID19. The prime requirement of blood penetration tests is an artificial blood with its physical properties similar to human blood. CSIR-NPL has taken a lead in developing a standard for an artificial blood, particularly for testing PPE kits. The artificial blood must possess the following four properties: (a) Surface Tension (0.042 ± 0.002) N/m, (b) pH (7.3 ± 0.1), (c) Viscosity (2.7 ± 0.3) mPa.s and (d) Conductivity: (12.0 ± 1.2) mS/cm, as per BIS standard 16,546:2016. To obtain the aforementioned properties,
15.16 The composition of ingredients used in the synthesis of artificial blood

![Contents of Synthetic Blood (1Litre)]

- Carboxy-methyl cellulose (2 g)
- Polyethylene Glycol Sorbitan Monolaurate (0.04 g)
- Sodium Chloride (2.4 g)
- Amananth Dye (1 g)
- Potassium Dihydrogen Phosphate (1.2 g)
- Disodium Hydrogen Phosphate (4.3 g)

Fig. 15.16 The composition of ingredients used in the synthesis of artificial blood

![National metrological traceability chain for physical parameters of artificial blood](image)

To support the nation’s need for seamless testing of PPE kits, CSIR-NPL has developed BND of artificial blood with its measurement parameters of physical and chemical properties traceable to national standards, as evident from the chain of traceability shown in Fig. 15.17.

15.3.1.5 Calibration Setup of Other Medical Devices

Apart from creating new calibration facilities for medical devices, as described above in the earlier sections, CSIR-NPL, has well-established calibration facilities for medical devices viz., clinical thermometer, blood pressure monitoring and magnetic resonance imaging devices and providing calibration services to the stakeholders of healthcare sector. The calibration measurement of physical and electrical parameters of clinical thermometer and blood pressure monitoring devices are traceable to primary standards of temperature and pressure, described in Chap. 3, whereas
the primary standard of magnetic field for magnetic resonance imaging devices is described in Chap. 6 in detail. Furthermore, CSIR-NPL is also in a process of extending its calibration capability to other biomedical equipment like ECG simulator, incubator analyzer, multiparameter simulator, electrical safety analyzer, etc. These facilities will support the accreditation body such as NABL to set up new centers or help them in providing accreditation to more testing and calibration centers of medical devices based on national standards and contribute to strengthening the medical device regulation. In this way, the development of primary standards for biomedical equipment and its dissemination to industries, secondary laboratories and hospitals will have a huge impact on National healthcare sector in reducing the health complications due to medical device errors.

15.3.2 Research and Development on Biosensors

A biosensor is an analytical device that uses specific biochemical reactions mediated by isolated enzymes, antibodies, nucleic acids, organelles or cell receptors to detect chemical compounds usually by electrical, thermal or optical signal.

CSIR-NPL has been actively engaged in the development of biosensors of clinical relevance for the past several years. In this context, extensive work has been done on the development of glucose, urea, cholesterol, uric acid and DNA biosensors. Glucose biosensor, the ‘NPL glucosense’ was developed at CSIR-NPL, (Fig. 15.18) and the technology was transferred to three companies viz Gama Instrumentation Pvt. Ltd, Faridabad, Haryana; Pulsatum Health Care Pvt. Ltd., Bangalore, Karnataka and Transgeniks, Ahmedabad, Gujarat.

The laboratory is currently engaged in the development of point-of-care biosensors for the diagnosis of chronic and infectious diseases and a few of them are highlighted and discussed briefly in the subsequent sections given below.

**Fig. 15.18** Electrochemical glucometer developed at CSIR-NPL
15.3.2.1 Technical Development of Biosensors for Chronic Diseases

Scientists at CSIR-NPL have been engaged in the synthesis of new nano-objects and exploitation of their extraordinary properties in the field of sensors for biomedical applications. Nanostructured materials of Pt-dendrimer, carbon nanotubes and single-layered graphene were used as a suitable matrix for biomolecular immobilization for the development of “Lab-on-a chip” for biomedical applications, especially in the diagnosis of cardiovascular and infectious diseases. The sensing performance of the biomaterials was investigated by electrochemical/Field effect transistors (FET) characteristic studies towards the quantitative detection of protein biomarkers of chronic diseases.

A screen-printed carbon electrode was modified with Pt nanoparticles encapsulated polyamidoamine (PAMAM) dendrimer to develop an impedimetric biosensor, for the quantitative detection of human cardiac biomarker troponin-I (cTnI). PAMAM-Pt was electrochemically deposited over SPCE and its 128 terminal carboxyl groups were used as anchors for the site-specific biomolecular immobilization of protein antibody, anti-cTnI, as shown in Fig. 15.19.

A single-frequency impedance analysis technique was utilized for biomolecular sensing of cardiac biomarker, cTnI, by monitoring the changes in phase angle with immunoreaction (antigen–antibody interactions) occurring at the electrode surface. A maximum change in the phase angle was obtained at a frequency of 100 Hz upon immunoreaction with a given concentration of analyte at the electrode surface. The fabricated immunosensor exhibited an electrochemical response in the range of 1 pg mL$^{-1}$ to 100 ng mL$^{-1}$ of clinical relevance [22].

![Fig. 15.19 Schematic representation of stepwise preparation of PAMAM-Pt and anti-cTnI-PAMAM-Pt/SPCE (Bio-SPCE) [22]](image-url)
A biofunctionalized reduced graphene oxide (rGO)-modified screen-printed carbon electrode (SPCE) was prepared, as shown schematically in Fig. 15.20, as an immunosensor for C-reactive protein (CRP) detection, a biomarker released in early stage acute myocardial infarction. In the electrochemical impedance measurement, an optimized frequency of 10 Hz was obtained, where a maximum change in a phase angle was observed with antibody-antigen reaction at the electrode surface.

At this optimized frequency of 10 Hz, the concentration-dependent response of immunosensor to CRP with change in phase angle was observed in the range of 10 ng mL\(^{-1}\) to 10 µg mL\(^{-1}\) in PBS. Sensing of analyte at such a low ac frequency with high selectivity and sensitivity makes this system a potential sensor for clinical applications [23].

Paper-based electronics have potential for the fabrication of simple, sensitive and disposable new generic clinical diagnostics for efficient employment in the low-resource settings and underdeveloped countries. Considering the precincts in the present methods, efforts were made towards the development of a low-cost and rapid method for the modification of paper using a very simple electrochemical deposition approach. The patterned screen printed paper electrodes (SPPE) were designed and PANI was deposited onto the paper electrochemically, as shown in Fig. 15.21.

These matrices were utilized for the detection of troponin, a cardiovascular biomarker and this approach has potential applications towards the development of cost-effective diagnostics. Screen printed Whatman filter paper has been chosen

Fig. 15.20  Schematic representation of the stepwise fabrication of the bioelectrode [23]
Fig. 15.21 Schematic representation of screen printed paper electrode for the detection of cardiovascular marker [24]

as the matrix for the biosensing applications. Polyaniline has been electrochemically polymerization using cyclic voltammetric technique. The cardiovascular antibody marker has been immobilized on to the polyaniline coated paper substrates using covalent immobilization technique using EDC-NHS chemistry. The substrates have been found to detect troponin in concentration range of 1–100 ng mL$^{-1}$ with sensitivity 5.5 $\mu$A/ng mL$^{-1}$ cm$^{-2}$ and response time of 150 s [24].

An array of 52 graphene field-effect transistors (GFETs) was developed using high-quality chemical vapor deposited graphene decorated with antibody-functionalized platinum nanoparticles (PtNPs) over microfabricated gold electrodes on a SiO$_2$/Si wafer, for the quantitative detection of breast cancer biomarker HER3. HER3-specific, genetically engineered thiol-containing single-chain variable fragment antibodies (scFv) was immobilized with PtNPs/GFET hybrid nanostructure to realize a biosensor for HER3, as shown in Fig. 15.22.

The Dirac point voltage of pristine GFET is in the range $-4.0$ to $+2.0$ V, with an average carrier mobility ($\mu$) of $1197 \pm 56$ cm$^2$ V$^{-1}$ s$^{-1}$ (Fig. 15.23a), showed a clean transfer of graphene over microfabricated gold electrodes on SiO$_2$/Si wafer. An increase in the carrier mobility ($\mu = 1330 \pm 14$ cm$^2$ V$^{-1}$ s$^{-1}$) with a positive shift in the Dirac voltage ($V_D = 26.4 \pm 1.0$ V) upon biomolecular immobilization of scFv (Fig. 15.23b), suggesting a decrease in charge scattering conforming an efficient attachment of biomolecule for sensing a target molecule.

The biosensor exhibited a concentration-dependent response to HER3 antigen as a function of change in Dirac voltage in the range 300 fg mL$^{-1}$ to 300 ng mL$^{-1}$ with a limit of detection of 300 fg mL$^{-1}$, showing its potential to be used as a label-free biological sensor for an early detection of breast cancer [25].

A Single-walled carbon nanotube (SWNT) based field-effect transistor (FET) was also developed using Polyamidoamine (PAMAM) dendrimer as anchor for site
specific biomolecular immobilization of protein antibody for the detection of cardiac biomarker, C-reactive protein (CRP), as shown in Fig. 15.24.

The source-drain current of the device decreases on immunoreaction with the target analyte of CRP in the regime of clinical significance, with a detection limit of ~85 pM [26].

The applications of microfluidic-based devices have grown exponentially due to excellent merits over traditional devices in terms of portability, bioanalysis at microscale, automation in drug discovery, and consumption of samples and reagents.
Some examples of integration of nanomaterials with microfluidic devices (lab-on-a-chip) for the fabrication of platforms for biosensing applications are presented. In one such study nanocomposite of nickel oxide nanoparticles (nNiO) along with multiwalled carbon nanotubes (MWCNTs), was integrated with photolithographic constructed microchannels of polydimethylsiloxane (PDMS). This nanocomposite chip of nNiO-MWCNT Chip was functionalized with a cholesterol oxidase (ChOx) and cholesterol esterase (ChEt), via an amide bond. Schematic of same is shown in Fig. 15.25. The response studies on this coenzyme microfluidic platform have shown excellent reproducibility and selectivity, and a sensitivity of 2.2 mA mM$^{-1}$ cm$^{-2}$. This integrated microfluidics biochip provides a promising low-cost platform for the rapid detection of biomolecules using minute samples [27].

Further, a label-free impedimetric lab on a chip (iLOC) is fabricated using protein (bovine serum albumin), and antiapolipoprotein B functionalized on similar nanocomposite system for detection of low-density lipoprotein (LDL). A cytotoxicity study on the synthesized CNTs, NiO nanoparticles, and their nanocomposite (CNT-NiO) in the presence of lung epithelial cancer A549 cell line using MTT assay has been carried out. The cell viability studies show promising response for CNT-NiO nanocomposite at a concentration of 6.5 µg/mL compared to individual CNTs. A chronocoulometry and impedance spectroscopic techniques were employed to study the binding kinetic and electrochemical activities of CNT-NiO-based iLOC. The iLOC shows excellent sensitivity of 5.37 kΩ (mg/dL)$^{-1}$ in a wide concentration range (5—120 mg/dL) of LDL. The binding kinetics of antigen–antibody interaction of LDL molecules show a high association rate constant of 8.13 M$^{-1}$ s$^{-1}$ [28].
Fig. 15.25  a The schematic of the microfluidic biochip is used for total cholesterol detection. b The photograph of a microfluidic biochip for cholesterol detection and c the magnified view of the optical microscopic image of the biochip [27]

15.3.2.2 Technical Development of Biosensors for Infectious, Food Toxin and Water Borne Diseases

Gonorrhea is presently recognized as the second most prevalent sexually transmitted bacterial infection (STI) and is a co-factor for HIV infection. Worldwide, there is an estimated annual incidence of 62 million new cases of gonococcal infections. Untreated gonorrhea has major risk factors for acquiring pelvic inflammatory disease (PID) that can lead to complications of infertility and tubal pregnancies and can result in conjunctivitis and pneumonia in newborn infants exposed during passage through an infected birth canal. Traditional laboratory diagnosis of this infection is carried out by culture, microscopy and PCR techniques are time-consuming (14–72 h) and are not reliable. Therefore, efforts are being made towards the development of a rapid STD sensing device in collaboration with AIIMS, Delhi and Safdarjung Hospital, Delhi. The response studies of probe DNA immobilized onto various platforms such as conducting polymers, nanomaterials, gold matrix and gold screen printed electrodes have been studied for electrochemical hybridization using standard complementary, non-complementary sequences and clinical samples. The studies carried out on clinical samples on highly reproducible gold substrates based DNA biosensor indicate that the sensor can detect presence of *N. gonorrhoeae* from
culture (0.5 McFarland) $10^8$ cells/ml, spiked sample and *N. gonorrhoeae* culture positive swab sample of patients. The specificity of the gold substrate based DNA hybridization biosensor has been studied using the control strains of *N. gonorrhoeae*, other pathogenic Neiseria species and other GNBs [29]. The nucleic acid electrode has also been tested using patient sample under similar conditions. These results reveal that the electrode is highly specific and can distinguish presence of *N. gonorrhoeae* from other species like *N. meningitidis* and other GNBs, i.e., *Escherichia coli*. Under the optimum conditions, this nucleic acid sensor can be used to detect complementary target DNA concentration in the range $[1 \times 10^{-6} – 0.5 \times 10^{-18} \text{ M}]$ with a detection limit of $1.0 \times 10^{-18} \text{ M}$ within 60 s of hybridization time at 25 °C. The sensor has been found to be very stable and the data is reproducible several times with improved detection limit. The biosensor has been validated using *N. gonorrhoeae* culture samples, spiked samples and positive swab sample of patients. Identification of the specific DNA sequence and the fabrication of biosensor with its performance has been patented in India and PCT.

The rapid growth in the development of biosensor has given a boost to the advanced evolution using biomaterials and improvements of sensing techniques for food-borne toxin Aflatoxin B1 detection. Although traditional techniques are available for quantification of this mycotoxin, but these techniques are quite expensive and time-consuming. Therefore, efforts have been made at CSIR-NPL for the fabrication of biosensors for food toxin detection. Nanocomposites of Graphene Quantum dots and gold nanoparticles (GQDs-AuNPs), were utilized as biomolecular immobilizing matrix for the construction of a biosensor for AFB1 detection in food content. GQDs-AuNPs composites were transferred on ITO coated glass substrate by electrophoretic deposition technique, followed by antibody immobilization for the fabrication of biosensor, as shown schematically in Fig. 15.26.

![Fig. 15.26 Schematic representation of the synthesis of GQDs-AuNPs composites and its electrophoretic deposition onto ITO-glass electrode leading towards the fabrication of biosensor for food toxin, Aflatoxin B1 (AFB1) detection [30]](image-url)
The biosensor has been tested with the real (spiked) maize sample using electrochemical impedance signal based transduction and was found to detect AFB1 concentration in the range of 0.1–2.5 ng mL$^{-1}$ \cite{30}.

Bisphenol A (BPA) is a synthetic compound, extensively used in food packaging industries and has emerged as a threat to the human health and environment, thus to detect bisphenol in an analytical range of 0.01–100 µM, an amperometric sensor has been developed using enzyme tyrosinase immobilized on to rGO and Mn$_3$O$_4$ NPS for a synergistic effect, resulting in improved sensitivity of 93.2 µA nM$^{-1}$ cm$^{-2}$ with an analytical range from 0.01 to 100 µM, and detection limit of a 10 nM \cite{31}.

### 15.3.3 Training and Academic Program and Consultancy Services

The biomedical laboratory is actively participating in academic program with Academy of Scientific and Innovative Research (AcSIR) through research and development in the core area of nanomaterials for biomedical applications together with providing biomedical metrology training and consultancy services to the accredited laboratories in establishing the secondary level calibration facilities for medical devices in the country.

### 15.3.3.1 Skill Development Program

Hands-on training services are being provided to the various stakeholders about the National measurement system, its handling and calibration of the sophisticated biomedical equipment, and its importance in supporting the medical device rule. The training programs are designed to familiarize the participants with the concepts on the importance of biomedical metrology, the importance of accurate and precise measurements, medical device regulations in India, calibration procedures for biomedical equipment, maintenance and operation of the equipment and practical examples on the evaluations of associated uncertainties with measurements, etc. The beneficiaries of these training programs include doctors, industries, accredited laboratories and biomedical engineers, etc. We have also conducted industry-institute interaction and meetings in the past to sensitize people about the significance of metrology in medical devices for risk-free healthcare services to the Nation. Such kind of training-cum-awareness programs support startups and creation of jobs in the healthcare sector.
15.3.3.2 Academic Program

Research and developmental activities pertaining to biomedical instrumentation have been carried out at CSIR-NPL for the last few years, both in medical metrology and synthesis of novel biomaterials as well for the development point-of-care diagnostic system for infectious and chronic diseases. This activity has resulted into knowledge generation and supported the theses work of doctoral and post-graduate students from various universities and Indian Institute of Technologies and which in turn are providing their services in nation-building through serving in various academic and/or industrial set up within the country.

15.4 Conclusions and Future Prospects

Implementation of Quality infrastructure in Medical device sector in India is crucial for the National healthcare system. In this regard, CSIR-NPL is playing a pivotal role in providing primary calibration facilities for biomedical equipment. It is constitutional that the guidelines of Medical device rule 2017 are implemented and regulated with an effective outcome. This chapter highlights current regulations pertaining to medical device rules and the contributions of CSIR-NPL and Role of other regulatory bodies of India. CSIR-NPL is rapidly expanding its calibration facilities and engaged in fundamental research work to support the same, through national and international collaborations. CSIR-NPL is providing primary calibration services to medical equipment such as Defibrillator analyzer, Magnetic Resonance Imaging, Clinical thermometers and Blood pressure measuring equipment etc. besides providing training to manufactures, testing and calibration laboratories, legal metrology officers, other stakeholders in the area of biomedical metrology and biomedical sciences. The laboratory is further making efforts to enhance the calibration facilities for other life saving biomedical equipment and their calibrators such as neonatal incubators, Infusion pump analyzer and electrical safety analyzer. Apart from providing primary medical equipment calibration services, CSIR-NPL is also working towards the futuristic goals of creating secondary level calibration laboratories at different locations within India through providing traceability, which will ultimately help in the successful implementation of “Swasth Bharat Mission” of GOI. Efforts will also be made in future to establish a certification scheme for medical equipment after due consultation with CDSCO to support the indigenous Medical device manufacturers under ‘Make in India’ program. It has also been emphasized that the medical device regulatory bodies need to minimize their overlapping roles and work synergistically in consultation with CSIR-NPL for the improvement and advancements in the quality infrastructure.

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