International Journal of Engineering Technology and Management Sciences
Website: ijetms.in Issue: 5 Volume No.7 September - October – 2023
DOI:10.46647/ijetms.2023.v07i05.025 ISSN: 2581-4621

Availability of Reference Materials for Improving Quality of Life within Scientific and Industrial Framework

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***Abstract*—** Established metrological traceability to SI (system international) is the strength of any reliable quality management system. Accreditation of facilities and Good laboratory practices in conducting studies drives all measurement involved in the system with traceability either through calibration or by use of Reference Material (RM). Whenever the process of calibration become not convenient, RMs could take up the role for assuring reliability in results with stated level of confidence with minimum possible uncertainty in results. Standardizing clinical diagnostics, qualifying different developmental stages of bio-medical devices and biomaterials, development and constructive use of radio nuclear techniques, control of environmental pollution, etc invites special attention in improving quality of life. Onsets of pandemic conditions like SARS – CoV 2 (severe acute respiratory syndrome -Corona Virus 2) triggers emergencies for regulatory approvals. Availability of certified property values of RMs has significant role in qualifying such tests and evaluations. They may support quick release of products like medical devices into market for routine use. Property value of RMs could be quantitative or qualitative. Even though a large quantum of work has established RMs with quantitative property value, the other type still remains as minimally addressed in many countries. Remarkable efforts done at international research laboratories supplies RMs traceable to NIST (National Institute Standards and Technology, USA), USP (United States Pharmacopeia), NPL (National Physical Laboratory) India etc. RM requirements in critical application areas like healthcare are not sufficiently visible to the scientific community and hence do not satisfy global demands. This feature presents an overview of present status on the issue.

***Keywords*—Reference Materials, Traceability, Metrology, Quality Systems, physico-chemical characterisation.**

I. INTRODUCTION

Quality of life is always associated with metrological advancements. Acceptability of scientific or industrial products and processes by regulatory requirements mandates traceable metrology. It becomes critical, in the context of high risk activities of healthcare, space research, defense management etc. In such cases, eventuality of practicing accredited metrological practices throughout the life cycle of a product or different phases of a process is very significant. Use of accredited calibrations and reference materials are thus becoming the integral part of activities that has concerns about reliability, safety and regulatory acceptance. RMs find significance in validation of procedures, traceable calibrations, estimating uncertainty of test methods, quality control measurements, Interlaboratory comparisons and proficiency testing [1]. Type of RM, its classification, and class of material are varied depending upon the application area of RMs. Also property value of RMs can be either quantitative or qualitative.

DOI:10.46647/ijetms.2023.v07i05.025 ISSN: 2581-4621

On reviewing international and national status, efforts in supply of RMs indifferent categories are done at appreciable levels by various governmental and non-governmental agencies. It is observed that RMs for Physico-chemical characterization and testing are well established across the world, whereas research on development of critical RMs for clinical applications and medical device development are under progressing stages. When cost and time are the influencing factors in such scenario, most of such developments are initiated by national laboratories under the control of governments. NIST RMs of NIST (National Institute of Standards and Technology) USA, and BND (Bhartiya Nirdeshak Dravya) of NPL (National Physical Laboratory) India are the typical examples of such attempts. This article discusses the recent status and development in the field of RM in the perspective of improving quality of life by their application in scientific and industrial applications [2, 3].

II. Current Scenario Overview

From year1912 at Royal Materials Testing Office in Berlin-Dahlem, and year 1916 at British Chemical Standards (BCS), developments of RM evolved through a long way by addressing the needs of science, industry, agriculture, and human health technologies [4]. Advancement in sophisticated analytical tools and challenges originated with them, activated the need for RMs.ISO17025 standards directs the use of RMs in testing and calibration laboratories for calibration and quality control purposes. ISO 17034 and relevant ISO guides provided clarity in the development and use of reference material. Worldwide, about 200 RM producers have an International Laboratory Accreditation Cooperation (ILAC) recognized accreditation.

Even though the pathways to establish the accreditation and regulatory approvals are well defined which took a defined minimum period, emergency situations like pandemic situations or onset of wars may ignite needs of approvals within very short duration's. Established quality management platforms can address such scenarios easily. COVID-19 scenario was atypical example of such emergency situation; which required metrological detection systems for viruses either by analytical instrumentation methods or through biochemical test methods. Controls for environmental pollution, application areas of radio nuclear techniques, etc. are some of the important areas need attention and care. Progress in research of such critical activities with regard to RM development are taken care by international bodies and governmental agencies with much importance.

III. Classification of RMs

Whenever material characteristics properties contribute to the performance of a process or product, RM become a decision making elements in industry, research, and testing services. It could be concerned with Physico-chemical properties, biological performance in in-vitro or in-vivo environments, engineering performance or properties like taste and odour etc. For using an item as RM, its identity or specific property values has to be well established by extensive characterization studies. Typical examples of RM type are listed as follows.

- Pure substances certified for their chemical elemental purity or impurities contents.
- Calibration standards in the form of control solutions or gas mixtures made from with chemical purity.
- Material matrices characterized for their composition of pure or synthetic material mixtures.
- Materials characterized for Physico-chemical properties like melting point temperature etc.
- Materials characterized for functional properties such as taste, biological reactivity in cellular environment, microbiological species, clinical specimens etc.
- Experimental control materials characterized for biological reactivity in in-vivo or in-vitro conditions.

RMs is broadly classified into certified reference material (CRM) and RM. By definition, material, sufficiently homogeneous and stable with reference to one or more specified properties, which has been established to be fit for its intended use in measurement or in examination. Whereas, CRMs are reference material, characterized by a metrologically valid approach for one or more specified

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properties, accompanied by an RM certificate that provides the values of the specified properties, associated uncertainties, and statements of metrological traceability [5].

IV. Significance of RM in Critical applications

Supply of CRMs is expensive in terms of time, cost and effort. But RMs, are homogeneous and stable materials having traceability to SI. When CRMs are not available, less expensive RMs can be made that are fit for purpose materials. Later with proper research and characterization they can be developed into CRMs [6]. Initiative across the scientific and industrial applications which has an impact on day to day social life is discussed here.

A. Physico chemical analysis

Characterization of Physico chemical properties against metrological standards is the first and foremost step in establishing the acceptance of materials and processes, for every industrial or scientific application. RMs in physico chemical analysis finds a wide application range for improving quality of life.

Latest example of RM needs for Physico-chemical characterization in the field of additive manufacturing processes or 3-Dimensional printing technologies using metal or polymer powders. Aerospace engineering and medical device industries utilize this advanced technique to address many unmet needs. Relevant physico-chemical characterization techniques are essential in qualifying the products, as mechanical behavior of 3-D printed parts depend on the chemical composition of the powder used. RMs and CRMs in metal classes like steel, Al, and Ti are being introduced for such applications [7, 8].

Gaseous CRMs in environmental analysis is an important tool in the data quality directive of the Global Atmospheric Watch Program of the World Meteorological Organization (WMO GAW), [Guidelines for the measurement of methane and nitrous oxide and their quality assurance; GAW Report-No. 185, WMO Geneva, (2009)].RM development in addressing environmental pollution by reactive gasses like dioxins and furans is one prospective area to be explored further [9, 10, 11].

Analytical characterization is one of the inevitable steps in the evaluation of medical device development. Be it of polymeric, metallic, or ceramic origin, a medical device has to be characterized thoroughly as per ISO 10993-18 to establish its equivalence with predicate devices and to estimate the toxicological risks. Chromatography techniques play a crucial role in the analytical characterization and toxicological assessment of devices. Certified reference materials (CRMs) have been used for the estimation of unknowns in chromatographic techniques. The selection of CRMs should be made sensibly to analyze samples precisely and accurately [12].

Aiming at enhancement of optical/light microscopy image data, an initiative called Quality Assessment and Reproducibility for Instruments & Images in Light Microscopy (QUAREP-LiMi) is established in the year 2020[13]. RM use will form an integral part of such programs and research in the field is hence an identified need to be addressed.

B. Radio nuclear applications

The International Atomic Energy Agency (IAEA) is established for cooperation in the nuclear field and seeks to promote the safe, secure and peaceful use of nuclear technologies. The IAEA Environment Laboratories produce certified reference materials for the measurement of radionuclide, trace elements and organic contaminants. These materials can be used for quality assurance and quality control purposes, as well as for method development, validation of analytical procedures and for training.

National level efforts are being initiated at many countries to address RM requirement in this critical area that has impact on health and environment. Risk levels warrant strict regulatory controls in this research [14, 15].

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C. Biological Evaluations in medical device development

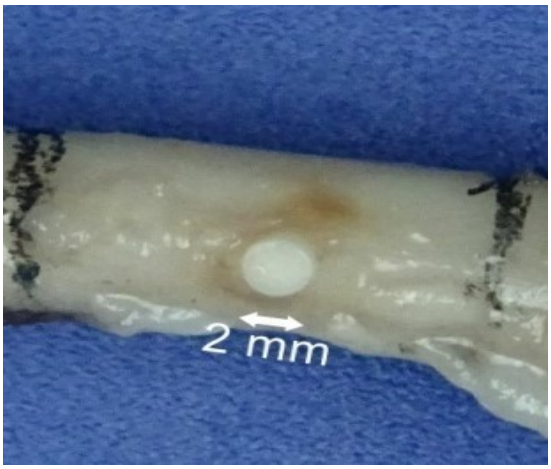

Fig. 1: Gross image of bone implantation site with Ceramic RM having 2mm diameter.

Materials used in medical devices development are to be qualified for safe use in clinical requirements. International standards in the series of ISO 10993 draw attention in this specialized application area through a set of preclinical in-vitro and in-vivo biological evaluations. Regulatory authorities like Food and Drug Administration (FDA) of the United States of America, Central Drugs Standard Control Organization (CDSCO) of India, provides approval for the biomedical devices based on such biological evaluations.

When RMs elicit positive or reactive response in test systems, they are called positive controls whereas RMs that do not indicate any adverse response are negative controls in biocompatibility evaluations. Image in Figure 1 is an example of negative control RM in biocompatibility evaluation. Biological evaluations cover cell compatibility, blood compatibility, compatibility with in bone and muscle implanted sites etc. Even though Indian reference materials (BND) are well established RMs, India need to advance its RM development activity for clinical use and medical device development [16].

Well characterized RMs has the role of experimental controls in an accredited quality system environment. Research and development for the supply of RM in biological evaluation requirements are initiated internationally at very few national laboratories. United States of America and Japan are having a reasonably good supply of such RMs.
Response of the materials at in-vitro cell culture environment or within the implanted sites of small or large animals is assessed against experimental controls. Figure 1 indicates RM in ceramic class in bone implantation studies. RMs used should be in the same class of material under test or experiment. RMs in metal, polymer, ceramic classes are suggested by ISO 10993 for experimental controls.

D. Nano sciences and technology

Recent technological advancements in science with nanomaterials, quality control measures in the field are introduced with ISO technical committee TC 229 and an arrangement of Working Party on Manufactured Nanomaterials (WPMN) as part of the Organization for Economic Cooperation and Development (OECD). A gap analysis was performed by mapping available RMs for nano medicine applications, which indicated that RM development in this specialised field is very primitive or non-available [17].
Minimally developed RM requirement, will be a driving force to establish expertise in this field for meeting stringent regulatory controls [18]. Gold and polystyrene based RMs are the ones currently available for the purpose.

E.Geological RMs

Chemical composition of geomaterials is in use to understand environmental and geological risks. For the acceptance of policy decisions in such scenario, well-characterized geological RMs (geoRMs) are required which makes study results traceable to SI. Mostly geoRMs are rocks and minerals of different chemical compositions. Occasionally coal or oil shale is also in use. National Institute of Standards and Technology-USA, Community Bureau of Reference-USA, and United States Geological Survey are some of the institutions conducting research in the area [19].

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F. Food reference materials

Regulatory procedures in food safety testing are critically relevant in every aspects of layman life. Use of RMS in analytical testing methods for food safety is very significant in controlling health issues in society [20]. Minimum nutrient requirements, food contamination and quality requirements for food testing laboratories are the aspects of food safety tests that need RMs for regulatory acceptance. Absence of accredited calibration or CRMs may lead to invalid decision making process [21]. Use of proper metrological tools help in avoiding conflicts in legal judgments, health hazards from mycotoxins, pesticides, or heavy metals, support in maintaining quality of food processing and its supply aiming at wellness of society. RM development in government or public sector research laboratories needs to come forward these societal needs[22, 23].

G. Clinical Use

CRMs in the form of matrices, derived from human samples are widely used for the reliability of clinical test results. Blood derived materials like serum and plasma are examples [24]. COVID -19 pandemic scenarios introduced technical needs to have remote diagnosis means with the support of sample collection, storage and transportation outside clinical premises. Initiatives on RM development in such situations are reported for the purpose of controls of tests [25].

A typical case study during COVID -19 pandemic periods illustrates the significance of RM as experimental controls of testing viral infections. SARS-CoV-2 detection by RT- PCR was identified as the need of the hour when the variants of virus spread over continents.

Even though various diagnostic tools were made available for SARS-CoV-2 detection, real time or quantitative polymer chain reaction (qPCR) based method was considered as the gold standard for COVID-19 diagnosis. In Real- time (RT –PCR) assays, specific target regions are identified after amplification of reverse –transcribed viral RNA. This method is highly sensitive and therefore ideal in detecting and tracking the infected (both symptomatic and asymptomatic) cases and has been a significant element in controlling the rapid spread of the pandemic. However, because of this fluorophore based assay's high sensitivity, incorporation of appropriate controls is a mandatory process and they aid in interpretation of results as well. Experimental controls employed in a conventional RT-PCR detection of SARS- Co-V-2 virus are a) Positive control b) Negative control and c) Internal control. Positive control incorporated with the test is expected to give amplification of SARS-CoV-2 target regions. It ensures that the amplification reactions are performing adequately and the reagents are working correctly. It helps in preventing generation of false negatives thereby increasing the confidence in the assay results. Negative controls help in preventing false positive occurrences possibly due to non-specific contamination of reagents with nonspecific amplicons or genetic material from previous reactions, environment, samples etc. A negative control is expected to provide no amplifications at all. Additionally, in case of SARS-CoV 2 detection false negativity can result from an insufficient sample collection or inadequate sample extraction methods. To mitigate this error, Internal controls are employed in RT PCR- diagnostic kits. Internal controls could be Endogenous or Exogenous. Endogenous internal controls use housekeeping genes to record the presence of sufficient sample material (collected well as extracted) for the amplification reaction. Target gene amplification is often compared with the reference/housekeeping gene amplification to rule out false negative results. Exogenous internal control involves the addition of an exogenous RNA material to each sample before extraction so that a spiked amplification reaction is expected in case of positive results. The kit manufacturer itself provides the controls for the assay. Incorporation of all the controls ensures the accuracy of accuracy of SARS-CoV-2 detection using RT-PCR assay [26].

Experimental controls are incorporated in any experiments to confirm that the adopted methodology is working well and the results obtained are authentic. Reference material rightly serves the purpose as the properties of RMs are homogenous and anticipated biological responses of the reference material being used as positive or negative control are well characterized. This will help in confidently reporting a subjective result. Hence RM development to use as controls in clinical tests is identified as a prospective area to manage health emergencies.

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V. Conclusions

Although ISO documents like ISO 17025, ISO Guide 35, ISO 10993 and ISO 17034 give clear directions in development and use of CRMS and RM, it is noted that demand for RMs is met for most of physico -chemical properties with quantitative measurement results. But it is not so established for qualitative characteristics associated with microbiology, cell biology, and other biological or clinical evaluation techniques. When accreditation of systems becomes the evidence of improvement in quality, the use of RMs become its integral part. This understanding demands the necessity of RMs for regulatory approvals, validation of systems, reliability of test results etc. But satisfying the demand is only possible when indigenous supply is established at individual countries. Initiatives of Bhartiya Nirdeshak Dravya for developing RMs at NPL, India can be a model for such requirement. Encouraging research in critical areas of healthcare and control of environmental pollutions needs strong support from government agencies in terms of rules, guidelines and infrastructure. It will definitely open pathways to improve quality of life globally.

Acknowledgements

Authors would like to acknowledge funding support from Department of Science and Technology, Ministry of Science and Technology.

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