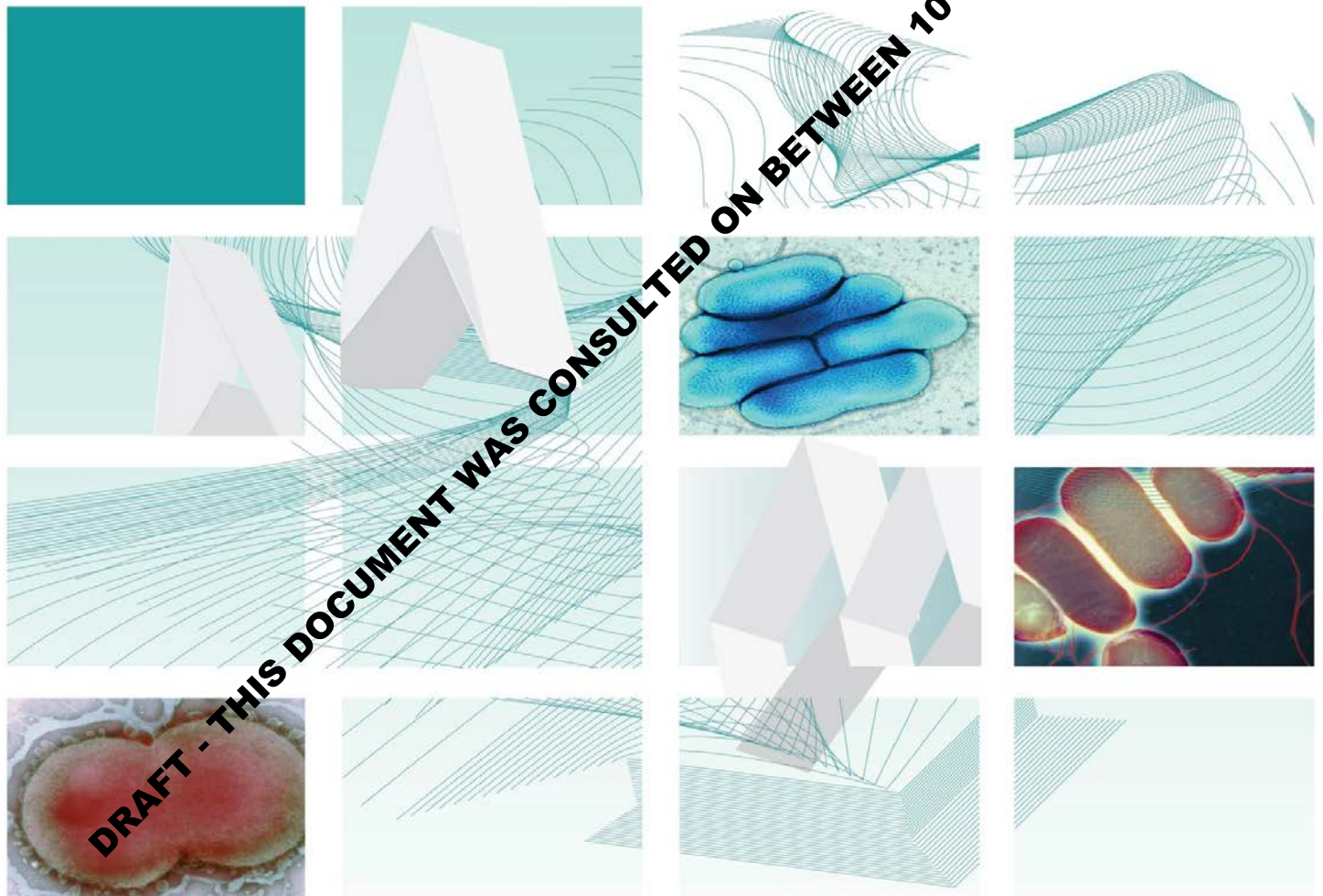




UK Standards for Microbiology Investigations

Matrix-Assisted Laser Desorption/Ionisation - Time of Flight Mass Spectrometry (MALDI-TOF MS) Test Procedure



Issued by the Standards Unit, Microbiology Services, PHE

Bacteriology – Test procedures | TP40| Issue no: dm+|Issue date: dd.mm.yy <tab+enter>

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Acknowledgments

UK Standards for Microbiology Investigations (SMIs) are developed under the auspices of Public Health England (PHE) working in partnership with the National Health Service (NHS), Public Health Wales and with the professional organisations whose logos are displayed below and listed on the website <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>. SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see <https://www.gov.uk/government/groups/standards-for-microbiology-investigations-steering-committee>).

The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the Medical Editors for editing the medical content.

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UK Standards for Microbiology Investigations are produced in association with:



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For full details on our accreditation visit: www.nice.org.uk/accreditation.

Amendment Table

Each SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@phe.gov.uk.

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

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UK Standards for Microbiology Investigations[#]: Scope and Purpose

Users of SMIs

- SMIs are primarily intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK.
- SMIs provide clinicians with information about the available test repertoire and the standard of laboratory services they should expect for the investigation of infection in their patients, as well as providing information that aids the electronic ordering of appropriate tests.
- SMIs provide commissioners of healthcare services with the appropriateness and standard of microbiology investigations they should be seeking as part of the clinical and public health care package for their population.

Background to SMIs

SMIs comprise a collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology from the pre-analytical (clinical syndrome) stage to the analytical (laboratory testing) and post analytical (result interpretation and reporting) stages.

Syndromic algorithms are supported by more detailed documents containing advice on the investigation of specific diseases and infections. Guidance notes cover the clinical background, differential diagnosis, and appropriate investigation of particular clinical conditions. Quality guidance notes describe laboratory processes which underpin quality, for example assay validation.

Standardisation of the diagnostic process through the application of SMIs helps to assure the equivalence of investigation strategies in different laboratories across the UK and is essential for public health surveillance, research and development activities.

Equal Partnership Working

SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies.

The list of participating societies may be found at <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>.

Inclusion of a logo in an SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing SMIs. Nominees of professional societies are members of the Steering Committee and Working Groups which develop SMIs. The views of nominees cannot be rigorously representative of the members of their nominating organisations nor the corporate views of their organisations. Nominees act as a conduit for two way reporting and dialogue. Representative views are sought through the consultation process.

[#]Microbiology is used as a generic term to include the two GMC-recognised specialties of Medical Microbiology (which includes Bacteriology, Mycology and Parasitology) and Medical Virology.

SIMs are developed, reviewed and updated through a wide consultation process.

Quality Assurance

NICE has accredited the process used by the SIM Working Groups to produce SIMs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of SIMs is certified to ISO 9001:2008.

SIMs represent a good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. SIMs are NICE accredited and represent neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using SIMs, laboratories should take account of local requirements and undertake additional investigations where appropriate. SIMs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. SIMs also provide a reference point for method development.

The performance of SIMs depends on competent staff and appropriate quality reagents and equipment. Laboratories should ensure that all commercial and in-house tests have been validated and shown to be fit for purpose. Laboratories should participate in external quality assessment schemes and undertake relevant internal quality control procedures.

Patient and Public Involvement

The SIM Working Groups are committed to patient and public involvement in the development of SIMs. By involving the public health professionals, scientists and voluntary organisations the resulting SIM will be robust and meet the needs of the user. An opportunity is given to members of the public to contribute to consultations through our open access website.

Information Governance and Equality

PHE is a Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions.

The development of SIMs are subject to PHE Equality objectives

<https://www.gov.uk/government/organisations/public-health-england/about/equality-and-diversity>

The SIM Working Groups are committed to achieving the equality objectives through effective consultation with members of the public, partners, stakeholders and specialist interest groups.

Legal Statement

Whilst every care has been taken in the preparation of SIMs, PHE and any supporting organisation, shall, to the greatest extent possible under any applicable law, exclude liability for all losses, costs, claims, damages or expenses arising out of or connected with the use of an SIM or any information contained therein. If alterations are made to an SIM, it must be made clear where and by whom such changes have been made.

The evidence base and microbial taxonomy for the SIM is as complete as possible at the time of issue. Any omissions and new material will be considered at the next

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review. These standards can only be superseded by revisions of the standard, legislative action, or by NICE accredited guidance.

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Suggested Citation for this Document

Public Health England. (YYYY <tab+enter>). Matrix-Assisted Laser Desorption/Ionisation - Time of Flight Mass Spectrometry (MALDI-TOF MS) Test . UK Standards for Microbiology Investigations. TP 40 Issue d. <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>

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Scope of Document

This SMI describes the test procedure, MALDI-TOF and its use in the examination of clinical specimens as mentioned in the UK SMI Identification (ID) documents. This document includes the mechanism as well as the limitations of the technique in its use in diagnostic microbiology laboratories.

For information on evaluation and validation of this method for use in the laboratory, refer to [Q1 - Commercial and In-House Diagnostic Tests: Evaluations and Validation](#).

Refer to specific ID documents for more information on the technical information/limitations of using this test procedure.

This SMI should be used in conjunction with other SMIs.

Introduction

Matrix-Assisted Laser Desorption/Ionisation - Time of Flight Mass Spectrometry (MALDI-TOF MS)

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is a soft ionisation technique used in mass spectrometry, allowing the analysis of biomolecules (such as DNA, proteins, peptide and sugars) and large organic molecules (such as polymers, dendrimers and other macromolecules), which tend to be fragile and fragment when ionised by more conventional ionisation methods. The ionisation is triggered by a laser beam. It is a rapid and highly reliable analytical tool for the characterisation of a diverse collection of microbes encountered in the clinical laboratory.

This technique can be used to analyse the protein composition of a bacterial cell, and has emerged as a new technology for species identification. It has been shown to be a powerful technique because of its reproducibility, speed and sensitivity of analysis. The advantage of MALDI-TOF MS as compared with other identification methods is that the results of the analysis are available within minutes to a few hours rather than several days. Without prior knowledge of microorganism type; users do not even need to know whether a bacterium or yeast is being tested. The speed and the simplicity of sample preparation and result acquisition associated with minimal consumable costs make this method well suited for routine and high throughput use¹.

Ultimately MALDI-based identification systems may prove the most cost-effective means of identification dependent only on how comprehensive the databases are². Another drawback is with the currently available commercial platforms. A number of well-established commercial manufacturers use their own algorithms, databases, software, and interpretive criteria for microbial identification, thereby making numerical data (ie, spectral scores) between these different commercial systems not directly comparable.

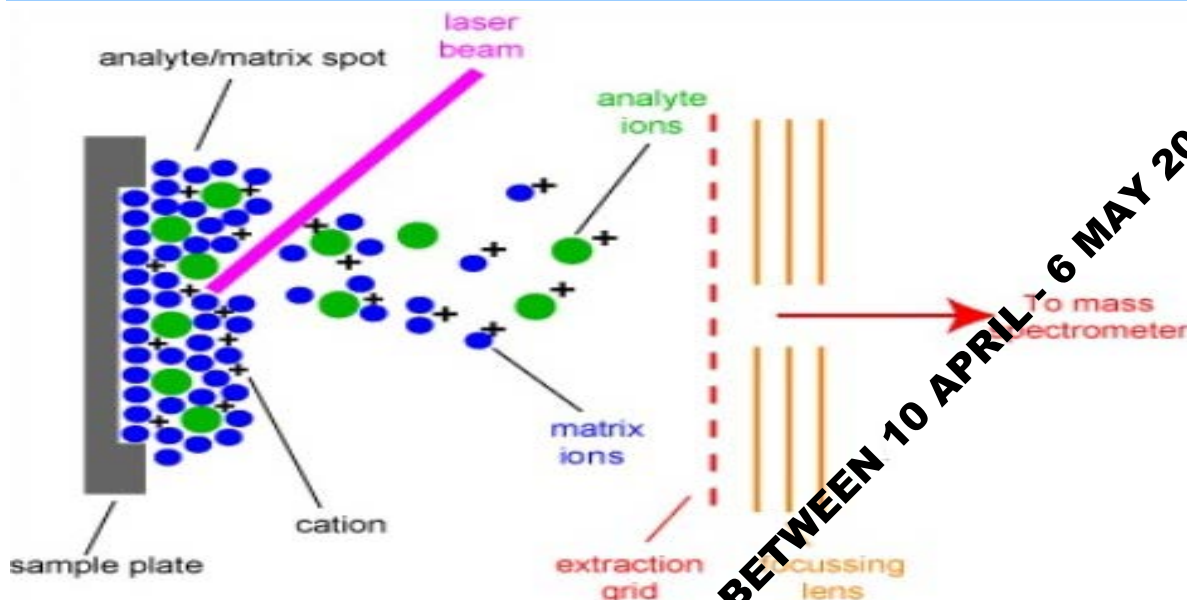
Given changing nomenclature and ongoing description of new species and emerging microorganisms, regular and ongoing updates to databases are imperative to ensure clinical utility. Databases should include entries representing major phylogenetic lineages within each species. It is possible for users to add their own mass spectral

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entries to enhance existing databases or create their own database by including locally important strains or strains not well represented in commercial libraries³.

This method has been used successfully in the identification of bacteria and fungi.

Mechanism of MALDI-TOF MS



Adapted from University of Bristol

The mechanism of MALDI-TOF MS is as stated:

- The target plate is placed into the ionisation chamber of the mass spectrometer. Spots to be analysed are shot by an ultraviolet N₂ laser desorbing microbial and matrix molecules from the target plate. The majority of energy is absorbed by the matrix, converting it to an ionised state.
- Through random collision in the gas phase, charge is transferred from matrix to microbial molecules.
- The cloud of ionised molecules is funnelled through a positively charged electrostatic field into the time of flight mass analyser, a tube under vacuum.
- The ions travel toward an ion detector with small analytes traveling fastest, followed by progressively larger analytes.

As ions emerge from the mass analyser, they collide with an ion detector generating a mass spectrum representing the number of ions hitting the detector over time. Although separation is by mass to charge ratio, because the charge is typically single for the described application, separation is effectively by molecular weight.

Technical Information/Limitations

Presence of spores

A limitation of this technique is the spectral interference due to the presence of spores in some organism species, for example *Clostridium* species. Younger cultures are used to minimise this interference⁴.

Differentiation between organisms

Another limitation of this technique is the inability of the mass spectrometry spectra to differentiate similar or closely related organisms such as *Escherichia coli* and *Shigella* species, some viridans streptococci and pneumococci, etc. Direct discrimination between strains such as Meticillin resistant *S. aureus* and Meticillin sensitive *S. aureus* strains is a great challenge for MALDI-TOF MS applications in diagnostic laboratories⁵.

Existing Taxonomical Databases

MALDI-TOF databases can be improved by enhancing existing databases or by laboratories creating their own database by including local important strains or strains not well represented or misrepresented in commercial libraries³. Some examples are the misidentification of *Propionibacterium acnes* as *Eubacterium brachy*, misidentification between viridans streptococci and pneumococci⁶.

Another problem commonly found in the routine identification by MALDI-TOF MS is error due to incorrect reference spectra in the database.

Difficulty in lysing cell wall structures

Some organisms possess capsules which prevent efficient lysis of cells and results in a weak extraction yield and hence poor spectral quality. This leads to problems with identification. Examples of such organisms are between *Streptococcus pneumoniae* and *Streptococcus mitis* as well as most strains of *Haemophilus influenzae* and *Klebsiella pneumoniae*⁶. The key to overcoming some of these limitations are in the extraction method used and quantity of inoculum used for extraction.

Users are encouraged to test all isolates in duplicate because invariably of the two spots, one has a better inoculum and gives a better log score (probability of correct identification). This maximises the chances of having a reportable result without further identification attempts and might be particularly valuable with mucoid colonies. If testing in duplicate is used, the user needs to have a "reconciliation strategy"^{7,8}. There must be an explicit reconciliation strategy in the local SOPs.

Commercial Platforms

Another drawback is with the currently available commercial platforms. A number of well-established commercial manufacturers uses its own algorithms, databases, software, and interpretive criteria for microbial identification, thereby making numerical data (that is, spectral scores) between these different commercial systems not directly comparable^{3,4}.

Note: Users should be warned that some MALDI-TOF MS commercial software might not be able to identify Hazard Group 3 pathogens unless the user applies with the commercial company for the full database, which will not normally be supplied due to

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bioterrorism concerns³. This could also potentially lead to additional testing of these isolates for further identification, thereby increasing the potential for exposure to laboratory staff.

Culture Media

Failure to identify some organisms may occur due to growth media used. The components of some media such as colistin-nalidixic acid agar or liquid media may result in potential interference^{4,6}.

Other examples that could lead to failure in identification include tiny or mucoid colonies, testing impure colonies, smearing between spots, failure to clean target plates and inoculating colonies in the wrong target plate locations^{3,4}.

Antimicrobial susceptibility is however not directly determined by this method as the species-specific proteins in the MALDI-TOF MS spectra are largely unaltered by antimicrobial susceptibility status³.

Direct testing of clinical specimens

This technology has been very useful for direct testing of clinical specimens - urine, cerebrospinal fluid and blood which has resulted in significant improvements to patient care and reduced turnaround time to result. Although a lot of studies have been done on this, further improvements in specimen processing of blood culture broths and urine will be required prior to implementation in clinical laboratories that will be faced with the challenge of selecting between MALDI-TOF MS methods and emerging molecular methods to identify bacteria from broth or directly from specimens^{4,9}.

Other limitations may include laboratories suffering financial loss on existing equipment due to acquiring the equipment needed for MALDI-TOF MS.

Extraction Methods

There are several extraction methods used in MALDI-TOF MS for the pre-treatment of clinical specimens/ isolates⁴.

There is no single best recommended extraction method. Users should ensure that they use an appropriate extraction method as recommended by the manufacturer so as to get accurate identification results as well as to demonstrate that protein profiles remain consistent with database fingerprints. For example, yeasts require a protein extraction procedure to be correctly identified⁶. Filamentous fungi still lack standardised extraction protocols.

Anaerobes can be identified using either chemical extraction or by using direct-smear methods. It has also been argued that in some cases, protein extraction may be detrimental to optimal spectral generation for anaerobes¹⁰.

For more information on the different recommended suggestions for MALDI-TOF MS sample preparations for use with different classes of organisms⁴, see appendix 2.

Misidentifications

Error may also occur by wrong result entry into laboratory information systems and errors in the reference spectra due to incorrect reference spectra in the database³.

Other strengths of MALDI-TOF MS

MALDI-TOF MS has other strengths. They include:

- It requires only a single colony to perform the test.
- Exposure risk is very low because samples are inactivated by extraction before use.
- Very adaptable – open system, and easily expandable by the users.
- This technique is green and has a small carbon footprint.
- Requires minimal consumables.
- Useful in identification of bacteria that are difficult to culture such as anaerobes, Mycobacteria, *Bartonella* species, *Legionella* species, etc¹¹.
- Minimal training required.

Quality controls

Users should ensure the extraction procedures are conducted properly by trained competent staff. It should also be noted that all reagents used are in date and stored away properly.

The performance of the extraction step and of the MALDI-TOF mass spectrometer may be checked by routinely testing a few selected bacterial strains, for which spectra are available in the database. If any changes are to be done to any of the steps in the MALDI-TOF MS such as change in reagents, specific changes in the extraction protocols, this should be validated by the laboratory in question before it is used routinely. However, where modified extraction methods have been used, users should ensure that this is compatible with the existing database and where it is not; a new database may be created and used with the modified protocol after validation.

Appropriate servicing and maintenance of the MALDI-TOF MS equipment is also essential in order to get accurate results. This should be done more frequently if equipment is heavily used or located in a dusty or crowded area⁶.

IT and Reports

Microbiology laboratories send important results to the medical microbiologists for validation and comments, before release to the users. With increasing centralisation, many microbiologists no longer have a microbiology laboratory on site and are entirely reliant on the information provided with the report, in order to decide whether further or different identification procedures are required. Ideally the MALDI-TOF MS would be interfaced with the laboratory information management systems (LIMS) so that the microbiologist could see how many identification attempts have been made without or with extraction and the log scores that define the probability of an accurate identification. When there is no interface, the details of the method use, the number of attempts and the log scores should be entered manually at least for the potentially "problematic" identifications. No identification system achieves 100% accuracy and the MALDI-TOF MS technique has a number of known weaknesses: the medical microbiologists must reconcile the laboratory identification with the clinical presentation and having information about the likely accuracy of the identification can help to decide when identification by alternative methods should be sought.

1 Safety Considerations¹²⁻²⁸

All work likely to generate aerosols must be performed in a microbiological safety cabinet. However, sometimes the nature of the work may dictate that full Containment Level 3 conditions should be used eg for the testing of *Brucella* species, *Bacillus anthracis*, etc in order to comply with COSHH 2004 Schedule 3 (4e).

Matrices are low molecular weight compounds, acidic and volatile in nature, with strong absorption property in UV/IR region. Different types of matrices are available in the market for use with MALDI-TOF MS, with different properties and applications. Follow manufacturer's instructions on how to use these as some are associated with significant occupational hazards such as eye, skin and respiratory toxicity.

Refer to the current guidance on the safe handling of all organisms documented in the other SMIs.

The above guidance should be supplemented with local COSHH and risk assessments.

Compliance with postal and transport regulations is essential.

2 Reagents and Equipment

Depending on the equipment that is being used, follow manufacturer's instructions.

There are two main approaches;

- Pure colonies on appropriate medium or plate
- OR
- Clinical specimens (eg direct blood culture material, urine, cerebrospinal fluid (CSF), or protein extract) can be used

3 Quality Control Organisms

Positive Control

N/A

Negative Control

N/A

4 Procedure and Results

- A bacterial or fungal colony (typically single) is picked from a culture plate to a spot on a MALDI-TOF MS target plate using a wooden or plastic stick, pipette tip, or loop

Note: Direct on-plate testing must be avoided with organisms hazardous to laboratory staff (for example, *Brucella* species and *Bacillus anthracis*). This must

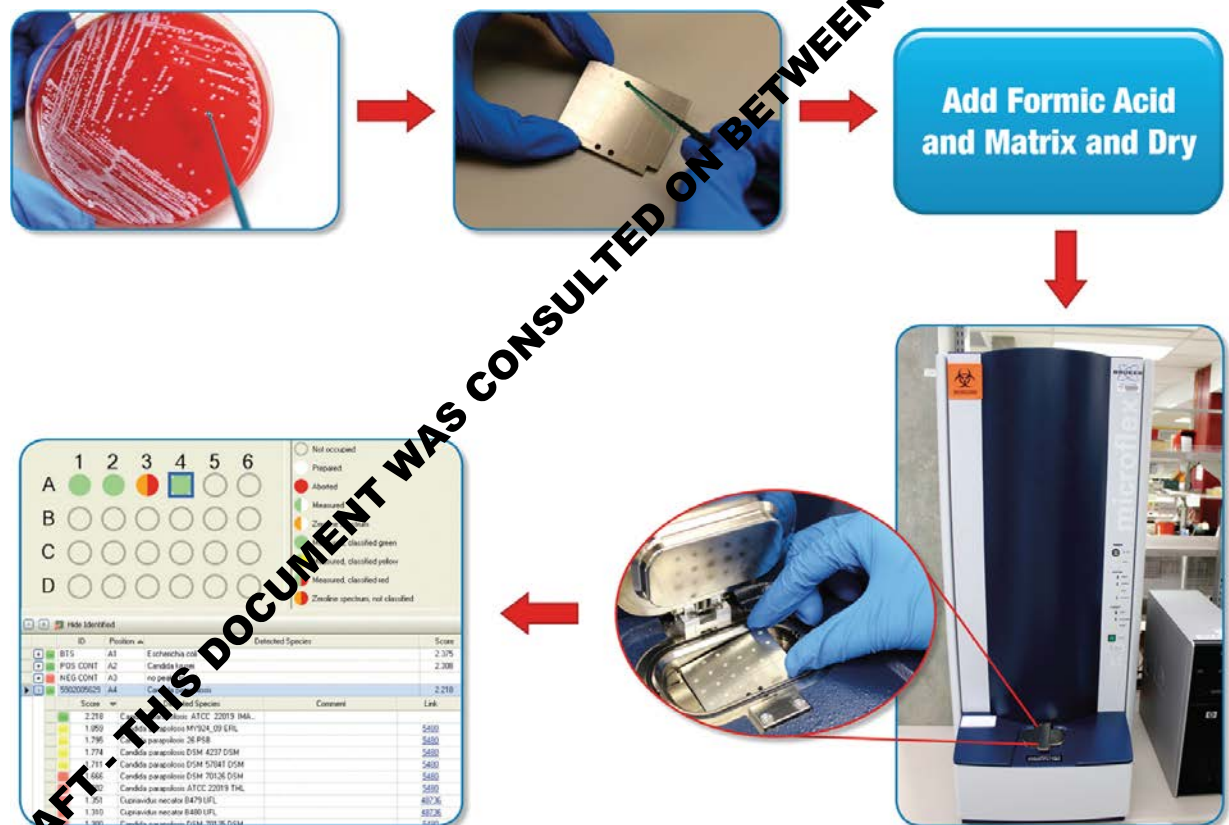
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be extracted with formic acid overlay as it kills most bacteria. This is done so as to avoid the risk of causing infection in staff handling these organisms.

- The spot on the target plate is then overlaid with 1–2 μL of matrix. Alternatively, bacterial or fungal cells could be treated with ethanol and formic acid / acetonitrile on the target plate
- Following a short drying period, the plate is placed in the ionisation chamber of the mass spectrometer for analysis
- A mass spectrum is generated and automatically compared against a database of mass spectra by the software, resulting in identification of the organism

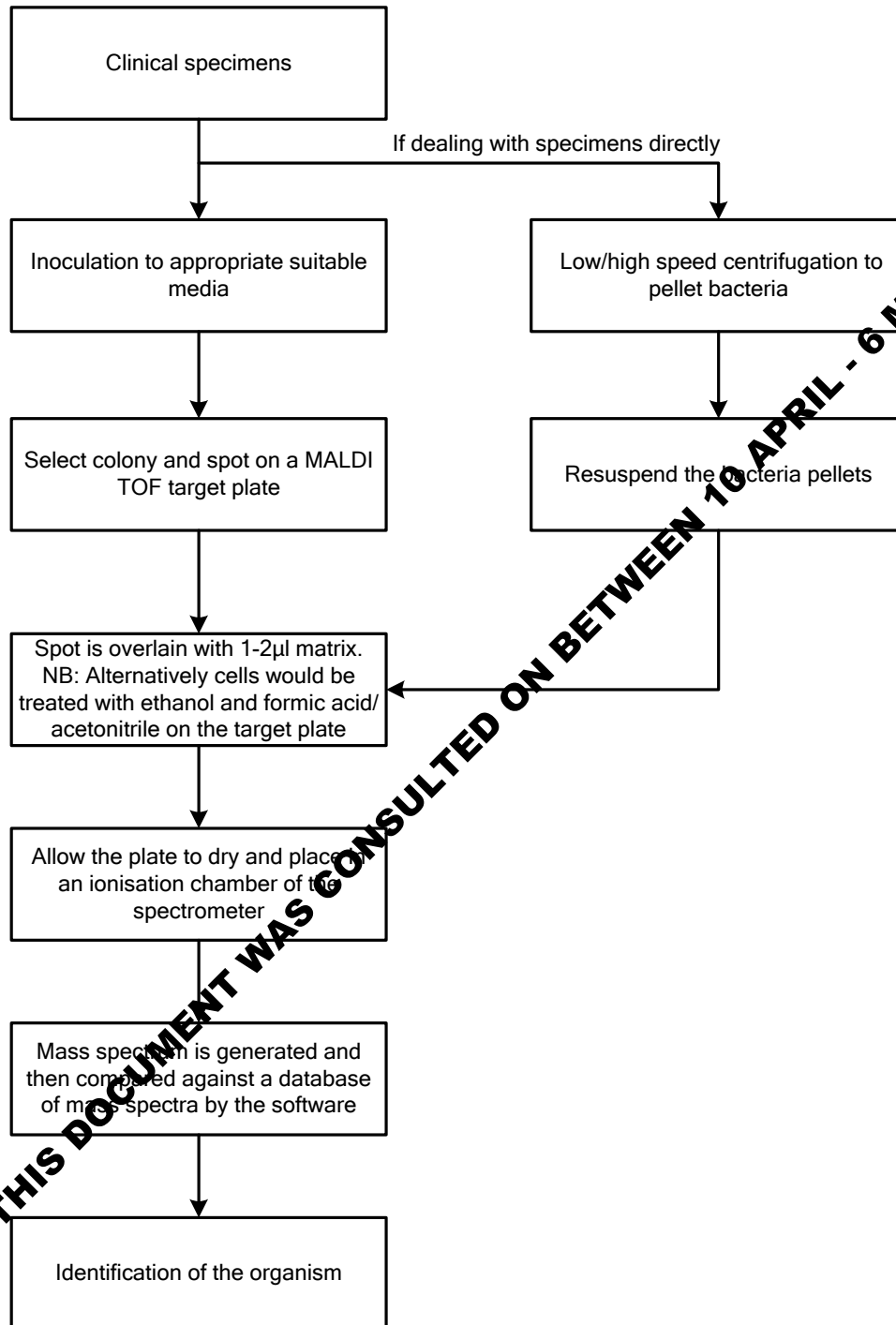
Note: Users must follow the recommendations given from the manufacturer regarding when the identification provided can be regarded as satisfactory at either species or genus level⁴.

MALDI-TOF MS illustration workflow (Courtesy of Robin Patel)³.



This MALDI-TOF MS workflow is for guidance only.

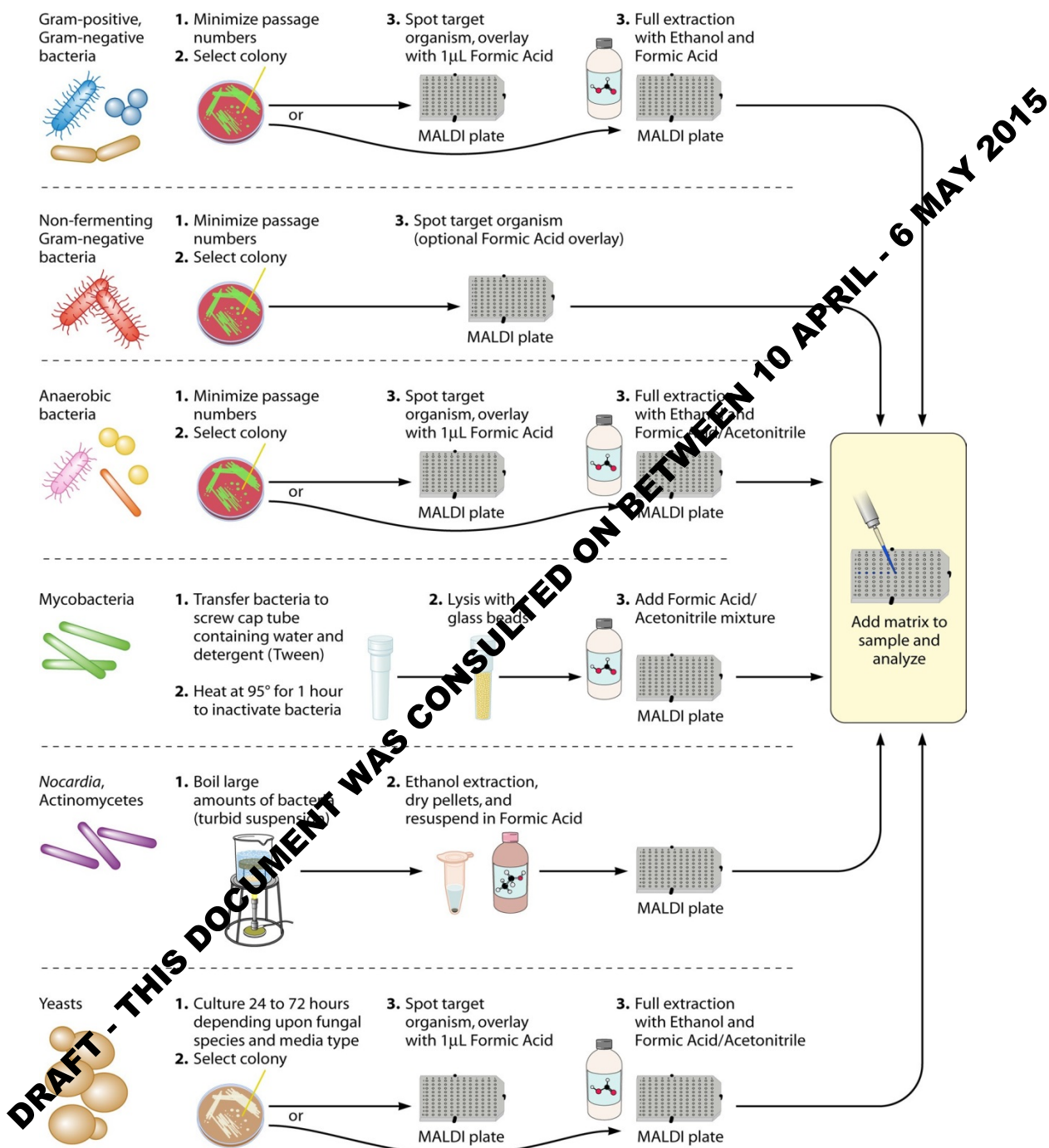
Appendix 1: MALDI-TOF MS Flowchart



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This flowchart is for guidance only.

Appendix 2: Suggestions for MALDI-TOF MS sample preparations for use with different classes of organisms



(Courtesy of Andrew E. Clark et al 2013) ⁴

Note: Proper biological safety precautions should be followed and most especially with respect to dangerous members of these groups of organisms.

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