Approaches to Provide Assurance for Biological Measurements

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Measurements of microbes and their communities are regularly performed to support routine applications such as clinical diagnostics, water testing, antimicrobial susceptibility testing, and biothreat detection, as well as emerging areas such as microbiome therapeutics and novel antimicrobial approaches with the potential to reduce antimicrobial resistance. Nevertheless, biological systems such as microbes are living, dynamic entities whose properties often lack a "ground truth" value, making them especially challenging to measure with confidence. Biological measurements such as these continue to be plagued by uncertainty regarding the level of confidence that should be applied to the results. How confident are we that the results reflect the actual property that is intended to be measured? Are the accuracy and precision of the results within an acceptable range? Introducing measurement assurance concepts into the process workflow is a critical component to support regulatory oversight and commercialization success of antimicrobial approaches such as ultraviolet disinfection.

Measurement assurance strategies seek to provide an infrastructure to increase confidence in measurement results, improve comparability, and consequently better inform decision making. The level of confidence required will depend upon the type of decisions being made. The higher the stakes, the greater the level of confidence needed, and therefore the greater the demand for relevant measurement assurance tools. For instance, initial research studies and experiments will likely have less stringent requirements for measurement assurance as compared to data collected to support regulatory applications. Measurement assurance tools could include cause and effect diagrams to identify sources of variability, design of experiments, process controls, interlaboratory studies, uncertainty analyses, validated methods, best practices, and of course, standards.

The term 'standards' can refer to several categories of tools designed to increase confidence in a measurement (Figure 1). For instance, documentary standards can be developed by stakeholder consensus in standards development organizations (SDOs) such as the International Organization for Standardization (ISO) or ASTM (American Society for Testing and Materials) International. These documents can include guides, methods, specifications, and practices, to name a few. Reference materials including NIST Standard Reference Materials are physical artifacts that serve as standards for applications such as instrument calibration, data normalization, and as highly quantified inputs into a measurement process. Other types of standards include standard reference data or databases, and standard reference instruments. When considering biological measurements, one needs to identify the standards that can be incorporated into a workflow to provide the needed level of assurance for a given measurement method and application space.

Microbial metrology at NIST focuses on measurement science, technology, and standards to increase confidence in quantitative measurements of microbes and their complex communities and to promote

responsible biotechnology innovation. Efforts to develop measurement assurance strategies encompass all levels of biological systems, from subcellular components such as DNA or metabolites, to individual cell properties, to cell systems such as microbial biofilms.

As an example, there is a dearth of biological, cell-based reference materials due to the complexity in producing and maintaining a stable, homogenous cell material and then characterizing the properties of that material. To this end, NIST is developing microbial cell reference materials, starting with a reference material consisting of vials of lyophilized yeast cells where the total number of cells per vial is characterized as the reference value. In addition, the colony forming units (CFU) per vial quantified under specified growth conditions is also provided. The yeast material can serve as a known, consistent input to assess accuracy and comparability of microbial cell enumeration methods. Additional reference materials consisting of bacterial cells in pure populations or as mixtures are under development to expand the cell-based reference materials selection. Materials such as these can also support interlaboratory studies by providing a homogeneous input material to elucidate reproducibility and sources of uncertainty for a given measurement process.

Overall, measurement assurance tools are a critical part of the infrastructure required to confidently use microbial measurements in applications including demonstration of efficacy of ultraviolet disinfection. Regular and proper usage of these tools can help decision-makers understand the level of confidence they should have in available data. While some tools do exist for microbial metrology, there is a growing need for additional tools including documentary standards and relevant reference materials to enable reproducible and comparable results. These measurement assurance tools directly support regulatory oversight for applications including the use of ultraviolet light disinfection in healthcare facilities.

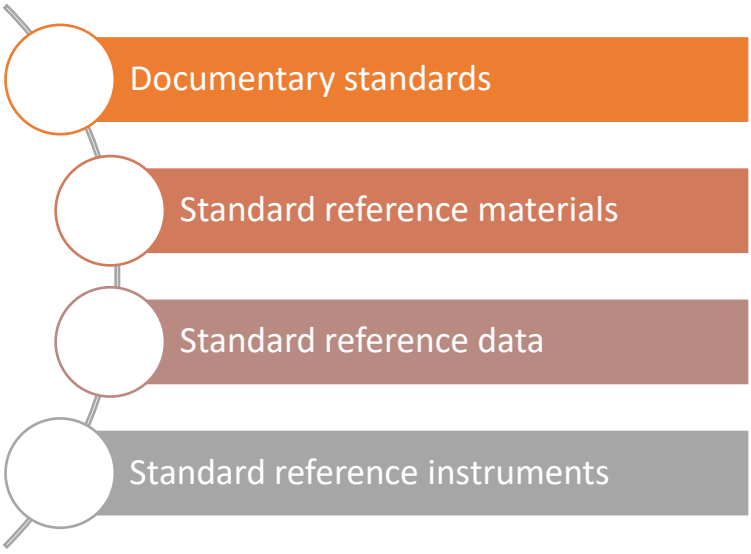

Figure 1. Examples of types of standards. This list is not exhaustive but serves as a demonstration that standards are more than just written documents.