SLOVENSKI STANDARD
oSIST prEN ISO 20776-2:2021

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Klinični laboratorijski preskusi ter diagnostični preskusni sistemi in-vitro - Preskus občutljivosti povzročiteljev infekcij in vrednotenje delovanja antimikrobno občutljivih preskusnih naprav - 2. del: Vrednotenje delovanja antimikrobno občutljivih naprav (ISO/DIS 20776-2:2021)

Clinical laboratory testing and in vitro diagnostic test systems - Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test - Part 2: Evaluation of performance of antimicrobial susceptibility test devices against reference broth micro-dilution (ISO/DIS 20776-2:2021)

Labormedizinische Untersuchungen und In-vitro-Diagnostika-Systeme - Empfindlichkeitsprüfung von Infektionserregern und Evaluation von Geräten zur antimikrobiellen Empfindlichkeitsprüfung - Teil 2: Evaluation der Leistung einer Vorrichtung zur antimikrobiellen Empfindlichkeitsprüfung (ISO/DIS 20776-2:2021)

Systèmes d’essais en laboratoire et de diagnostic in vitro - Sensibilité in vitro des agents infectieux et évaluation des performances des dispositifs pour antibiogrammes - Partie 2 : Évaluation des performances des dispositifs pour antibiogrammes contre méthode de référence de microdilution en bouillon (ISO/DIS 20776-2:2021)

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11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems

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Clinical laboratory testing and in vitro diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test —

Part 2:
Evaluation of performance of antimicrobial susceptibility test devices against reference broth micro-dilution

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

This document cancels and replaces the first edition (ISO 20776-2:2007), which has been technically revised.

The main changes compared to the previous edition are as follows:

— Revision in the title of part 2 to better align with the intended information;

— Addition of an Introduction – not presented in the original version.

— Revised Terms and Definitions as follows:

— Removed definitions for Category agreement, susceptible, intermediate, resistant, non-susceptible, major discrepancy, minor discrepancy, very major discrepancy, breakpoint test, zone diameter;

— Added definition for contemporary isolate and removed definitions for fresh isolate, recent isolate;

— Added definitions for reproducibility, bias of the test method, sensitivity analysis, specificity analysis, organism group;

— Added definition for qualitative test and removed definition for breakpoint test;

— Revised definitions for minimum inhibitory concentration test, breakpoint, quality control, discrepancy;

— Moved general requirements for a performance evaluation as a separate section, to the overview (now renamed general section) under test methods;

— Reordered Test methods section;

— Revised quality control section, and referenced EUCAST and CLSI documents for quality control ranges;

— Revised reference method section to add variability;

— Revised strain selection section and incorporated new definition of contemporary isolates;

— Revised reproducibility testing section;

— Revised discrepancy resolution section;

— Combined data analysis and acceptance criteria sections;

— Revised Accuracy of test device section to remove category agreement;

— Revised data analysis for MIC devices to remove category agreement. Added bias requirement;

— Removed acceptance for breakpoint AST devices;

— Added section for acceptance criteria for qualitative AST devices and included sensitivity and specificity requirements;

— Revised sections for quality control of test device and reproducibility of test device;

— Revised bibliography;

— Added Annexes A - Evaluation the Performance of MIC Tests, B - Rationale for Bias Analysis, and Annex C - Sensitivity and Specificity Analyses for Qualitative Tests

A list of all parts in the ISO 20776 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

In vitro antimicrobial susceptibility tests are performed on micro-organisms suspected of causing disease, particularly if the organism is thought to belong to a species that may exhibit resistance to frequently used antimicrobial agents. The tests are also important in resistance surveillance, epidemiological studies of susceptibility and in comparisons of new and existing agents.

Dilution procedures are used to determine the minimum inhibitory concentrations (MICs) of antimicrobial agents for antimicrobial susceptibility testing. MIC methods are used in resistance surveillance, defining and identifying wild type phenotypes, comparative testing of new agents, to establish the susceptibility of organisms that give equivocal results in routine tests, for tests on organisms where routine tests may be unreliable and when a quantitative result is required for clinical management. In dilution tests, micro-organisms are tested for their ability to produce visible growth in broth (broth dilution) containing serial dilutions of the antimicrobial agent or on a series of agar plates (agar dilution).

The lowest concentration of an antimicrobial agent (in mg/l) that, under defined in vitro conditions, prevents the appearance of visible growth of a micro-organism within a defined period of time is known as the MIC. Careful control and standardization are required for intra- and inter-laboratory reproducibility of broth MIC tests. The MICs of quality control strains generally span three doubling dilutions with a dominant central value, but may have a four-dilution range.

Broth micro-dilution denotes the performance of the broth dilution test in micro-dilution trays. Broth micro-dilution is now one of the most common methods used globally to perform antimicrobial susceptibility tests.

This document is a revision of a previous ISO document (ISO 20776-2: 2007, *Clinical laboratory testing and in vitro diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices — Part 2: Evaluation of performance of antimicrobial susceptibility test devices*). The document is designed for the evaluation of antimicrobial test devices against the standard broth micro-dilution reference method (ISO 20776-1:2019) using pure cultures of aerobic bacteria that are easily grown by overnight incubation on agar and grow well in standardized micro-dilution trays containing standardized Mueller-Hinton broth (volume of ≤200 µl), which may need to be modified depending on the antimicrobial agent being tested.

Quantitative MIC and qualitative evaluations detailed in this revised document measure the accuracy, reproducibility, and quality control of tests performed with antimicrobial test devices that generate MIC values against the standard broth micro-dilution reference method. Antimicrobial agar disc diffusion tests are not included in this revision.

This document has been revised using the premise that the MIC test is an in vitro assay, subject to intra- and interlaboratory assay variation. When making the comparison between any derivative test and that of the reference method, it is appropriate to apply measures of assay performance only and not result interpretation. For this reason, and because interpretive categories were removed from the revision of the companion document ISO 20776-1, categorical agreement (CA) and its associated terminology, as described by the U.S. Food and Drug Administration (FDA), the Clinical and Laboratory Standards Institute (CLSI) M23 document, and other international documents, has not been applied. Avoiding an assessment of CA also assists in reducing the requirement to reassess assay performance automatically when the only change has been a breakpoint change (which is external to the assay itself).

This document applies to new performance evaluations initiated after the acceptance date of the standard; studies conducted prior to the acceptance date of this document may not need to be re-designed and/or re-analysed using these criteria. Studies conducted prior to these standards or acceptance of this document follow standard practice or guidance at the time of the study.

For derivative tests with more than 3 two-fold dilutions, assay performance is assessed with tools designed to measure accuracy using Essential Agreement (EA) and bias, and precision using EA only. For derivative tests with 1-3 concentrations, assay performance is assessed using standard sensitivity and specificity measures.

Clinical laboratory testing and in vitro diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test —

Part 2: Evaluation of performance of antimicrobial susceptibility test devices against reference broth micro-dilution

1 Scope

This document establishes acceptable performance criteria for antimicrobial susceptibility test (AST) devices that are used to determine minimum inhibitory concentrations (MIC) of bacteria to antimicrobial agents in medical laboratories.

This document specifies requirements for AST devices and procedures for assessing performance of such devices. It defines how a performance evaluation of an AST device is to be conducted.

This document has been developed to guide manufacturers in the conduct of performance evaluation studies.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 20776-1:2019, *Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices — Part 1: Broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
antimicrobial susceptibility test device
AST device
device including all specified components used to obtain test results that allow MIC determination of bacteria with specific antimicrobial agents

Note 1 to entry: Specific components of the device include inoculators, disposables and reagents, media used to perform the test, and readers. Non-specific components, such as swabs, pipettes and tubes, are not part of the device.

3.2
reference method
reference method described in ISO 20776-1 most recent version. This reference method describes dilution procedures to determine the minimum inhibitory concentration of antimicrobial agents

3.3
minimum inhibitory concentration
MIC
lowest concentration that, under defined in vitro conditions, prevents visible growth of bacteria within a defined period of time

Note 1 to entry: The MIC is expressed in mg/l.

3.4
minimum inhibitory concentration test
MIC test
test that is capable of determining an *MIC* [3.3] covering a range of at least four consecutive doubling dilutions, and for which Essential Agreement (EA) can be determined

3.4.1
on-scale MIC test result
result from a *MIC test* [3.4] when there is growth in at least one dilution below the MIC endpoint and no growth in at least one dilution above

3.5
breakpoint
specific values of parameters, such as *MICs* [3.3], on the basis of which bacteria can be assigned to clinical categories such as "susceptible" (S) or "resistant" (R)

Note 1 to entry: For current interpretive breakpoints and interpretive categories, reference should be made to the latest publications of organizations employing this *reference method* [3.2] (e.g., CLSI(1) and EUCAST(2)).

3.6
qualitative test
test that has the principal objective to provide a qualitative result (e.g., using a *breakpoint* [3.5] or screening concentration)

Note 1 to entry: Such tests have a limited range of 1-3 doubling dilutions.

3.7
quality control of antimicrobial susceptibility tests
quality control includes the use of carefully selected bacterial strains with given expected *MIC* [3.3] results

Note 1 to entry: *MICs* [3.3] of antimicrobial agents for control organisms should be within the ranges given in the latest versions of the CLSI M100 document[1] or the EUCAST Quality Control document.[3] It is not possible to provide a single Quality Control Table.

3.8
reproducibility
extent to which consistent results such as MICs are obtained when the test is repeated

3.9
evaluation of test results

3.9.1
discrepancy
difference in a result between the test method (either a *MIC test* [3.4] or a *qualitative test* [3.6]) and the *reference method* [3.2] (ISO 20776-1) outside the region of essential agreement (*MIC test* [3.4]), or outside the region of sensitivity and specificity (*qualitative test* [3.6])

3.9.2
essential agreement
EA
MIC [3.3] result obtained with the *AST device* [3.1] that is within plus or minus one two-fold dilution step from the *MIC* [3.3] value established with the *reference method* [3.2] (ISO 20776-1)

Note 1 to entry: Used for *MIC* [3.3] devices.

Note 2 to entry: Another representation of the concept is:

$\frac{N_{EA}}{N} \times 100$, where:

N_{EA} is the number of bacterial isolates with an EA;*N* is the total number of bacterial isolates tested

Note 3 to entry: The overall EA is expressed as a percentage.

3.9.3
bias of the test method
evaluation of test device results to determine whether the results that differ from the *reference method* [3.2] are significantly skewed or predominantly in one direction

Note 1 to entry: Used for *MIC tests* [3.4].

3.9.4.1
sensitivity analysis
<screening or *breakpoint* [3.5] test> measure of agreement between test device results and *reference method* [3.2] results that are positive or above a published *breakpoint* [3.5] Can also be considered as positive percent agreement when reference results are interpreted as positive

Note 1 to entry: Used for *qualitative tests* [3.6].

Note 2 to entry: See Table 1 .

Table 1 — Sensitivity analysis for a qualitative (screening or breakpoint) test

		Reference method		Total
		(-) or no growth	(+) or growth	
Test method	(-) or no growth	a	b	a+b
	(+) or growth	c	d	c+d
Total		a+c	b+d	Sum of (a,b,c,d)
Sensitivity = $100 \times [d \div (b+d)]$				

3.9.4.2
sensitivity analysis
<three-dilution *qualitative test* [3.6]> measure of agreement between test device results and *reference method* [3.2] results that have the *MICs* [3.3] at the high end of the scale

Note 1 to entry: Used for *qualitative tests* [3.6].

Note 2 to entry: See Table 2 .

Table 2 — Sensitivity analysis for a three-dilution qualitative test

	Reference method			Total
	≤ Low MIC	Middle MIC	≥ High MIC	