Mabtech IRIS™/ASTOR™ system specifications

Introduction

Mabtech IRIS™ and Mabtech ASTOR™ are FluoroSpot/ELISpot and ELISpot only readers, respectively, that both use the software Mabtech Apex™ enabling exact spot centre determination using the RAWspot™ technology. The FluoroSpot technique allows the detection of cells secreting multiple analytes such as cytokines or immunoglobulins by separate LED excited fluorescent signals. The ELISpot technique similarly allows the detection of cytokine or immunoglobulin secreting cells but uses detection based on enzymatic color-change of a precipitating substrate. The resulting spots in ELISpot or FluoroSpot are analysed on the plate membrane by the readers.

Both readers have been developed by Mabtech AB in Nacka Strand, Sweden, whose quality management system complies with ISO 9001:2015 and ISO 13485:2016. They are CE-marked for the EU directives for Electromagnetic compatibility, Low voltage, Machinery and Restriction of Hazardous substances directives. and safety approved according to RoHS, REACH, WEEE, FCC and ICES. The readers themselves are intended for research use only and not for diagnostic procedures. However, the qualities of Mabtech IRIS and Mabtech ASTOR enable use in regulated laboratories after user qualification.

Mabtech IRIS™ and Mabtech ASTOR™ validation

Each reader is built, validated and calibrated at Mabtech's headquarters at Nacka Strand, Sweden, and from there shipped to the end users world-wide. Every released Mabtech IRIS and Mabtech ASTOR is calibrated to match the light intensity of the established readers and is given a unique machine default exposure for each LED. These individually set machine default exposure values are then used by Mabtech Apex software when scanning ELISpot and FluoroSpot plates. Each reader is supplied with validation documentation that describes the validation results.

Installation and operation qualification at customer's site

A new installation of a Mabtech reader is made by a qualified person from Mabtech. We install the reader and validate that the self-calibrating XY table is correct, optics are fully functional and that the LEDs are calibrated. The validation is made using a calibration plate generated at Mabtech containing spots with all fluorochromes used in our kits, one for each filter in Mabtech IRIS: LED380, LED490, LED550 and LED640. In addition, standard ELISpot plates are utilized for validation of the ELISpot analysis in Mabtech IRIS as well as Mabtech ASTOR.

Upon installation, the Mabtech technician makes sure that the calibration plate generates the same spots counts for LED380-, LED490-, LED550- and LED640-excited spots as it did when the machine was assembled and approved at Mabtech headquarters. This assures that the reader has not suffered from any damage during transport and that the instrument matches reference readers at Mabtech.

All procedures are documented in an installation, qualification and operation qualification document. In addition to installation and operation qualification, Mabtech offers a general introduction to the reader and a hands-on training with staff, set up according to the customer's requirements.

Reader self-calibration

Every time the reader is started, a self-calibration procedure will commence. No maintenance except normal cleaning of the external parts, i.e., wiping off the machine with a damp cloth, is necessary.

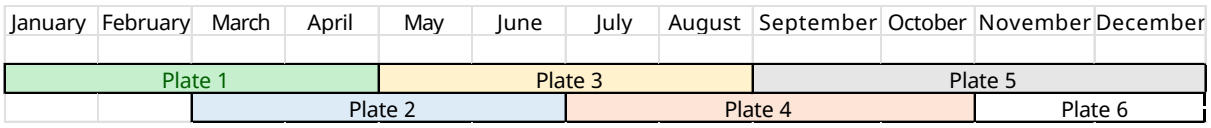
Equipment performance control

Mabtech IRIS has been tested in an endless loop running 1 815 four-color plates, that equals 10 plates a week, every week of the year for 3.5 years, to assess long-time usage of the reader. No changes were seen on the cables nor the reader's capacity to quantify spots in ELISpot or FluoroSpot.

Any potential deviation of a reader's performance will be seen as altered spot counts. There can be several reasons for this:

1. The reader is out of focus.
2. The Area of Interest (AOI) cannot automatically identify the well.
3. The light sources are malfunctioning.
4. The software algorithm cannot perform the calculations.

We suggest that the user reads the same plate as a reference plate every month and calculates the coefficient of variation (CV) between the readouts. The plates should display between 400-800 Alkaline Phosphatase-BCIP/NBT-developed spots, preferably human IFN-γ spots from PHA stimulated PBMC. The CV should be below 5% between the initial and last reading. Please note that spots are slowly weakening with time and a minor decrease in spot number can be anticipated. We recommend that the reference plate is replaced every four months with overlapping readouts of the plates in accordance with the recommended scheme below:



In addition, a fluorescent validation plate provided by Mabtech can be read on a quarterly basis to collect sensor measurements from the LED lights used in the FluoroSpot mode of Mabtech IRIS. These sensor values can be compared to the data from the previous readout. The sensor CV between the readouts should be below 15 %.

Annual service

Mabtech offers a service package including an annual check-up of the reader. The performance will be evaluated, and the hardware adjusted if necessary with the consent of the user.

Mabtech IRIS™, Mabtech ASTOR™, and CFR21 part 11

CFR21 part 11 is a set of guidelines issued by the US Food and Drug Administration (FDA) regarding the use of computerized systems in clinical investigations and how acquired source data must meet the same elements of data quality as that of signed paper records. Mabtech IRIS and Mabtech ASTOR are controlled by the software Mabtech Apex that have been constructed to meet the applicable requirements of CFR21 part 11.

The requirements stated by the FDA applicable to Mabtech Apex are i) the access to the software must be limited to authorized personnel; ii) the information history must be possible to track by an audit trail. In Mabtech Apex each ELISpot and FluoroSpot reading specifies all changes that have been made to the data, so that auditors can reconstruct study conduct in relation to data collection and verify the quality and integrity of the data; iii) the ability to change date or time must be limited to authorized personnel. In Mabtech Apex, timestamps and dates are part of the data files and the software do not allow changes to the time settings.

In Mabtech Apex, the above listed requirements are fulfilled as described. Limited access is handled from start when users must select a username and provide a unique password. After repeated failed attempts, the user is locked out. Creation of new user accounts is limited to the administrator. The administrator controls user access to create new templates and the time period of user access. Furthermore, the administrator defines whether to use Machine Default exposure values for LEDs or manually set values. Date, time, user and machineID are always generated and stored for each saved plate. History files are automatically created and specify the chronological order of all events from plate creation to last saving. This includes all elements that control source data: users, algorithm settings, spot counts, RSV-values, time stamps, machineID, etc.

In addition to the basic criteria of CFR21 part 11, extra layers of control have been added to preserve the integrity of the true RAW data from every ELISpot and FluoroSpot plate analyzed by the system. This is achieved through the following technical innovations:

All ELISpot and FluoroSpot wells captured in Mabtech IRIS and Mabtech ASTOR are saved and processed as image RAW files. These contain the untouched signal input straight from the image sensor and are free of the user bias that would be introduced by settings such as sharpness, digital gain, color, hue and saturation. From the moment of capture, the image RAW files are never changed or altered by the software. As a result, the true RAW data are always maintained and cannot be concealed by any user, including the administrator.

Captured RAW images, count-files generated by the RAWspot algorithm and the audit trail of each plate are individually validated by a checksum system in the software. Upon reading, each file is automatically passed through a checksum function and a unique block of data is generated for each file type. Upon saving, the history audit file is given a unique checksum block of data. Every time a plate is opened, the checksum validation is re-run and controlled against the stored copy, making sure that it matches the original checksum value. If any of these image RAW files, count files or history files are removed, altered or manipulated, the checksum validation will ultimately fail when opening the plate and will provide an integrity warning. If no warnings are provided, data integrity is assured.

A start-up test report is automatically generated every time the user starts Mabtech IRIS and Mabtech ASTOR, and the reader goes through the start-up steps (OFF=>BOOTING=>READY). The user can access the report by clicking on a hyperlink in the software. The reports are also automatically saved locally at C:\ProgramData. This feature enhances the audit trail and makes it possible for users to sign off on reports where the status of the reader has been validated prior to readout of plates.

False-positive spots caused by artefacts such as fibers and dust can be excluded by the user with the masking system in Mabtech Apex. The false spots are removed from display by adding a mask, without deletion of any data. The retention of data is important, since it enables an auditor to remove the mask applied and review the original RAW data.

Good clinical laboratory practice compatibility

Good Clinical Laboratory Practice (GCLP) is a set of standards that provides guidance on implementing Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) principles to the analysis of samples from a clinical trial. GLP is a quality system that covers the organisational process and the conditions under which non-clinical laboratory studies are planned, performed, monitored, recorded, archived and reported. It aims to promote the generation of valid, high quality test data. The GCP principles are international, ethical, and scientific quality standards for designing, conducting, performing, monitoring, auditing, recording, analysing, and reporting clinical trials that involve the participation of human subjects. Compliance with the practices assures that data and reported results are credible and accurate, and that the rights, safety, and confidentiality of trial subjects are protected. If a customer would like to apply Mabtech IRIS or Mabtech ASTOR in their GCLP regulated environment the following need to be taken into consideration:

1. Equipment: Validation of the reader as well as installation, training and maintenance should be completed in the specific environment for use.
2. Standard Operating Procedures (SOPs) for handling, maintenance, etc. should be established by the user.
3. Computer systems: Procedures for the software such as audit trail, controlled user restrictions and time stamps should be established.

CE mark

The readers have been tested and approved according to the EU directives for Electromagnetic compatibility, Low voltage, Machinery and Restriction of Hazardous substances directives. International standards (e.g. IEC 61010-2-101) that regulate the safety requirements for electrical equipment for measurement, control and laboratory use for in vitro diagnostic medical device have been applied to ensure compliance.

ISO 9001 and ISO 13485

The Quality Management System at Mabtech AB complies with the quality management standards ISO 9001:2015 and ISO 13485:2016. The compliance is audited annually by external audits and the certificates have been maintained without interruption since 2006 when Mabtech first aimed for certification. The scope of the certificates is: Development, manufacturing, marketing and sales of monoclonal antibodies and immunoassay instruments for *in vitro* applications in biomedical science Service of immunoassay instruments. The ISO certificates are available for download on Mabtech's web site.

Jesper Larsson
Head of Instruments
Mabtech 2021-11-25

www.mabtech.com

Contact Details
Email: iris@mabtech.com
Phone: +46 8 716 27 00
Fax: +46 8 716 27 01

Mailing Address
Mabtech AB
Box 1233
SE-131 28 Nacka Strand
Sweden

Visiting Address
Mabtech AB
Augustendalstorget 9
SE-131 52 Nacka Strand
Sweden

Organisation/Finance
Organisation no: 556 276-8225
VAT no: SE556276822501