Abstract To play their role as essential tools for the achievement of comparability and traceability of measurements, the upcoming generation of certified reference materials will continue to be the subject of increased requirements related to their preparation, characterization, monitoring, documentation, and distribution. An analysis is made of the most important aspects not only related to the physical form of future CRMs, the determination of their shelf-life, and their certification, but also to increased requirements related to their distribution, including required additional documentation. Two examples of cost breakdown demonstrate the need for improved productivity of certification projects and more efficient marketing.

Introduction

First European Reference Materials focused on the certification of elements in stable matrices. Since the beginning of the twentieth century, iron and steel reference materials were produced in Germany and in the United Kingdom. In 1958, European collaboration in this area started within the European Coal and Steel Community (ECSC) Working Group 20. It gave rise to what later became the “EURONORM” reference materials. Today, around 200 Euronorm reference materials exist, mainly for metals, alloys, ores, concentrates, etc.

With the advent of nuclear energy in the 1950s, a large number of nuclear and isotopic reference materials was developed in nuclear centers such as the Atomic Energy Research Establishment in Harwell (UK), Commissariat à l’Energie Atomique in France, and, on the European level, at the Central Bureau for Nuclear Measurements (CBNM) in Geel, Belgium, where major facilities for high precision and accuracy mass-spectrometric measurements of nuclear materials (actinides, boron, lithium, etc.) were set up.

In the mid-1970s, the Bureau Communautaire de Référence (BCR) was created by the European Commission. With the support of the “METRE” program of the European Commission’s Joint Research Centre, it started to produce the first European Community non-nuclear reference materials, the “BCR CRMs”, which till the end of the 1970s were heavily industry oriented (non-ferrous metals, ores, etc.).

The certification of all these reference materials was quite “measurement focused”. They consisted in general of real materials taken out of the industrial production (metals, ores, etc.), characterized by interlaboratory comparisons or synthetically produced (e.g., isotopic) mixtures characterized by “definitive” methods (gravimetric preparation, isotope dilution mass spectrometry, coulometry, etc.).

Even if the focus was still on elemental analysis, with the advent of more environmentally oriented certification projects in the 1980s, the awareness that homogeneity and stability studies are an integral part of any certification process became visible (e.g., in the production of BCR Guidelines [1]). Automatically, it was realized that more emphasis had to be put on transformation, stabilization, homogenization, and packaging techniques, leading to the establishment – in support of BCR – of dedicated, large capacity production facilities for highest quality biological and environmental candidate reference materials at CBNM [2].

This awareness increased dramatically in the 1990s, with the advent of environmental reference materials certified for organic compounds, chemical species, and organo-metallic compounds, extractable elements, etc., but also for food, clinical, and bio-technology reference materials. The logical consequence of this trend is that the

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requirements of today can no longer be compared to those of the 1970s and that the obligations of producers of CRMs have completely changed. This is to a certain extent already reflected in the ISO Guides related to reference materials and more specifically in ISO Guide 34 [3]; it will be more in future, when ISO Guide 35 will also have been revised [4]. They must make sure that in future EU certified reference materials remain an essential tool in achieving the comparability and traceability required for the implementation and monitoring of European legislation and standardization, the protection of public health and environment, the optimization of industrial processes, and the promotion of international trade.

**Physical form**

Ideally, reference materials should be as similar as possible compared to the sample to be analyzed. In reality, the physical form of any reference material is always a compromise between the “as real as possible” sample requested by the user and the “as stable and homogeneous” sample required to achieve certification with the lowest possible uncertainty. Over the last two decades, many samples of biological materials of vegetal or animal origin were, therefore, transformed into fine (< 125 μm or even less), dry powder using techniques such as cryo-grinding in combination with freeze drying. Supplemental reasons for this choice were the low costs of storage and transport of freeze-dried powder samples, as well as their excellent stability under extreme transport conditions, which is an important factor when samples have to cross borders.

With the increasing development of reference materials for clinical analysis, however, producers became aware that insufficient matrix matching with real samples is not only an “inconvenience” that is largely compensated by the difference in cost; it can make the CRM quite useless due to lack of “commutability” [5] – i.e., the ability of a material to show inter-assay properties comparable to those of patients’ samples – as was frequently experienced, e.g., with freeze-dried reference materials of animal or even human origin. If reference materials are not commutable with in-vitro diagnostics kits in use in clinical laboratories, reference methods are required to assign values to intermediate commutable calibrators or calibrator panels, a task generally carried out in reference laboratories. The disadvantage of such a procedure is not only that the uncertainty is increased by the additional assignment step and that reference methods can generally not be implemented outside reference laboratories, but also that only very small numbers of CRM samples are sold, with the consequence that the costs of the CRM production and its long-term stability monitoring can hardly be justified any longer. Hence, commutable CRMs are extremely important to ensure an unbroken traceability chain from the CRM to the end-users of in-vitro diagnostics. This insight led to a complete reconsideration of the way of thinking at IRMM, going more for “fresh” materials deep-frozen and stored at very low storage temperature (e.g., −70°C) and distributed using dry ice transportation. This change in policy, initially induced by problems in clinical chemistry, will also affect other areas such as food and feed, speciation, sediments, sludge, etc.

Moreover, the evolution from reference materials certified for their total elemental content to reference materials certified for bio-available or extractable contents will also lead to a reconsideration of the level of grinding: coarse particle size and wide “natural” distribution, e.g., of soil, instead of fine homogeneous powders. Also the subsequent homogenization and bottling techniques will therefore need to be revised. It will also emphasize the need for:

- Increased and more precise between-bottle homogeneity control, and subsequent accounting for the resulting uncertainty in the quoted CRM uncertainty [6]
- More precise specification of instructions for use
- Accurate determination of the minimum representative sample size based on extended within-bottle homogeneity controls [7]

**Shelf-life determination**

As a consequence of increasing certification of more potentially unstable reference materials during the last two decades, more specific requirements related to short-term and long-term stability studies were already put forward, and laid down in, e.g., the BCR Guidelines [1]. However, the upcoming need to fix shelf-life or expiry dates, mainly due to demands for documented periods of validity of certificates stemming from accreditation bodies and the perception that long-term stability monitoring is often not conclusive, quickly led to serious questioning of the organization and the quality of these studies. So far, their outcome was often only a good feeling translated in terms of “absence of demonstrated instability”: a qualitative statement that is neither useful nor sufficient to cover the liability of the producer nor to fulfill the satisfaction of the user. Obviously, today, there is a clear need for better quantitative information that guarantees the user that the sample he gets is still valid within the certified uncertainty range. This requires more and better stability measurements, planned at the very beginning of the reference material project, which cover the full selling period of the CRM and which are preferably carried out using isochronous measurements in order to achieve the lowest possible measurement uncertainty [8]. This is an expensive but unavoidable consequence of increased requirements and needs for potentially unstable CRMs.

**Certification measurements**

Even if it is no longer the only concern of CRM producers, the quality of the estimation of the mean value of a certified parameter of a CRM batch is still an important prerequisite for the international acceptance of any CRM.