FINAL PUBLISHABLE REPORT

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Project full title	New underpinning standards for improved bio-analytical measurement in Biotechnology & In vitro Diagnostics

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Internal Funded Partners: 1. LGC, United Kingdom 2. PTB, Germany	External Funded Partners:	Unfunded Partners:

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1 Overview

This Support for Impact (SIP) project leveraged outputs from two previously completed EMRP projects, SIB54 (Bio-SITrace) and HLT08 (INFECT-MET), which used state of the art techniques to develop methodology and guidelines for achieving traceability and comparability in biological measurements. Knowledge gained during these projects was inputted into 4 new documentary standards and revision of an existing documentary standard through two ISO committees, ISO/TC 276 (Biotechnology) and ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems), as well as supporting events to disseminate these standards and guidelines to user communities. The project's primary supporter, DIN, and the ISO/TC 212 WG2 & 4 and ISO/TC 276 WG3 conveners, recognised that the traceable measurement of biomolecules is a key problem in many sectors and is fundamental to the progress of biotechnology and clinical diagnostics.

2 Need

Accurate measurement of biological analytes (nucleic acids, proteins and cells) is increasingly important across many sectors including healthcare, environment, biotechnology and food. However, a lack of higher order reference methods and standards is a major hindrance for deriving traceability and measurement comparability, which impacts upon accreditation and regulatory development and compliance. This in turn compromises patient and consumer safety and efficacy of products.

The scope of the ISO/TC 276 (Biotechnology) technical committee called for metrology support into emerging standards to support innovations in biobanking, cell and gene therapeutics and diagnostics. Additionally, ISO TC212 WG2 (Reference systems) required incorporation on biomeasurement SI traceability into revisions of a fundamental standard on metrological traceability (ISO 17511).

Key outputs of SIB54 (Bio-SITrace) included proof of concept papers and traceability chains for accurate and traceable quantification by counting of nucleic acids and cells. This project inputted these outputs directly into the drafting of ISO 20395 (Requirements for evaluating the performance of quantification methods for nucleic acid target sequences -- qPCR and dPCR); ISO 20391 (Cell counting -- Part 1: General guidance on cell counting methods & Part 2: Experimental design and statistical analysis to quantify counting method performance) and ISO 17511 (In vitro diagnostic medical devices -- Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples).

Key outputs of HLT08 (INFECT-MET) included best practice guidelines for accurate measurement of microbial pathogens in clinical matrices. This project inputted this knowledge directly into the drafting of ISO 17822-2 (In vitro diagnostic test systems -- Qualitative nucleic acid-based in vitro examination procedures for detection and identification of microbial pathogens -- Part 2: Quality practices for nucleic acid amplification).

3 Objectives

The specific technical objectives of this SIP were concerned with providing detailed practical guidance for industrial and clinical end users of the outputs:

1. To incorporate the outputs from SIB54 Bio-SITrace for the quantification of nucleic acids and cells into ISO/TC 276 (Biotechnology), in order to support their wider dissemination and uptake.
2. To incorporate the outputs from SIB54 Bio-SITrace and best practice guidance from HLT08 INFECT-MET for the quantification and traceability of nucleic acids in clinical matrices into ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) in order to support their wider dissemination and uptake by the clinical community.

4 Results

Objective 1

To incorporate the outputs from SIB54 Bio-SITrace for the quantification of nucleic acids and cells into ISO/TC 276 (Biotechnology) in order to support their wider dissemination and uptake.

ISO 20395:2019 (Biotechnology — Requirements for evaluating the performance of quantification methods for nucleic acid target sequences — qPCR and dPCR)

LGC (as BSI nominated UK expert) led on the development of this new documentary standard under ISO/TC 276 WG3 (Analytical Methods), leading on the drafting of the standard incorporating outputs from a previously completed EMRP project SIB54 (Bio-SITrace) for the quantification of nucleic acids.

As project lead, LGC attended, presented and defended the successive working drafts and scope of this standard at regular ISO/TC 276 WG 3 meetings and ensured that the standard met the timelines dictated by the WG3 secretary in a timely manner.

Technical work on this standard was completed in July 2019 by formal acceptance of the Draft International Standard (DIS) vote. The promotion to Final Draft International Standard (FDIS) was recommended in March 2019 and the standard was published in August 2019.

The document provides generic requirements for evaluating the performance and ensuring the quality of methods used for the quantification of specific nucleic acid sequences (DNA/RNA) derived from biological sources such as viruses, prokaryotic and eukaryotic cells, cell-free biological fluids (e.g. plasma or cell media) or in vitro sources (e.g. oligonucleotides, synthetic gene constructs and in vitro transcribed RNA).

ISO 20391-1:2018 (Biotechnology — Cell counting — Part 1: General guidance on cell counting methods)

PTB and LGC contributed to the new international standard ISO 20391-1 (Biotechnology - Cell counting - Part 1: General guidance on cell counting methods) developed under ISO/TC 276 WG3 (Analytical Methods). This standard covers various approaches for cell counting.

A key input from SIB54 (Bio-SITrace) was the importance of volume measurements for quantitative measurements of cell concentrations. This included the importance to distinguish absolute concentration measurements (cells per volume) and relative concentration measurements (differential cell counting), as well as the use of calibrators in relative concentration measurements to achieve quantitative results. The standard was published in January 2018.

ISO 20391-2:2019 (Biotechnology — Cell counting — Part 2: Experimental design and statistical analysis to quantify counting method performance)

PTB and LGC contributed to another new documentary standard developed under ISO/TC 276 WG3 (Analytical Methods) incorporating outputs from SIB54 (Bio-SITrace). More specifically, the method to assess pipetting errors (Annex A in ISO 20391-2) was amended based on the measurement approach used under SIB54 (Bio-SITrace).

Technical work on this standard was completed in February 2019 by formal acceptance of the Draft International Standard (DIS) vote. The promotion to Final Draft International Standard (FDIS) was recommended in June 2019 and the standard was published in August 2019.

Objective 2

To incorporate the results and best practice guidance developed in SIB54 Bio-SITrace and HLT08 INFECT-MET for the quantification of nucleic acids in clinical matrices into ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) in order to support compliance with Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices and wider dissemination and uptake by the clinical community.

ISO/FDIS 17511 (In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples)

Active participation in ISO/TC 212 WG 2 (Reference systems) by LGC successfully resulted in the inclusion of new key text and exemplar traceability chain demonstrating SI traceability for nucleic acids and cell counting and key publications from SIB54 (Bio-SITrace) project referenced in the revision of this international standard.

The revision of ISO 17511 successfully reached the Draft International Standard (DIS) stage in April 2019, was approved as a Final Draft International Standard (DIS) in January 2020 and will be published later in 2020.

ISO/DIS 17822-2 (In vitro diagnostic test systems — Nucleic acid amplification- based examination procedures for detection and identification of microbial pathogens — Part 2: Laboratory quality practice guide)

LGC played an active part within the drafting committee for this new standard developed under ISO/TC 212/WG 4 (Microbiology and molecular diagnostics). LGC contributions to the drafting of this standard have ensured HLT08 (INFECT-MET) outputs on the management and reduction of contamination and methods for evaluating extraction efficiency have been included and project publications referenced.

The document successfully reached the DIS stage in November 2019. As of March 2020, the ISO 17822 Draft International Standard (DIS) has been approved to progress to FDIS and should be published later in the year.

The standard is important in the context of providing quality requirements underpinning comparable measurement in the important area of infectious disease molecular diagnostics.

5 Impact

To raise awareness of the ISO standards developed under this projects 6 presentations were given at relevant clinical stakeholder meetings and workshops including the 33rd Congress of the International Society for Advancement in Cytometry (CYTO 2018), Molecular Dx Europe, Digital PCR Congress (SynGen Series) and the Joint Committee for Traceability in Laboratory Medicine (JCTLM) Members' and Stakeholders' workshop.

Direct impact for the primary supporter

ISO/TC 276 (Biotechnology) is concerned with standardisation in the field of biotechnology processes. The Bio-stand consortium led the development of one new documentary standard and inputted into the development of two further documentary standards within the TC 276 committee. These standards will be fundamental base documents and will provide guidelines for evaluating and ensuring the quality of nucleic acid quantification and cell counting required specifically to support the analytical requirements of both ISO/TC 276 WG2 (Biobanks and bioresources) and ISO/TC 276 WG4 (Bioprocessing). They will also support the broader biotechnology, R&D, industrial biotechnology, engineering biology, gene editing, and advanced therapeutics industries, which have to comply with quality and emerging regulatory requirements.

ISO/TC 212 212 (Clinical laboratory testing and in vitro diagnostic test systems) is concerned with standardisation and guidance in the field of laboratory medicine and in vitro diagnostic test systems. The Bio-stand consortium inputted into the development of two standards, which were being revised/developed within the TC 212 committee. These standards describe metrological traceability for in vitro diagnostic devices (ISO 17511) and the particular laboratory practice requirements to ensure the quality of detection, identification and quantification of microbial pathogens using nucleic acid amplification-based methods (ISO 17822). These standards will help users and developers of such clinical tests to comply with Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices.

Direct impact on biotechnology industry

The standards developed in this SIP will provide confidence in the data produced and be useful for selecting or optimising a measurement process. They will also provide supporting performance parameters that may be utilised during performance qualification of a particular measurement process. Biotechnology and bioscience industry data with higher measurement confidence will enable data interoperability, reduced risks and costs, engender regulatory confidence and compliance and facilitate international trade.

Direct impact on healthcare providers and diagnostics developers

The standards developed in this SIP will be used by IVD medical device manufacturers, medical laboratories and research and development laboratories that develop nucleic acid amplification-based in vitro diagnostic examination procedures for the detection and identification of microbial pathogens in human specimens. In this context, these guidelines both support molecular IVD manufacturers and molecular diagnostic laboratories to demonstrate conformity with IVD regulatory requirements worldwide, so enhancing molecular diagnostic comparability and clinical confidence in patient reporting.

Wider industry impacts

Accurate measurement of biological analytes (nucleic acids, proteins and cells) underpins the future of many sectors including healthcare, environment, biotechnology, and food. Application of the standards developed in this SIP will provide generic support to practitioners in the field undertaking such measurements and help ensure compliance with the analytical quality and metrological traceability requirements of the In vitro diagnostic medical device regulation (IVDR) which entered into force in 2017.

Economic and Societal impact

Low reproducibility rates within Life Science measurements undermine cumulative knowledge production and contribute to both delays and costs of product development. Whilst it is difficult to put a precise figure on the amount of money that can be saved as a result of the standards produced in this SIP, it can be assumed that even a low level of uptake will have significant cost benefits.

Laboratory developed biomolecular tests serve an increasingly important role in health care today. They also have become significantly more complex and higher risk, with several notable examples of inaccurate tests placing patients at otherwise avoidable risk. The standards produced in this SIP will help to mitigate against the use of inaccurate and unreliable tests.

6 List of publications

n/a

7 Contact details

n/a