

MicroSEQ™ ID Rapid Microbial Identification System:

the complete solution for reliable genotypic microbial identification

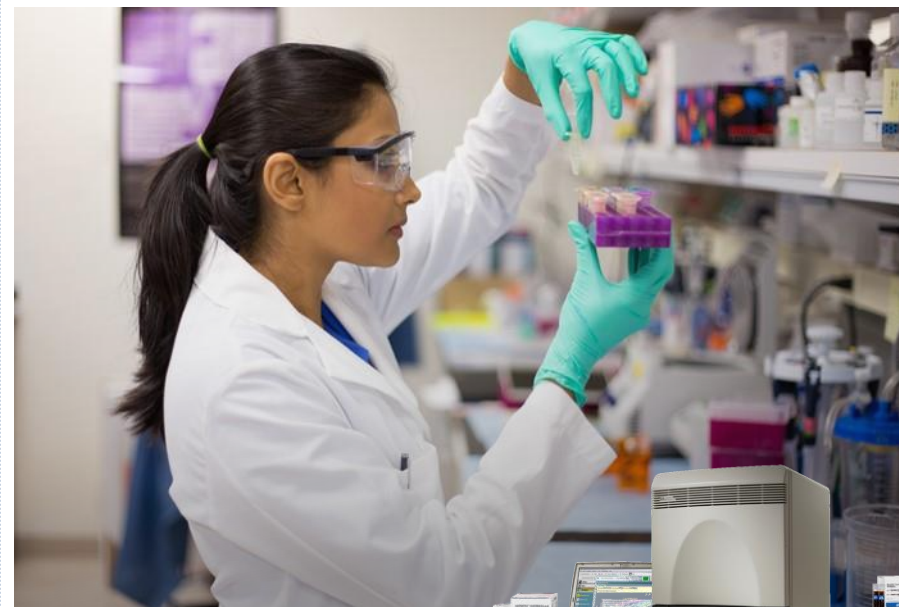


The world leader in serving science

Rapid molecular methods for pharmaceutical manufacturing

Product Safety

Microbial Identification and Detection



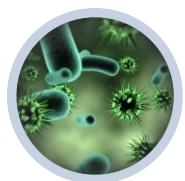
Product Quality

Impurity Analysis

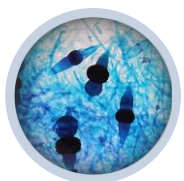


DNA Sequencing

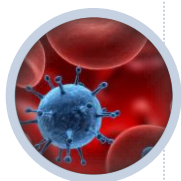
Real-Time PCR



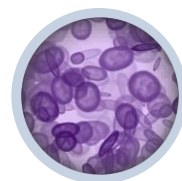
Bacterial ID



Fungal ID



Virus Detection



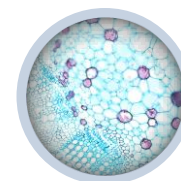
Mycoplasma



Residual DNA



Protein A



Custom HCP

Pharmaceutical Analytics

Focus on product safety and product quality



Expanding beyond research to pharmaceutical manufacturing and commercialization

MicroSEQ™ ID Microbial Identification System



Genotypic microbial identification solution based on molecular, sequence based analyses of ribosomal genes in bacteria and fungi.



Identification by phylogenetic classification based on sequence analyses of ribosomal genes in bacteria and fungi.

Top Pharma companies worldwide use Applied Biosystems™ Identification System

MicroSEQ™ Identification

- 10 of Top 10
- 24 of the Top 25
- 15 multi-site adoptions in Top 25

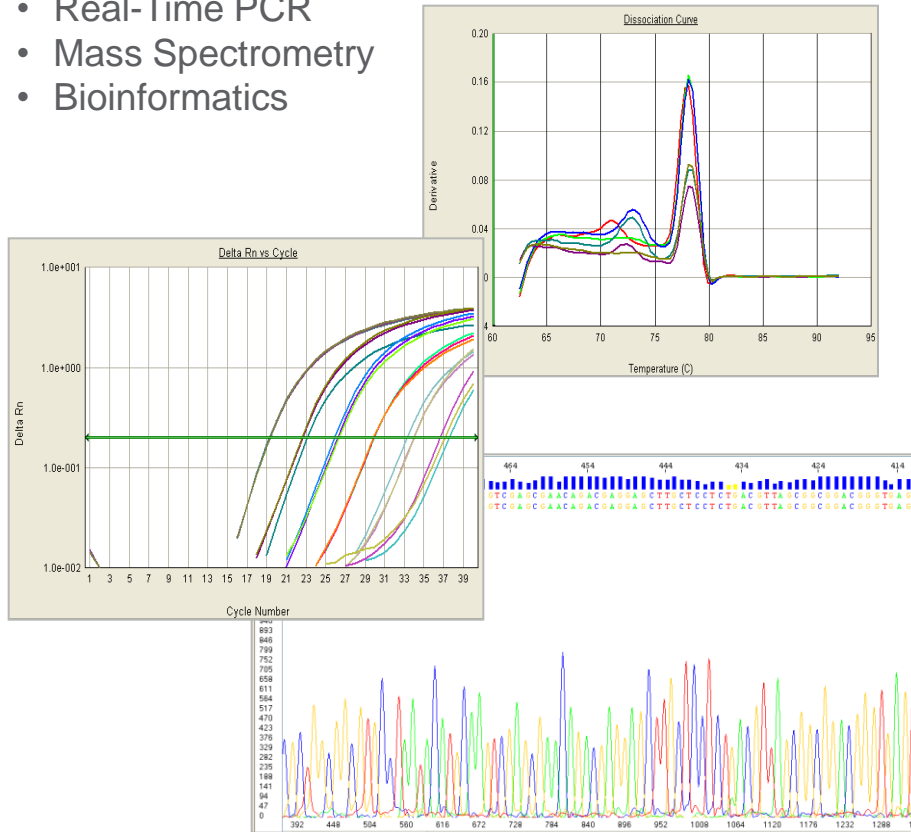
* List of Top 50 Pharma from Pharmaceutical Executive, May 2008

Designed to support the recommended qualification guidelines from

- International Conference on Harmonization (ICH)
- The US Pharmacopeia (USP)
- The European Pharmacopeia (EUP)
- The Japanese Pharmacopeia (JP)

Technologies Applied to Pharmaceutical Manufacturing

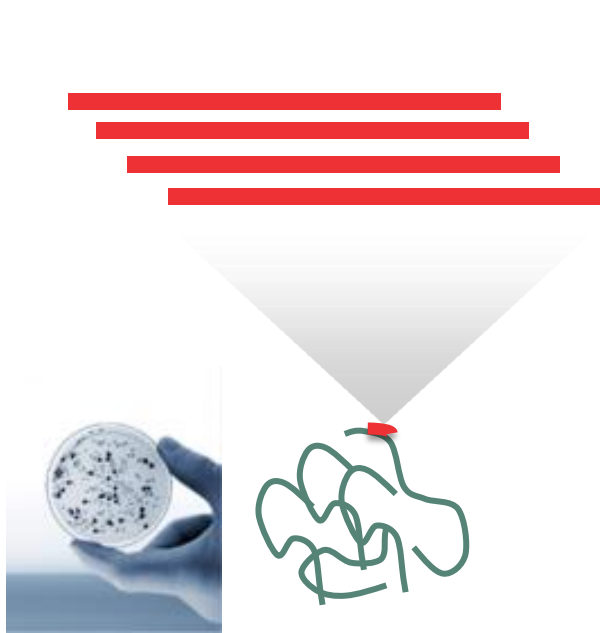
- DNA sequencing
- PCR
- Real-Time PCR
- Mass Spectrometry
- Bioinformatics



- Regulated market requires validation
- Consistent product safety and quality are critical
- Traditional techniques being replaced with rapid molecular methods where accuracy and time to results (TTR) are critical
- Complete solutions preferred
- Global presence and support

Unmet customer needs well aligned with AB technologies and capabilities

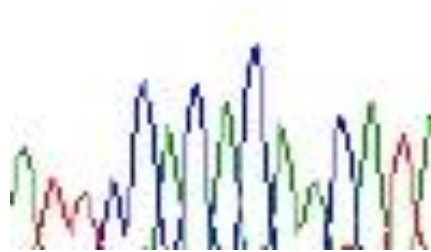
MicroSEQ™ ID Core Technology



1. Amplification by PCR

Amplification of ribosomal region from genomic DNA by PCR

ATTCACACAACATA
160 190



2. DNA Sequencing

Sequence of amplified region

The MicroSEQ ID software interface. The top section shows a microscopic image of bacteria. Below it, the text reads: "MicroSEQ® ID Microbial Identification Software Version 3.0". A disclaimer states: "For Research Use Only. Not for use in diagnostic procedures. For Windows XP, Vista, and 7. Registration Type: [unreadable]". The "life technologies" logo is in the bottom right. Below the disclaimer is a table with the following entries:

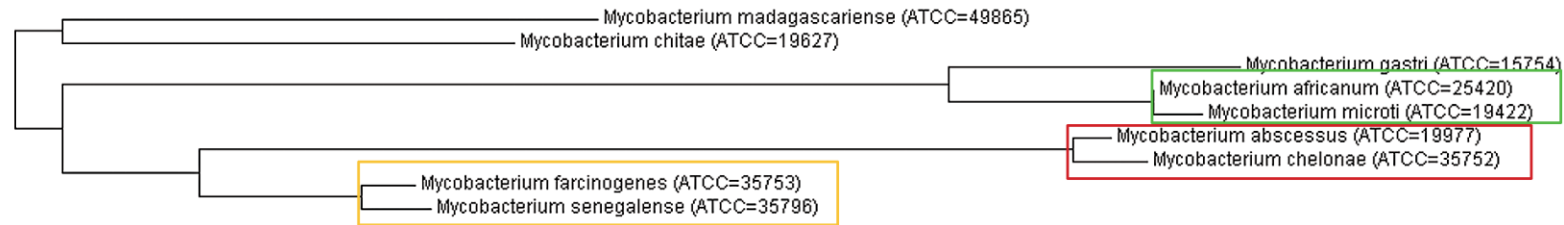
Library Entry Name
Ralstonia pickettii* (ATCC=27511)
Ralstonia insidiosa (DSM=17714)
Ralstonia mannitolilytica (ATCC=BAA-716)
Ralstonia solanacearum* (ATCC=11696)
Ralstonia syzygii* (ATCC=49543)

3. Identification

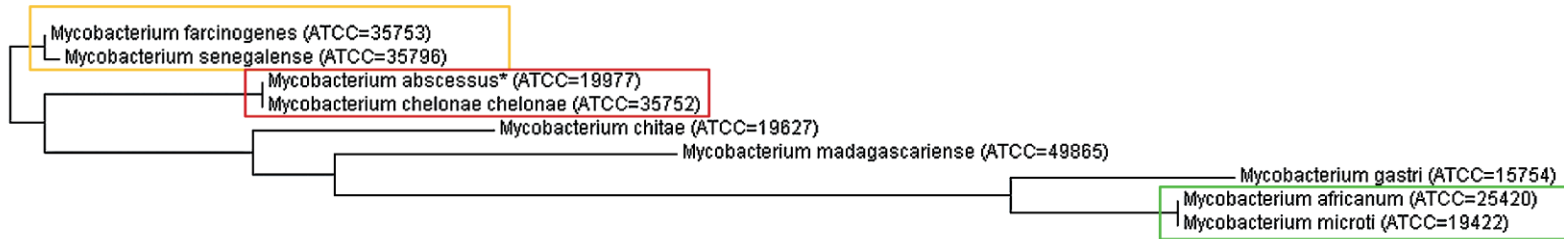
Identification based on comparison of sequence to a reference database

Phylogenetic relationships between organisms can be determined by DNA sequence-based methods

_____ = 0.2069%



_____ = 0.5892%



Confirmation of Identification

- Organism falls in the correct/ predicted group based on identification

Additional information with phylogenetic relationship

- To determine how well sequence will be able to discriminate between very closely related organisms or groups of organisms

MicroSEQ™ ID Microbial Identification System



Rapid

Typically <5h from culture to answer



Accurate & specific

ID culturable and not-easily-cultured organisms



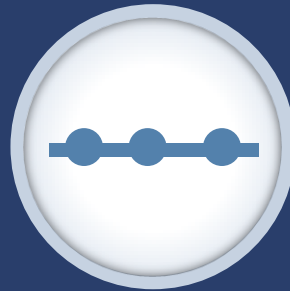
Range of organisms

Discriminate thousands of species



Universal protocol

No prior knowledge of organism properties needed



Streamlined workflow

Standardized simple workflow is easy to validate



Support network

Worldwide technical and validation support and custom capabilities

MicroSEQ™ ID Microbial Identification System

High throughput comparative DNA sequencing system for identification of bacteria and fungi

3500 and 3500XL DNA sequencing instruments

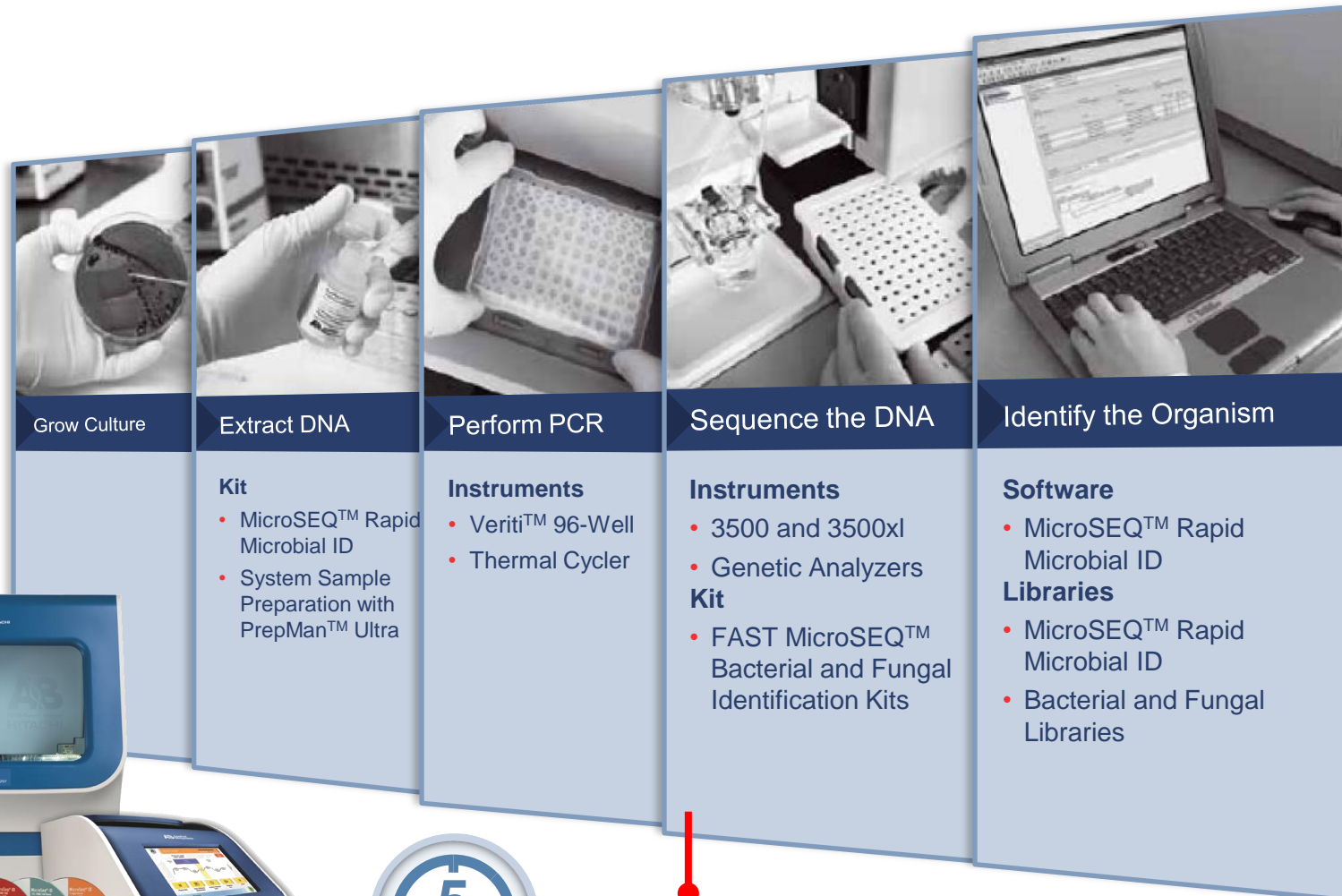
- FAST Bacterial 500 16S ID Kit
- FAST Fungal D2 ID Kit
- Full Gene 16S ID kit
- PrepMan Ultra Sample Preparation
- PCR and Sequencing clean-up kits



- MicroSEQ™ ID Software
- Validated Bacterial and Fungal libraries

*PCR Thermal
Cycler*

MicroSEQ™ Rapid Microbial ID System Workflow with 3500 genetic analyzer



~5 hours from isolated colony to ID

Quality controlled kits for bacterial and fungal identification

Bacterial Identification

Sample Preparation

- PrepMan Ultra

PCR

- Fast 500
- 500
- Full gene

Sequencing

- 500
- Full gene

Clean-up

- PCR clean-up
- Sequencing clean-up

Fungal Identification

Sample Preparation

- PrepMan Ultra

PCR

- Fast fungal
- Fungal

Sequencing

- Fungal

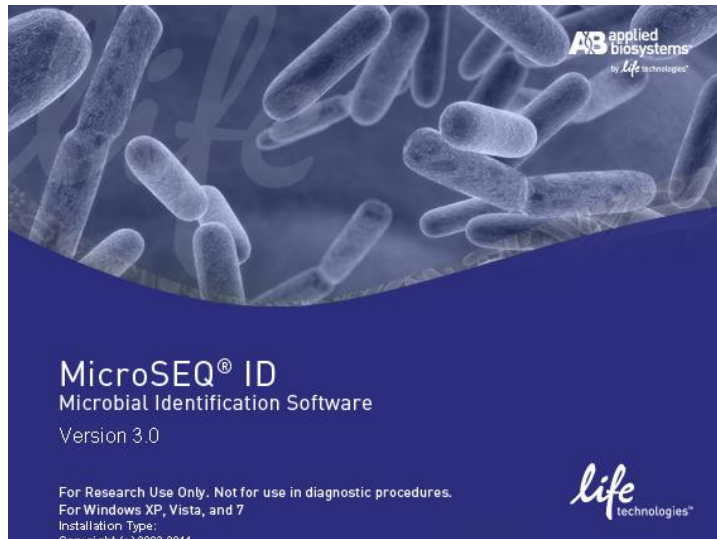
Clean-up

- PCR clean-up
- Sequencing clean-up

Universal protocol for all microorganisms

MicroSEQ™ Rapid Microbial ID Software

Enables accurate identification to the species level



Library Entry Name	% Match
Ralstonia pickettii* (ATCC=27511)	100.0
Ralstonia insidiosa (DSM=17714)	97.28
Ralstonia mannitolilytica (ATCC=BAA-716)	96.36
Ralstonia solanacearum* (ATCC=11806)	95.29
Ralstonia syzygii* (ATCC=49543)	95.06

- Compare unknown sequence to library
- Create Reports and Phylogenetic trees
- Security, Audit and esig capabilities
- Autoanalysis software transfers data from the data collection software to an MSID project
- Automatically identify unknowns using customer editable parameters
- Set up and run plates on the instrument using the MicroSEQ™ ID software (Single User Interface)

MicroSEQ™ Rapid Microbial ID Software

Enables accurate identification to the species level

The screenshot displays the MicroSEQ ID software interface. The main window shows a list of specimens and their identifications. A red circle highlights the identification of specimen 951 as *Staphylococcus epidermidis*. Below this, a detailed table shows the match results for specimen 952, with a red circle highlighting a 100.0% match to *Staphylococcus epidermidis* (ATCC=14990). A phylogenetic tree is also shown, with a red circle highlighting the genetic distance of 0.00% between specimen 951 and *Staphylococcus epidermidis* (ATCC=12228).

Specimen	Identification	Description	Comment
950	<i>Bacillus pseudomycoloides</i>	Auto-ID for Species	
951	<i>Staphylococcus epidermidis</i>	Auto-ID for Species	
952	<i>Staphylococcus epidermidis</i>	Auto-ID for Species	
954	<i>Staphylococcus hominis</i>	Auto-ID for Species	
955	<i>Staphylococcus epidermidis</i>	Auto-ID for Species	

Specimen	Library	Library Entry Name	% Match	Consensus...	Library Entry L...	% of Consensus ...	Total Mismatches
952	AB_Bacterial500Lib_2.2	<i>Staphylococcus epidermidis</i> (ATCC=12228)	100.0	497	496	100.20	0
952	AB_Bacterial500Lib_2.2	<i>Staphylococcus epidermidis</i> (ATCC=14990)	100.0	497	496	100.20	0
952	AB_Bacterial500Lib_2.2	<i>Staphylococcus caprae</i> (ATCC=35538)	99.18	497	496	100.20	4
952	AB_Bacterial500Lib_2.2	<i>Staphylococcus capitis capitis</i> (ATCC=27840)	99.97	497	496	100.20	5
952	AB_Bacterial500Lib_2.2	<i>Staphylococcus capitis ureolyticus</i> (ATCC=49326)	99.97	497	496	100.20	5

Specimen : 951
 = 0.1413%
 951 and *Staphylococcus epidermidis* (ATCC=12228)
 Genetic Distance 0.00%

Phylogenetic Tree:

- Staphylococcus epidermidis* (ATCC=12228)
- Staphylococcus epidermidis* (ATCC=14990)
- Staphylococcus caprae* (ATCC=35538)
- Staphylococcus capitis capitis* (ATCC=27840)
- Staphylococcus capitis ureolyticus* (ATCC=49326)

MicroSEQ™ Rapid Microbial ID Software

Validated Libraries

The image displays three overlapping screenshots of the MicroSEQ software interface, each showing a table of validated microbial entries. The tables are organized into columns for Genus, Species, and Subspecies. The top screenshot is titled 'MICROSEQ ID 16S rDNA LIBRARY', the middle one 'MICROSEQ ID 16S FUNGAL DNA LIBRARY', and the bottom one 'MICROSEQ ID 16S FULL GENE DATABASE LIBRARY'. Each table lists various bacterial and fungal species, such as *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*.

Bench Validated

- 16S 500: 2020 entries
- 16S Full Gene: 1262 entries
- D2 (Fungal): 1114 entries

Updates Include:

- New entries
- Updated nomenclature

- Entries represent the most common organisms seen in environmental monitoring

Largest, most comprehensive validated libraries for bacteria and fungi

MicroSEQ™ IQ/OQ Program

Helps

laboratories overcome critical system qualification through a collaborative partnership with Thermo Fisher Scientific

Enables

Improved productivity

Flexibility

to adapt to the qualification requirements of each participating laboratory

IQ/OQ Service typically include:

- Consultation with client to determine needs
- Statement of work to define project
- Detailed verification test plan and documentation
- System installation verification
- Sequence of system operations qualification
- Microbial identification verification
- Accuracy report
- Reproducibility report
- System software installation and security verification
- Software exporting, importing, archiving, and printing verification
- Phylogenetic tree and custom library verifications
- Detailed data analysis and review
- Consultation on experimental process and results
- Recommended guidelines for Performance Qualification (PQ)

MicroSEQ™ Implementation Program

The program covers assistance on laboratory design and workflow as well as additional training based on specific laboratory needs

Program typically includes:

- Assistance in setting up a laboratory according to good molecular laboratory practices
- Checklist of installation material requirements and installation procedures
- Introduction to the basics of DNA-based vs. traditional culture methods
- Introduction to the basics of genotypic methods
- Organization of throughput from a few to hundreds of samples per day
- Practical sessions on the MicroSEQ™ System workflow
- Software training
- Analysis flow from data collection to identification
- Acceptance criteria for quality analysis
- Interpretation of sequencing/ID results
- Routine system maintenance
- Data archiving
- Recommendations for Performance Qualification protocols



MicroSEQ™ Implementation Program



To complete the program, a final training session is also provided to assist in the Performance Qualification (PQ) process.



The aim of the program is to help users complete Performance Qualification (PQ) as quickly as possible, usually within the six-month time frame of the program.

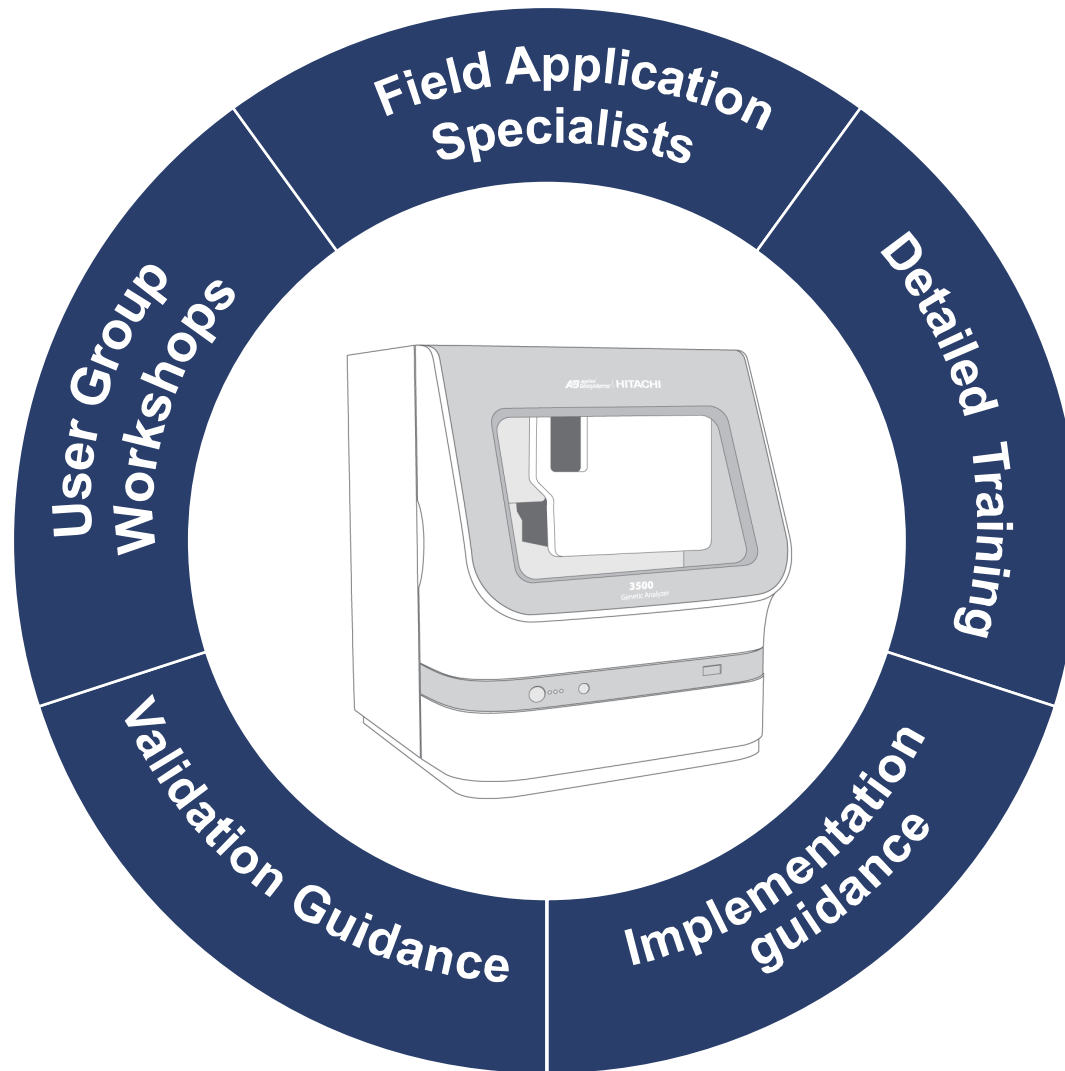
MicroSEQ™ ID PQ Consultation Program



Customizable service that typically includes:

- 1** Expert consultation with Thermo Fisher Scientific product specialist
- 2** Customizable PQ protocol provided as a word processing document and developed with input from product specialist
- 3** Spreadsheet to easily determine consumables package required for the study
- 4** On-site support from Thermo Fisher Scientific product specialist during the execution of the PQ

Worldwide support network



MicroSEQ™ Rapid Microbial Identification System



Rapid Results

Subculturing typically requires days to results
Typically <5 hrs from pure culture/plate



Accurate and Specific

Discriminate thousands of species
No subjective interpretation



Suitable for All Types of Microorganisms

Culturable and not-easily-cultured types



No Prior Knowledge of Organism Required

Challenge for classic methods, e.g. gram staining



Standardized

Universal protocol for fungal and bacterial microorganisms



Support Network

Worldwide technical and validation support and custom capabilities



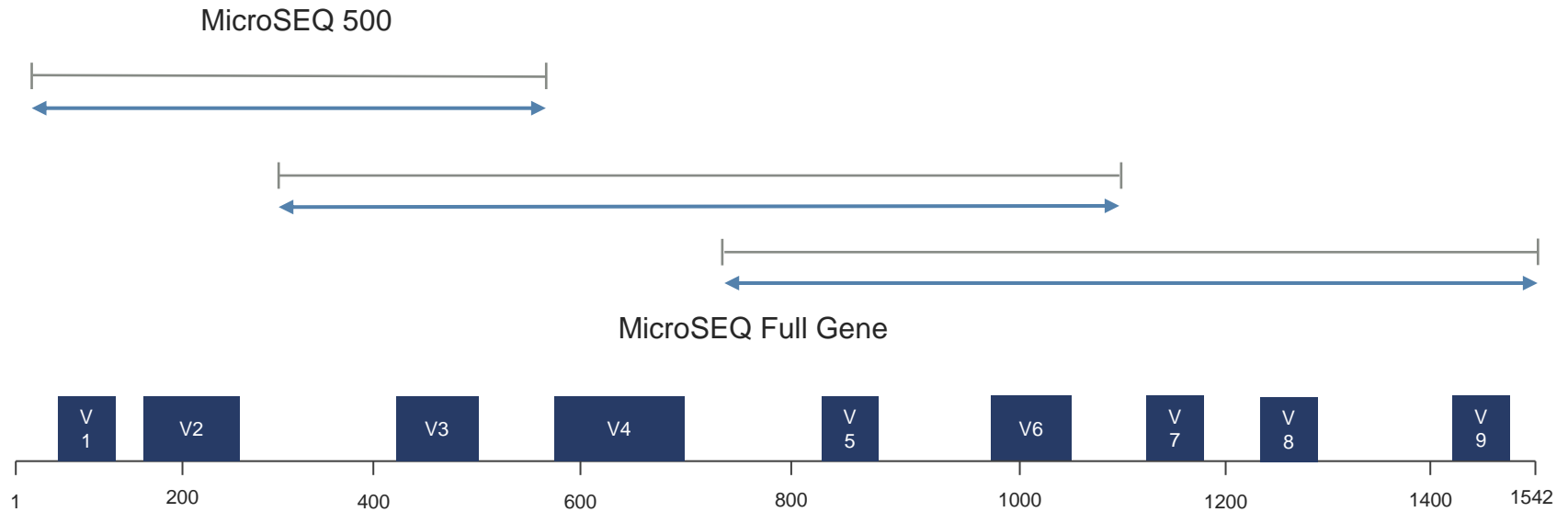
Legal Disclaimer

For Research Use Only. Not for use in diagnostic procedures.

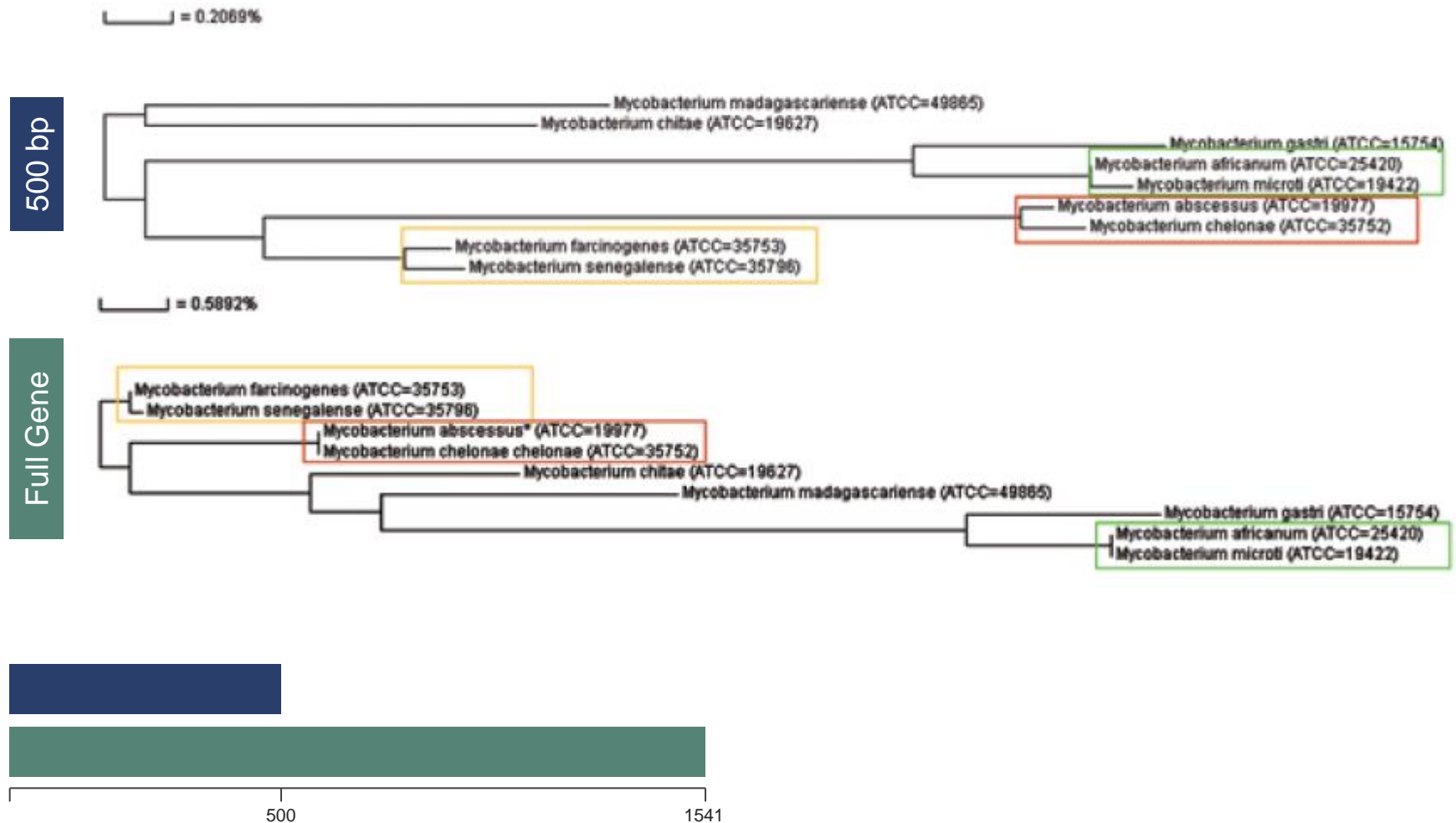
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Appendix

Microbial identification can be obtained by sequencing the 16S ribosomal gene



Sequence of the full 16S gene helps resolve closely related groups



MicroSEQ™ Rapid Microbial ID System

3500 Genetic Analyzer throughput increase

Higher number of capillaries lead to higher throughput



8 Capillary set

	3130	3500	3130 XL	3500 XL
Capillaries	4	8	16	24
IDs per 8hrs	10	16	25	52
IDS per 24 hrs	20	52	80	156

MicroSEQ™ Rapid Microbial ID System



Highly accurate

- Genotypic method based on 16s rRNA (bacteria) and D2 region (fungi) sequencing
- Extensive validated libraries

Actionable results in less than 5 hours

- Easy five-step workflow
- Intuitive software with Autoanalysis

Re-qualification in as little as 5 working days

- Fast IQ/OQ implementation
- Features to assist with 21 CFR Part 11 compliance

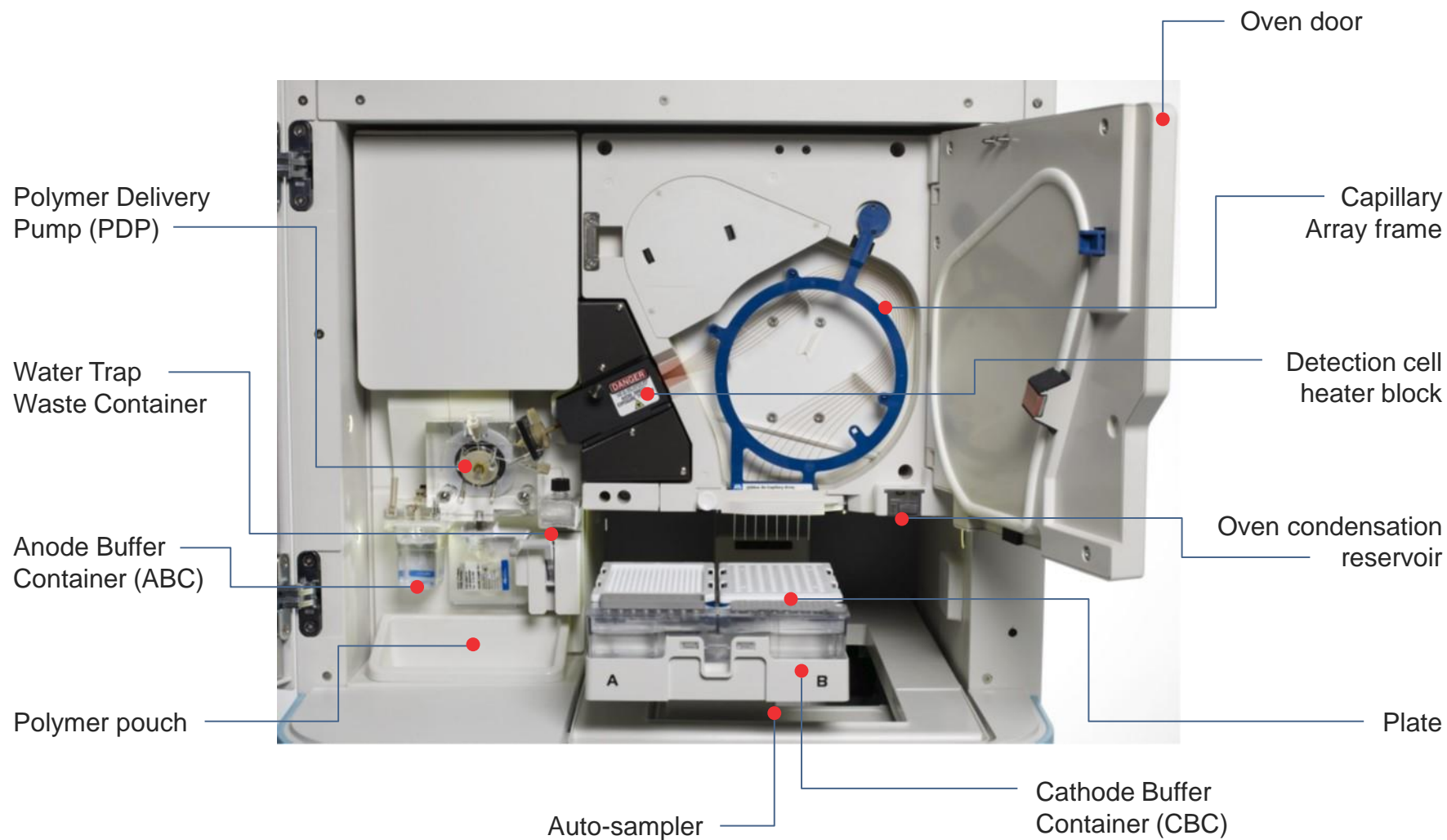
Financial impact

- Helps reduce re-testing
- Helps reduce contract lab cost

Powered by state-of-the art genetic analyzer

- High throughput
- Plug and play consumables
- Maintenance scheduling and tracking

3500 Series: System Hardware Features



MicroSEQ® ID v3.0 software

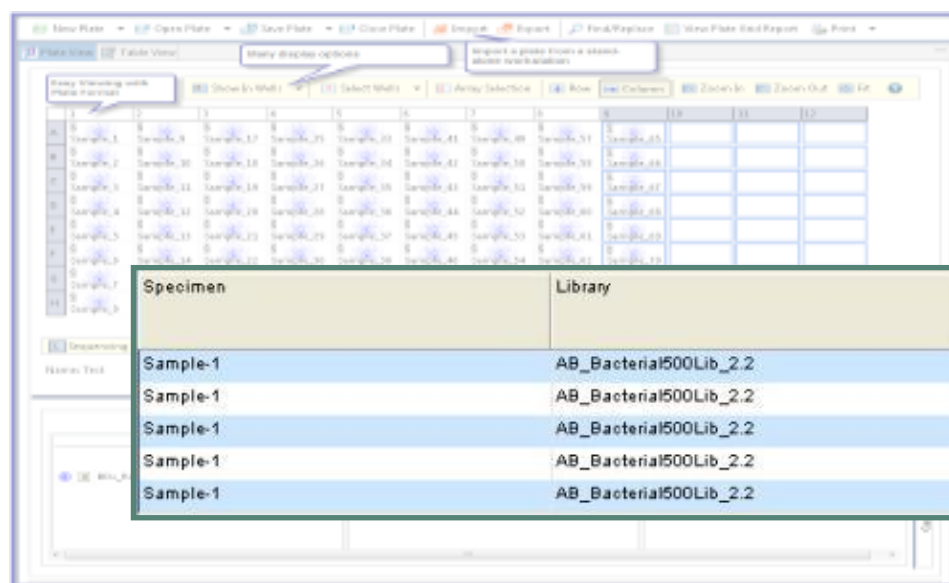
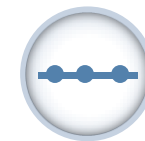


Library Entry Name	% Match
Ralstonia pickettii* (ATCC=27511)	100.0
Ralstonia insidiosa (DSM=17714)	97.28
Ralstonia mannitolilytica (ATCC=BAA-716)	96.36
Ralstonia solanacearum* (ATCC=11696)	95.29
Ralstonia syzygii* (ATCC=49543)	95.06

MicroSEQ ID Software version

Feature	1.0	2.x	3.0
Compare unknown sequence to library	✗	✗	✗
Create Reports and Phylogenetic trees	✗	✗	✗
Security, Audit and esig capabilities	Audit only	✗	✗
Autoanalysis software transfers data from the data collection software to MicroSEQ™ ID projects		✗	✗
Automatically identify unknowns using customer editable parameters			✗
Set up and run plates on the instrument using the MicroSEQ™ ID software (Single User Interface)			✗ (3500 only)

Easy and accurate data collection through autoanalyses



Specimen	Library	Library Entry Name	% Match	Consensus Length	Library Entry Length	Total Mismatches
Sample-1	AB_Bacterial500Lib_2.2	Ralstonia pickettii* (ATCC=27511)	100.0	494	489	0
Sample-1	AB_Bacterial500Lib_2.2	Ralstonia insidiosa (DSM=17714)	97.28	494	489	13
Sample-1	AB_Bacterial500Lib_2.2	Ralstonia mannitolilytica (ATCC=BAA-716)	96.36	494	489	18
Sample-1	AB_Bacterial500Lib_2.2	Ralstonia solanacearum* (ATCC=11696)	95.29	494	487	23
Sample-1	AB_Bacterial500Lib_2.2	Ralstonia syzygii* (ATCC=49543)	95.06	494	486	24

- Automated reagent check
- Easy manageable maintenance schedule
- Autoanalysis manager
- Improved features to assist compliance with 21CFR part 11



- Reduced set-up time
- Reduced maintenance down-time
- Ease of data retrieval and analysis
- Efficient approval process
- Better information control

Rigorous Library Validation Process

Validation Certificates

APPLIED BIOSYSTEMS
MICROSEQ ID SOFTWARE V3.0
END USER SOFTWARE LICENSE AGREEMENT
and
LIMITED PRODUCT WARRANTY

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Software Release Certificate

Product: MicroSEQ® ID Software Version: 3.0

The subject software, 4464194 Rev A - KIT, MICROSEQ ID SW V3.0 and 4464195 Rev A - KIT, LICENSE MicroSEQ ID V3.0 LITE 1 LIC, has been tested and is validated to perform successfully in accordance with requirements of the specifications and requirements for use.

Applied Biosystems' products are developed in conformance with the design control and general quality system requirements of ISO 9001. Product documentation includes, but is not limited to, user and service manuals, product specifications and service bulletins. Design documentation is retained in a Design History File.

A top-level product development procedure is supported by detailed procedures specifying requirements (including documentation and record keeping) for design input and output, planning, design review, validation, verification and design change.

For software, specific deliverables of this process include (but are not limited to):

Product Requirements Document

The software requirements have been formally defined and approved
Requirements are written to show traceability to design qualification
The definition and approval is done for every release

Functional Specification

Product requirements are translated into detailed specifications
Design reviews are held and documents updated and approved

Product Configuration Control

Source code is controlled
All source files are versioned on a secure server

Test Plan

Acceptance testing is performed when a build is released by development to the Verification and Validation group. This is followed by regression testing of the specific fixes made in the released build. Finally, functional testing based on formal

test cases is performed. At least one build has a full round of all testing performed before a milestone release.

Test Procedures and Test Data

Test procedures are written based on the functional specification
A traceability matrix is maintained to align product requirements to functional specification and finally to test procedures and test cases.

Software Release Notice

Release Notes
Marketing and Service Bulletins
Full versions: Full versions are released to incorporate new functionality
Bug fixes/ patches are created and released on an as-needed basis. All patches are included in subsequent product releases.
Other: Maintenance versions can incorporate both new functionality and bug fixes
These versions are made available to the entire customer base

The existence of these documents and the standard operating procedures used in their production are formal requirements of the Applied Biosystems Quality Management System (QMS). The integrity of the Applied Biosystems QMS is routinely audited as meeting the requirements of ISO 9001, the internationally recognized standard for quality assurance.

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Certified by the following this 27th day of September, 2011.

Lola Oyebola
Manager, NPI Quality

P/N: 4364615 Rev D

MicroSEQ™ Rapid Microbial ID System

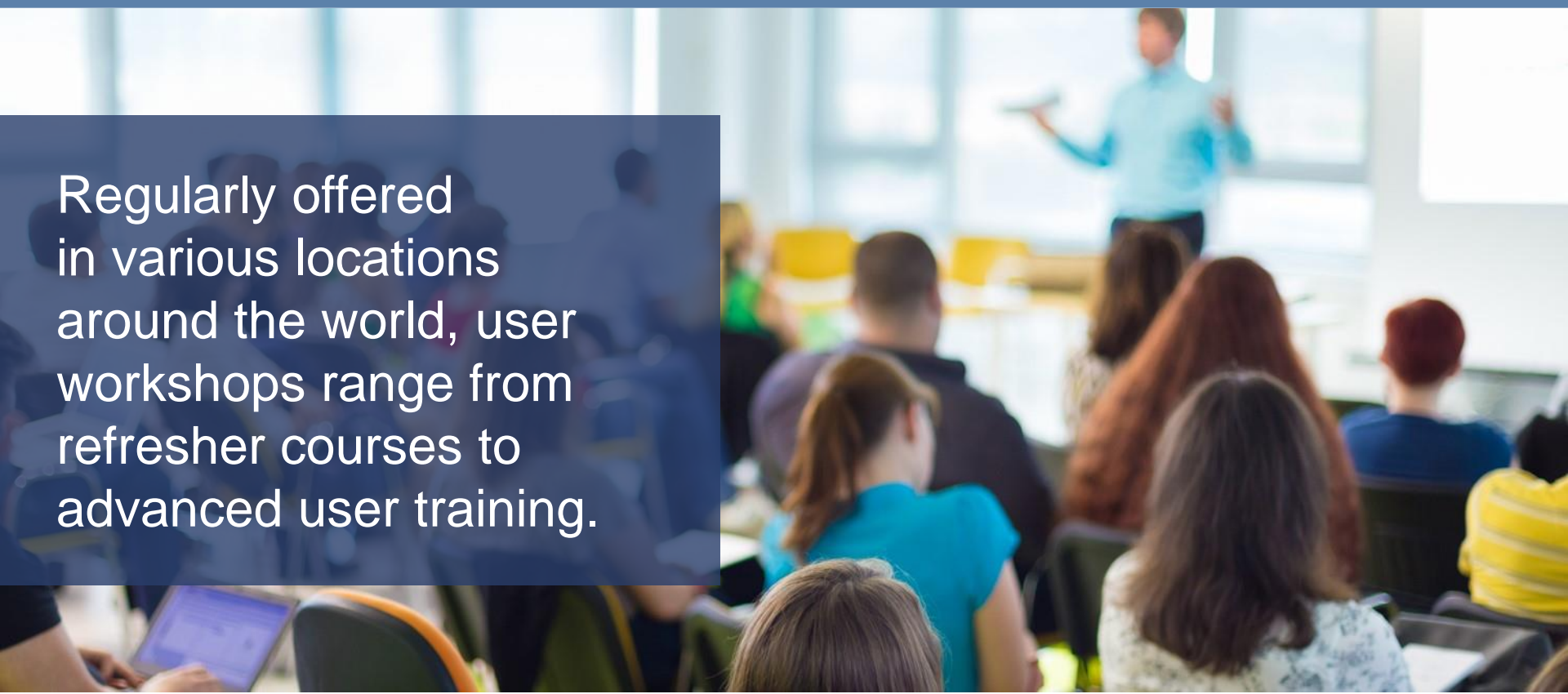
Cost per test

	MicroSEQ® IDs/week	8	16	24	48	96	144	192	240	480
MSID cost per ID (Edge clean-up cartridge)	3500	\$46.98	\$42.94	\$41.59	\$40.34	\$39.71	NCE*	NCE*	NCE*	NCE*
	3500xl	\$46.82	\$42.15	\$40.96	\$39.71	\$38.73	NCE*	NCE*	NCE*	NCE*
	3130	\$40.03	\$39.73	\$39.64	\$39.64	\$39.64	NCE*	NCE*	NCE*	NCE*
	3130xl	\$38.56	\$38.19	\$38.07	\$37.95	\$37.51	NCE*	NCE*	NCE*	NCE*
MSID cost per ID (Edge clean-up plate)	3500	\$38.56	\$38.56	\$33.17	\$33.17	\$31.29	\$31.08	\$30.98	\$30.92	\$30.79
	3500xl	\$38.40	\$33.73	\$32.54	\$31.29	\$30.31	\$30.12	\$29.95	\$29.86	\$29.74
	3130	\$31.61	\$31.31	\$31.22	\$31.22	\$31.22	\$31.22	\$31.08	\$31.05	\$31.05
	3130xl	\$30.14	\$29.77	\$29.65	\$29.53	\$29.09	\$29.24	\$29.09	\$29.18	\$29.18

NCE*=Not Cost
Effective

The new 3500 system delivers near equal cost for all but infrequent users

User Workshops



Regularly offered in various locations around the world, user workshops range from refresher courses to advanced user training.

Delivered by Thermo Fisher Scientific experts, these programs help enhance productivity through rapid implementation of and continuous training on our fastest and most accurate microbial identification systems.

User Workshops

User workshops, designed to optimize use of the MicroSEQ™ Microbial Identification System, are regularly offered in various locations around the world.



Refresher workshops cover elements of the MicroSEQ™ Microbial Identification System, lab setup and workflow, and basic data analysis.



Advanced workshops cover in-depth topics on the use of the powerful MicroSEQ™ Identification software, such as interpretation of the MicroSEQ™ % match score, how to use the phylogenetic tree tools, creating custom libraries, and using the BLAST™ search function. Optional consultations with Applications Scientists are also offered.

