
Publishable Summary for 20SIP03 Bio-stand 2

New underpinning standards for improved bio-analytical measurement in infectious diseases

Overview

New and emerging pathogenic microbes coupled with increasing prevalence of antimicrobial resistance threaten the effective prevention and treatment of an ever-increasing range of infectious diseases. Driven by the emergence of novel pathogens and the misuse of antimicrobial drugs, a key and achievable goal in the fight against infectious disease is the advancement of clinical test methods to enable doctors to rapidly identify the causative agent and determine the correct therapy to use. This project aims to maximise end user uptake of key outputs from EMPIR JRP 15HLT07 AntiMicroResist, which developed methodology and guidelines for achieving traceability and comparability in the measurement and diagnosis of infectious diseases. The project will contribute toward the standards development through ISO/TC 276 (Biotechnology) and ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems). This will accelerate the progress in biotechnology and clinical diagnostics.

Need

Molecular detection, where specific pathogenic gene sequences are detected and quantified is increasingly applied to guide infectious disease diagnosis and to guide and monitor treatment. Numerous nucleic acid (NA)-based tests are increasingly being used for the quantification of pathogens, such as HIV viral load, or for the diagnosis where thresholds are required to assist in improving clinical specificity, such as COVID-19.

However, despite the increasingly widespread use of NA quantification technologies, undertaking assays to a high quality and achieving comparability can be challenging. A current lack of higher order reference measurement procedures and materials is a major hindrance for deriving traceability and comparability, which impacts upon regulatory development, accreditation and compliance. This in turn compromises the efficacy of diagnostic tests and ultimately patient safety. Poor reproducibility rates within newly developed molecular diagnostic methods (such as those applied in response to SARS-CoV-2) undermine their potential, limiting the national and international response and means that patients do not benefit from this potentially powerful technology.

New standards and guidance provided thereby are needed to enable the diagnostic setting to generate data with higher measurement confidence, which will enable data interoperability, reduced risks and costs, engender regulatory confidence and compliance and facilitate international trade. They are also needed for the Clinical Diagnostics sector for use by In Vitro Diagnostics (IVD) medical device manufacturers, medical laboratories and R&D laboratories that develop NA amplification based IVD examination procedures. In this context, these guidelines support molecular diagnostic laboratories to demonstrate conformity with IVD regulatory requirements worldwide. This will result in improved patient care and reduced costs to society. To ensure these new standards have the maximum impact to these end users, they must be written with a comprehensive understanding of the metrological challenges associated with these measurements.

EMPIR JRP 15HLT07 AntiMicroResist project established best practice guidance for NA detection and quantification, which now would benefit from wider dissemination to user communities through the standards described.

Objectives

The overall aim of this project is to deliver practical impact from the outputs of 15HLT07 AntiMicroResist by incorporating them into standards to support the clinical diagnosis of infectious diseases.

The specific objectives of this project are:

1. To incorporate the outputs from EMPIR JRP 15HLT07 AntiMicroResist for the detection and quantification of SARS-CoV-2 into a new Technical Specification (ISO/CD TS 5798) under ISO/TC

276 (Biotechnology) and ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) joint working group and to support their wider dissemination and uptake.

2. To incorporate the outputs from EMPIR JRP 15HLT07 AntiMicroResist for the application of sequencing methods for pathogen detection and the identification of drug resistance into a New Work Item on the use of targeted and non-targeted sequencing when applied as a diagnostic and epidemiological tool under ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) and to support their wider dissemination and uptake.

Results

To incorporate the outputs from EMPIR JRP 15HLT07 AntiMicroResist for the detection and quantification of SARS-CoV-2 into a new Technical Specification (ISO/CD TS 5798) under ISO/TC 276 (Biotechnology) and ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) joint working group and to support their wider dissemination and uptake.

Technical expertise gained in EMPIR JRP 15HLT07 AntiMicroResist for the detection and quantification of SARS-CoV-2 and scientific results obtained in this project were incorporated into ISO/TS 5798 (Requirements and recommendations for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nucleic acid amplification methods). The technical specification was published in April 2022. Technical inputs included description of isothermal amplification methods, the utility of digital PCR as a potential reference measurement procedure to quantify SARS-CoV-2 viral load, and the analytical performance of tests in this field in general.

To incorporate the outputs from EMPIR JRP 15HLT07 AntiMicroResist for the application of sequencing methods for pathogen detection and the identification of drug resistance into a New Work Item on the use of targeted and non-targeted sequencing when applied as a diagnostic and epidemiological tool under ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) and to support their wider dissemination and uptake.

The ISO/TC 212/WG4 committee approved drafting a New Work item proposal on the use of microbial sequencing (metagenomics) techniques to support infectious disease diagnosis and management at the October 2021 meeting.

Further discussion on the New Work item proposal on the use of microbial sequencing (metagenomic) techniques to support infectious disease diagnosis and management was held at the ISO/TC 212 WG4 meeting in October 2022. As a similar proposal had been submitted to the ISO TC 276/212 joint working group, it was recommended to merge the proposals and register a New Work item proposal as ISO/PWI 8219 (Sequencing and clinical application to infectious diseases).

Discussions on the New Work item proposal on the use of microbial sequencing (metagenomic) techniques to support infectious disease diagnosis and management continued at the ISO/TC 212 WG4 meeting in May 2023. The proposal (ISO/PWI 8219 (Requirements for the identification and characterisation of microbes using sequencing direct from clinical specimens in the management of infectious disease)) was approved to go out for ballot to the National Standards committees for approval as a New Work Item.

Impact

Following publication, a summary of the key recommendations of ISO/TS 5798 was presented at the 38th Annual NRL Workshop on Infectious Disease. The application of ISO/TS 5798 to external quality assurance was also emphasised at a webinar on 'Standards of the detection of SARS-CoV-2 by nucleic acid amplification methods for strengthening public health system and facilitating trade in APEC (Asia-Pacific Economic Cooperation) economies'. ISO/TS 5798 was also highlighted at the Qiagen Innovation Forum and the 10th Gene Quantification Event.

ISO/TS 5798 was used by the Primary Supporter (DIN) to create DIN CEN ISO/TS 5798:2023-03 (In-vitro-Diagnostika-Systeme – Anforderungen und Empfehlungen für Qualitätsverfahren für den Nachweis des Coronavirus 2 des Schwere Akuten Respiratorischen Syndroms (SARS-CoV-2) mittels Nukleinsäureamplifikation (ISO/TS 5798:2022); Deutsche Fassung)).

ISO/TC 276 (Biotechnology) Standards

ISO/TS 5798 (Requirements and recommendations for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by nucleic acid amplification methods) provides guidelines for evaluating and ensuring the quality of molecular diagnosis of infectious diseases specifically to support the ISO/TC 276

(Biotechnology) and ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) joint working group. Continued work of the joint working group is planned for preparation of a standard describing detection of emerging SARS-CoV-2 variants.

ISO/TS 5798 brings confidence in the data produced and be useful for selecting or optimising a measurement process. The Quality Practice provides supporting performance parameters that may be utilised during performance qualification of a particular measurement process. IVD industry data with higher measurement confidence will enable data interoperability, reduced risks and costs, engender regulatory confidence and compliance and facilitate international trade. The technical specification is intended to be used by medical laboratories, laboratory customers, in-vitro diagnostics developers and manufacturers, as well as by institutions and organisations performing and/or supporting SARS-CoV-2 research.

ISO/TC 212 (Clinical laboratory testing and in vitro diagnostic test systems) Standards

The proposal of a New Work Item will focus on the use of microbial sequencing (metagenomic) methods for the identification and quantification of microbial pathogens using sequencing-based methods. Is it intended to benefit IVD medical device manufacturers, medical laboratories and research and development laboratories that use non targeted approaches to identify the causative pathogen when it is unknown (such as in identifying SARS-CoV-2 as the causative agent for COVID-19) or when a large number of potential aetiological agents could be the cause of the condition being investigated. In this context, it will support molecular diagnostic laboratories applying microbial sequencing (metagenomic) diagnostic approaches to demonstrate conformity with IVD regulatory requirements worldwide such as EU Regulation 2017/746 on in vitro diagnostic medical devices. This in turn will improve patient safety, reduce risks and costs to the industry and facilitate international trade.

Project start date and duration:		01 May 2021, 36 months	
Coordinator: John Black, LGC		Tel: +44 (0) 208 943 7000	E-mail: john.black@lgcgroup.com
Project website address: n/a			
Primary Supporter: Lena Krieger, DIN e.V.			
Internal Funded Partners:		External Funded Partners:	Unfunded Partners:
1. LGC, United Kingdom			
2. PTB, Germany			