SAMPLE PRODUCT DOSSIER
for WHO Prequalification

Simu POC CD4 System
THE Manufacturing Company®
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for WHO Prequalification

Simu POC CD4 System
THE Manufacturing Company®
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<th>Definition</th>
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<tr>
<td>CD4</td>
<td>cluster of differentiation 4</td>
</tr>
<tr>
<td>CE</td>
<td>Conformité Européenne</td>
</tr>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EP</td>
<td>essential principles</td>
</tr>
<tr>
<td>EQA</td>
<td>external quality assurance</td>
</tr>
<tr>
<td>FMEA</td>
<td>Failure Mode and Effects Analysis</td>
</tr>
<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HQ</td>
<td>headquarters</td>
</tr>
<tr>
<td>IFU</td>
<td>instructions for use</td>
</tr>
<tr>
<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>IVD</td>
<td>in vitro diagnostic medical device</td>
</tr>
<tr>
<td>LED</td>
<td>light-emitting diode</td>
</tr>
<tr>
<td>LOB</td>
<td>limit of blank</td>
</tr>
<tr>
<td>LOQ</td>
<td>limit of quantitation</td>
</tr>
<tr>
<td>OQ</td>
<td>operational quality</td>
</tr>
<tr>
<td>POC</td>
<td>point of care</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QASI</td>
<td>Quality Assessment and Standardization for Immunological measures</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>R+D</td>
<td>research and development</td>
</tr>
<tr>
<td>R²</td>
<td>coefficient of determination</td>
</tr>
<tr>
<td>ROW</td>
<td>rest of world</td>
</tr>
<tr>
<td>SOP</td>
<td>standard operating procedure</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
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1. INTRODUCTION

1.1 Purpose of the sample product dossier

The purpose of this sample product dossier is to provide manufacturers with an example of a product dossier required for WHO Prequalification of a diagnostic. The product dossier should contain evidence submitted by the manufacturer to demonstrate to WHO that the diagnostic is of acceptable quality, is safe and performs optimally when used (as intended by the manufacturer). Evidence will take the form, for example, of results of testing, certifications, standard operating procedures, systems and any other documentation necessary to support quality, safety and performance. As such, this sample product dossier contains the results of testing, extracts of standard operating procedures and other information that may be of relevance in support of an application for prequalification of a point of care (POC) CD4 diagnostic.

1.2 Content of the sample product dossier

This dossier is based on a fictitious diagnostic, the Simu POC CD4 System and its fictitious manufacturer, THE Manufacturing Company. As the product and its manufacturer do not exist, any related aspect that has been described within the sample product dossier are purely for the purposes of demonstrating the type of information that may be included in a product dossier submitted to WHO Prequalification.

1.3 Completeness of the sample product dossier

Because of its invented nature, the information provided is considered exemplary and not necessarily the full level of detail that may be required to fulfil a WHO Prequalification requirement. At times the information is presented in summary format. Additionally, the abbreviation “XXX” is used extensively to describe materials that do not exist, but again is incorporated to provide an example of the type of information that may be required. Further instructions are also provided in red coloured boxes to indicate where additional information may be expected.

This sample product dossier is still in development and not all prequalification requirements have been addressed. WHO will continue to incorporate relevant sections. However, again it is important to note that the purpose is to provide an example and as such this sample product dossier can never be considered to represent all that evidence that may be needed to meet WHO Prequalification requirements. Each manufacturer is responsible for identifying the type and volume of evidence that will be sufficient. WHO Prequalification staff are available to assist manufacturers at any point in the prequalification process. Staff may be contacted by email at diagnostics@who.int.

1.4 Format of the sample product dossier

The format of this sample product dossier follows that contained in WHO Publication PQDx_018 “Instructions for Compilation of a Product Dossier”. The numbering system used matches those in this WHO guidance. This document can be found on the WHO website (www.who.int) at the following link:

1.5 Feedback of the sample product dossier

This is the first sample product dossier produced by WHO to assist manufacturers of diagnostics. Comments on the sample product dossier and its utility are welcomed by WHO at diagnostics@who.int.

2. INTENDED AUDIENCE

This document has been created to assist manufacturers who wish to submit a product dossier for a point of care (POC) CD4 diagnostic. This document provides an example of how a WHO Product Dossier should be compiled in accordance with the instructions and format described in the WHO Prequalification document “PQDx_018 Instructions for Compilation of a Product Dossier”. This document is available at http://www.who.int/diagnostics_laboratory/evaluations/100506_pqdx_018_dossier_instructns_v1.pdf?ua=1.

3. THE PRODUCT DOSSIER

3.1 WHO product dossier elements

For the purposes of WHO Prequalification – Diagnostics, the product dossier is a selection of records and documents compiled by a manufacturer from their existing records and documents to provide evidence that the IVD submitted for WHO prequalification conforms to the Essential Principles of Safety and Performance of Medical Devices¹ and meets other WHO requirements.

During the WHO review of a product dossier, WHO will take into account the information that was previously submitted in the Prequalification of Diagnostics – APPLICATION FORM: WHO Document PQDx_015. Therefore, manufacturers should ensure that the content of the product dossier is consistent with the information submitted with the application form and that any changes in the information submitted with the respective application form are promptly notified to WHO. Furthermore, inadequacies identified at the application form stage and communicated by HO to the manufacturer are expected to be addressed as part of the product dossier submission.

3.2 When to submit a product dossier

Manufacturers should only submit a product dossier to WHO Prequalification when formally requested to do so by WHO. Dossiers that are submitted without a request from WHO will be returned to the manufacturer without review.

Manufacturers should ensure that the dossier contains all the information as is prescribed in “PQDx_018 Instructions for Compilation of a Product Dossier”. The prequalification procedure may be terminated if the dossier does not contain the prescribed information, or where the information supplied is inadequate to complete the prequalification assessment effectively or where the requested information is not provided by the manufacturer within a specified time period.

4. WHO PRODUCT DOSSIER CHECKLIST

Prequalification of Diagnostics

The attached Product Dossier contains information in support of the previously submitted Prequalification of Diagnostics – APPLICATION FORM (Document PQDx_015) for the following product:

<table>
<thead>
<tr>
<th>PQDx Number</th>
<th>PQDx XXXX-XX-XX</th>
</tr>
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<tbody>
<tr>
<td>Product Name</td>
<td>Simu POC CD4 System</td>
</tr>
<tr>
<td>Manufacturer Name</td>
<td>THE Manufacturing Company</td>
</tr>
</tbody>
</table>

Dossier Content Requirement | Provided | Location: |
<table>
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<tbody>
<tr>
<td>NOTE: The below numbering tallies with the Instructions for compilation of a product dossier PQDx_018.</td>
<td></td>
<td>Volume/Section Page number – Page number</td>
</tr>
</tbody>
</table>

4. Dossier Format

| 4.1. Dossier is clearly presented | Yes/No | Entire Dossier |
| 4.2. Layout and order as per instructions | Yes/No | Entire Dossier |
| 4.3. English language and units of measure used | Yes/No | Entire Dossier |

5. Product

| 5.1. Regulatory versions of this product | Yes/No | 1 / 5 9–15 |
| 5.2. Product description including variants (configurations) and accessories | Yes/No | 1 / 5 10–13 |
| 5.3. Essential principles (EP) checklist | Yes/No | 1 / 5 13–14 ANNEX 1 |
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| 6.2.1. Overview of manufacture | Yes/No | 1 / 6 22 |
| 6.2.2. Sites of manufacture | Yes/No | 1 / 6 23 ANNEX 8 |
| 6.2.3. Key suppliers | Yes/No | 1 / 6 23–24 |</p>
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<tr>
<th>Section</th>
<th>Yes/No</th>
<th>Pages</th>
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| 8.1. Labels                                                            | Yes/No | 1 / 8 55–57  |
| 8.2. Instructions for use                                             | Yes/No | 1 / 8 58–62  
Includes Job Aid |
| 9. Commercial History                                                 | Yes/No | 1 / 9 63  
Includes Job Aid |
| 9.1. Countries of supply                                               | Yes/No | 1 / 9 63  |
| 9.2. Adverse events and field safety corrective actions               | Yes/No | 1 / 9 63  |
**Manufacturer Declaration:**

The undersigned authorized contact person for the Manufacturer makes the following declarations on behalf of the Manufacturer and, in signing this product dossier checklist form, declares that he/she has the authority to bind the Manufacturer.

I declare that:

- I am authorized to represent the manufacturer specified in this prequalification product dossier (the "Manufacturer") for the purposes of WHO prequalification of diagnostics programme of the product specified in this product dossier (the "Product").

- All the information provided in this product dossier is current and correct.

- This product dossier contains all the information as is prescribed in the *Prequalification of Diagnostics Programme – Instructions for Compilation of a Product Dossier* (Document PQDx_018).

- The Manufacturer will notify WHO of all changes and variations to the Product prior to implementation of the changes.

- The Manufacturer will notify WHO of any changes to the regulatory approval status for the Product, such as suspension or withdrawal of regulatory approval, in all countries of manufacture and supply.

Name of the Authorized Contact Person for the Manufacturer:____________________

Signature of the Authorized Contact Person for the Manufacturer:_________________

Date:__________________

Please Note. The Checklist submitted to WHO must be signed and dated.
5. THE PRODUCT

5.1 Regulatory versions of this product

The Simu POC CD4 System (also referred to as “the System”), produced by THE Manufacturing Company, is comprised of 3 essential, dedicated components. These are the Simu POC CD4 System Cartridge, the Simu POC System Reader (suitable for use with all Simu POC System Cartridges) and the Simu POC CD4 System Control Cells. None of these dedicated components can be used or interchanged with components or systems from other manufacturers.

There are three regulatory versions of the Simu POC CD4 System Cartridge:
1. The CE marked version, Product Codes X1234-CE (100 Test Cartridge Pack) and X1235-CE (250 Test Cartridge Pack).
2. The Asia Pacific version, Product Code X1234-AP and X1235-AP, approved for supply by regulatory authorities in Korea, China, Indonesia.
3. The Rest of the World (ROW) version. Product Codes X1234-ROW (100 Test Cartridge Pack) and X1235-ROW (250 Test Cartridge Pack).

The ROW version is the product submitted for WHO Prequalification.

There is only one regulatory version of the Simu POC System Reader (Product Code INS 1234). This version has CE marking.

There is only one regulatory version of the Simu POC CD4 System Control Cells (Product Code CONTC 1234). This version has CE marking.

There is only one regulatory version of the packs of ancillary items comprised of lancets, specimen transfer devices and alcohol swabs (Product Code ANC 6789). These have CE marking.

All data submitted in this application were generated solely using the ROW version of the product.

There are no differences in design or documented manufacturing processes amongst the regulatory versions. All the materials used in manufacture are from the same suppliers and quality assured by the same processes. The differences in the regulatory versions are due to different lot release criteria and testing. The CE marked and ROW versions are evaluated pre-release against the quality control (QC) panels described in this document; the Asia Pacific version is evaluated pre-release secondarily against the CE marked and ROW versions, as well as against mandatory QC materials provided by the various national authorities.

Because of these differences, each regulatory version has specific labels and instructions for use that clarifies the version.

There have been no previous versions of this system, nor has THE Manufacturing Company developed, manufactured or distributed any systems of similar intended use.
5.2 Product description including variants (configurations) and accessories

5.2.0 Product Description

The Simu POC CD4 System, consisting of the Simu POC CD4 System Cartridge, the Simu POC System Reader (suitable for use with all Simu POC cartridges) and the Simu POC CD4 System Control Cells, is for the determination of CD4+ T-cell counts in patients. The legal manufacturer is “THE Manufacturing Company”. Early in development it was decided that a single cartridge using a single instrument would best meet the users’ needs. Different configurations for use with capillary and venous blood were avoided. For the intended uses and users an instrumental reading was thought most appropriate.

As such, the System is comprised of a small molded hand-held reaction device (the Simu POC CD4 System Cartridge) and associated reader (Simu POC System Reader). Under routine conditions, the quality of the System is monitored by the regular use of the Simu POC CD4 System Control Cells.

The Simu POC CD4 System Cartridge is prefilled with reagents, and consists of two EDTA – coated chambers of exact dimensions, a reception chamber and a reaction chamber. The design is such that the need to pipette a precise volume of blood is eliminated.

The Simu POC System Reader counts the output quanta. Patient identification can be inputted and thus linked with the patient results. The Simu POC System Reader has the ability to drive a non-device related output device. This output device can be a printer, or an external computer. Alternatively, the results can be manually recorded. The chosen method is left to the discretion of the user.

The Simu POC CD4 System Control Cells (packs of two bottles, one bottle representative of a normal CD4 count, one bottle representative of a low CD4 count) are used for routine monitoring of performance of the Simu POC CD4 System. These cannot be used with other systems for the determination of CD4 quantitation.

5.2.1 Intended Use:

a. The Simu POC CD4 System detects the CD4 protein specifically on the surface of CD4+ T-cells and uses that measurement to quantitate the number of CD4+ T-cells / μL in whole capillary blood or venous blood collected into EDTA.

b. The test is intended as an aid to management of patients with pre-diagnosed HIV infection.

c. The test is specifically intended to be used to help monitor the state of the immune system of an HIV-infected patient by following changes in the numbers of CD4+ T cells before and during anti-retroviral therapy.

d. The product is semi-automated; the Simu POC System Reader automatically calculates, records, stores and outputs the results from each patient’s blood sample.

e. The test is quantitative: it gives a numerical result, traceable to an accepted standard measurement with an uncertainty value and a defined range over which the output is validated.

f. The system is validated for use on capillary blood or venous whole blood collected in EDTA. The use of other anticoagulants has not been validated.

g. The test has been validated in specimens from patients older than 5 years, on young adults and on adults originating from Europe, America (USA) and East Africa.

h. The test is part of a system designed to be used at the point of care (POC) or for the delivery of the testing and results near to the patient. Thus it has use in decentralized diagnostic settings.
5.2.2 Intended User:

The intended user is a healthcare worker with minimal training in pathology practices but fully trained in taking blood specimens: typically in a small district hospital, health centre or in a physician's office. This product is not for self-testing.

5.2.3 A general description of the principle of the assay method or instrument principles of operation

The Simu POC CD4 System is an immunophosphorescent method for the enumeration of CD4+ T-cells. It uses a dual monoclonal antibody system to detect markers on the surface of CD4 cell populations. These antibodies are housed in the reaction chamber in the cartridge where the reaction between the monoclonal antibodies is activated by the addition of the blood specimen.

Neither of the monoclonal antibodies is specific for CD4 T-cells but no cell population other than CD4 T-cells react with both monoclonal antibodies. One of the monoclonal antibodies which binds to the CD4 surface protein, is labeled with reagents that phosphoresce, but only when the other monoclonal antibody, which is specific to T-cells, also binds. This prevents counting of cells which are not CD4+ T-cells but which might carry the CD4 protein (e.g. monocytes) and so will react with the monoclonal antibody specific for CD4 protein. The propriety technology ensures specificity for CD4 T-cells.

After a whole blood specimen is introduced into the cartridge, a set volume is released from the reception chamber into the reaction chamber. Excess blood remains safely contained in the cartridge within the reception chamber due to a uni-directional valve preventing loss. At this point the cartridge is introduced into the Simu POC Reader. Insertion of the cartridge activates the Simu POC Reader.

The Simu POC Reader will immediately alert the user if too little blood has been introduced into the Cartridge. Fifteen minutes after introduction into the Simu POC Reader, the phosphorescence reader is activated. The reaction chamber in the Cartridge is positioned between an LED emitting light and a photodetector in the Reader which is extremely sensitive to phosphorescent light. The hardware converts the signal from the photodetector into data that is directly proportional to the number of CD4+ T-cells in the reaction chamber which drives an ammeter to display the number of CD4+ T-cells, expressed in cells / μL. This overcomes the main problem of methods that are reliant on the level of CD4 molecules per cell being constant (rather than counting individual cells) in all disease and infection states, or rely on the volume of the cells being constant, or rely on not detecting free CD4. The displayed results and accompanying data can be sent to a printer, stored externally and/or transmitted via the wireless antenna.

The phosphorescent signal is unchanged over an ambient temperature incubation range of 10–40°C. Likewise it is unaffected by humidity or vibration (refer Stability Studies XXX – available on request).

5.2.4 A description of the components of the assay

The Simu POC CD4 System consists of the following dedicated components:

1. The Simu POC CD4 System Cartridge, which comes in 2 pack sizes, Product Codes X1234 (100 Test Cartridge Pack) and X1235 (250 Test Cartridge Pack).
2. The Simu POC System Reader, Product Code INS 1234.
3. The Simu POC CD4 System Control Cells, Product Code CONTC 1234.
Ancillary items required for performing the assay are venipuncture apparatus, and/or equipment required for the collection of capillary blood by finger stick collection, including lancets, specimen collection devices, and alcohol swabs. THE Manufacturing Company will supply on request, packages of ancillary items, comprised of lancets, specimen transfer devices and alcohol swabs required for finger-stick collection (Catalogue Number ANC 6789). As no items for venous blood collection are available from THE Manufacturing Company, the user is advised to use appropriate items to collect such samples.

The reagents for the system are contained in the Simu POC CD4 System Cartridge. As described in Section 5.2.3, the Cartridge houses the two monoclonal antibodies noted. The first antibody is anti-CD4-phosphoresce (CDXXX) The second is anti-lymphocyte (CDXXX). The antibodies are in an inorganic buffering solution containing bactericides and fungicides. This solution also contains EDTA. The monoclonal antibodies were raised in engineered mouse cells and are produced in continuous cell culture by standard methods.

The system has two control measures to assure quality. The Simu POC CD4 System Control Cells allow the user to monitor performance on a routine (daily) basis. These consist of modified CD4+ cells in a medium that mimics whole blood. These modified cells are calibrated in the System against known concentrations of CD4+ T-cells obtained using an accepted reference method for CD4 counting. Their use is not lot dependent, meaning that they can be used to monitor any lot number of Simu POC CD4 System Cartridge. The stated concentration of CD4+ cell equivalents can be traced back to the accepted method within the stated uncertainty of measurement (see ISO 17511).

The second control is incorporated into the System Reader. Here the volume of blood introduced is determined by incorporation of a strain gauge. A warning message will be displayed if insufficient blood has been introduced. The risk management section of this dossier defines some of the residual risk in this system.

The Simu POC System Reader reads any Simu POC System Cartridge, that is, it is not specific to the Simu POC CD4 System. Other Simu POC System products also utilize this reader. This is described in more detail in Sections 5.2.0 and 5.2.3.

5.2.5 A description of the specimen collection and transport materials provided with the product or descriptions of specifications recommended for use

Either venous whole blood in EDTA anticoagulant or fingerstick whole blood can be used. The performance of other specimen types has not been investigated.

The ancillary pack of lancets, specimen transfer devices and alcohol swabs can be purchased separately if needed. The lancets are auto-retractable with a 1.5 mm blade size. The specimen transfer device, a calibrated inverted cup device, is used to deliver the required volume. If this device is not used, other specimen transfer devices that deliver between 20μL and 30μL of whole blood can be used. The assay does not require accurate specimen volume delivery, rather it requires a minimal volume. Error messages will display on the reader if insufficient specimen has been delivered. The alcohol swab, containing 70% isopropyl alcohol, is not critical for functioning of the device. For ease of use, the swab provided has dimensions of 6 cm by 6 cm. Smaller swabs can be used but have been identified as being less user friendly in the field.
5.2.6 For instruments of automated assays: a description of the appropriate assay characteristics or dedicated assays

The Simu POC CD4 System has been described in Section 5.2.3 above. The System will detect counts between 10 to 2000 cells/µL.

5.2.7 For automated assays: a description of the appropriate instrumentation characteristics or dedicated instrumentation

The Simu POC System Reader (also known as the Reader) has been described in Section 5.2.3 above. The Reader requires standard pouch lithium-ion rechargeable batteries.

5.2.8 If applicable, a description of any software to be used with the product

Dedicated software is incorporated in the Simu POC System Reader. No additional software is required.

5.2.9 If applicable, a description or complete list of the various configurations/variants of product that will be made available

The Simu POC CD4 System Cartridge comes in two pack configurations – 100 Test Cartridge Pack (X1234) and 250 Test Cartridge Pack (X1235).

5.2.10 If applicable, a description of the accessories, and other products that are intended to be used in combination with the diagnostic

The accessories are as described in Section 5.1 and other parts of Section 5.2:

- Simu POC System Reader (Catalogue Number INS 1234). This instrument can only be used with Simu POC System Cartridges. The Reader requires standard pouch lithium-ion rechargeable batteries.
- Simu POC CD4 System Control Cells (Catalogue Number CONTC 1234). The pack consists of 2 bottles of control cells, one which will provide a result for CD4 count in the normal range, and one that represents a low CD4 count. This product is for dedicated use only with the Simu POC CD4 System cartridges. The use of these cells is critical for day to day verification of the Simu POC CD4 System but will not necessarily give accurate results on other devices or instruments.
- Packs of sterile lancets, specimen transfer devices and alcohol swabs for the collection of capillary whole blood are provided as the separate Catalogue Numbers ANC 6789. These are provided as a convenience as they are widely available and are not critical to the results.
- Blood collection tubes are required for collection of venous blood. They must contain EDTA as anti-coagulant.

5.3 Essential principles (EP) checklist

The general evidence we have provided in support of the safety, quality and performance of our product is in accord with GHTF/SG1/N063:2011 Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices. The evidence is summarized in the Essential Principles checklist, provided in ANNEX 1.
Although this product has low pre-market regulatory oversight in Europe, the company acknowledges that, according to the international (GHTF/IMDRF) IVD classification scheme, the Simu POC CD4 System would be classified as a Class D IVD, given the importance and impact of a CD4 result in countries of intended use (low and middle income countries). We have classified this according to the guidance provided in GHTF/SG1/N045:2008 *Principles of IVD Medical Devices Classification*. The risk posed by an erroneous result in these countries is considered much greater than if the system is used in a high income country, where the CD4 result is often ancillary to other pathology results in the management of HIV. In anticipation of increasing adoption of the GHTF and IMDRF regulatory frameworks worldwide, THE Manufacturing Company has ensured that all aspects of the quality management system will conform with requirements for conformity assessment according to the GHTF regulatory framework (refer to GHTF/SG1/N46:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*).

As such, the evidence supporting the Essential Principles, in particular in reference to performance of the test system, is submitted as Section 7 of this dossier, as well as other evidence of manufacturing and quality management provided throughout this dossier. The level of detail we have provided to you is in accordance to the requirements for Class D IVDs as described in GHTF/SG1/N46:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*. All original data and files are kept at headquarters and are available on request. This information is controlled under our quality management system.

### 5.4 Risk analysis and control summary

We have included a copy of the Risk Management Policy of THE Manufacturing Company has been provided in the following pages (refer ANNEX 2 – DOC QMRM POL1). As an output of this higher level policy document, there are several Standard Operating Procedures (SOPs) related to risk assessment procedures, specifically defining the make-up of risk assessment teams for each stage of design, process, user and patient risk analyses. The SOPs lead to the the Failure Mode and Effects Analysis (FMEA) output documents ANNEX 3 Simu POC CD4 System Design Input FMEA, ANNEX 4 Simu POC CD4 System User & Patient Risk FMEA, ANNEX 5 Simu POC CD4 System Process FMEA, ANNEX 6 Simu POC CD4 System Supplier Management FMEA, and to the Simu POC CD4 System Residual Risk Statement which describes any residual risks and their control by warning statements.

A series of control measures arises from the risk assessment – these are listed in the risk analyses and also shown on the flow diagram of the manufacturing process. The effectiveness of the controls and changes in eliminating the identified risk is shown in the FMEA. Some of the risks, such as instability of various sorts, common (but not specific) interfering agents, are well documented and were considered (and addressed) in the early Research & Development Planning Phase. The data is presented in Section 7 of this dossier. Instability and allowable life-times have been evaluated for specimen type, for the shelf life of the cartridge itself (and for the Control Cell) using several independent manufactured lots, for the life of the materials once opened or taken from its pouch, the length of time between adding specimen to cartridge and for the length of time after adding specimen to cartridge for which the result is valid. Common interfering materials and specimen types (Refer CLSI EP07-A2 *Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition*) as well as potential analyte-specific interferents, for example malaria with its effects on red blood cell haemolysis and tuberculosis with its effects on CD4 bearing monocytes, are defined during risk analyses and evaluated by field testing.
5.4.1 Simu POC CD4 System Residual Risk Statement

Following optimisation of the Simu POC CD4 System design and performance characteristics by comprehensive testing in-house and in the hands of intended users, as verified when testing populations representative of the intended patient population, THE Manufacturing Company considers the remaining risks to users and patients are minimal and acceptable for the Simu POC CD4 System. CD4 testing is used for monitoring the status of a patient, not for diagnosis. The outcome of a single test will be used in the context of a knowledge of other factors related to the patient and any unlikely, unexpected test result will be balanced by the major clinical value for patients who would otherwise have limited or no access to monitoring.

The remaining risks to manufacture, continuity of supply, and to manufacturing staff are also minimal and acceptable in view of the training and safety measures in place for our staff and the supplier management and material testing specified for this product.

Documented evidence to support these statements is filed on site in the Risk Management and Control Report of the Risk Management File for this product. This report contains the assessment of all remaining risks after implementation of risk control measures. This report is subject to continuous review, based on experience with the System, to ensure the positive status of the benefit versus risk profile remains unchanged.

Signed: Date: Head of QA, “THE Manufacturing Company”: responsible for risk management and control.

Signed: Date: Head of R&D, “THE Manufacturing Company”: responsible for design and process risk control

Signed Date: Head of Manufacturing, “THE Manufacturing Company”: responsible for risk management and control related to supply of product, safety in the facility, respect for the environment.

NOTE: Submitted documents must be signed and dated
6. DESIGN AND MANUFACTURING INFORMATION

The Research and Development Department of THE Manufacturing Company (987 Somewhere Street, Somewhere in Europe EU-1234, Europe) is responsible for the control of design of the System. The Research and Development Department was responsible for all design aspects and design validation of the Cartridge by the manufacturing site at company headquarters. Headquarters manufacturing, apart from developing the prototypes in conjunction with the Research and Development Department, undertakes all aspects of manufacture for cartridges for the European market and the Rest of the World regulatory version. Although manufacturing of the reader is outsourced to an ISO 9001 certified manufacturer of electronic equipment (Imaginative Diagnostic Designers, Top Street Industrial Estate, Some Country, Europe), the design, specification and quality requirements were provided by the Research and Development Department, and control of design rests with this group. Manufacturing of the Asia Pacific marked versions of the cartridge occurs in our Asia Pacific factory (123 Roundabout Road, Somewhere in Asia). Design transfer to that factory is under strict control of the Research and Development Department, according to Standard Operating Procedure (SOP) XXX, in accord with ISO TIR 14969:2004. Following the development plan there is a risk assessment followed by full staff training, qualification of all the manufacturing processes, re-verification of cartridge performance against the specifications and re-validation of the Quality Assurance release-to-market requirements.

The Instructions for Use are printed locally, with translation where necessary from the authorised English version by suitably qualified and licensed scientific/medical translators and approved by our local staff. Other labelling is controlled and printed locally. International symbols (ISO 15223 part 1:2012 and part 2:2010) are used wherever possible, other translation is by local licensed scientific/medical translators.

Packing materials, vials and bottles are sourced locally, and every lot quality assured and validated for use prior to acceptance of the manufacturer. Any changes to packaging materials are evaluated by risk assessment; any changes to packaging such as vials and bottles, or their labels, in immediate contact with product require a re-validation of stability as described in SOP XXX.

The Design Control System is shown in Figure 1 Section 6.1 of this dossier. Although the process is shown as a linear flow, in fact product design is an iterative process. Each stage might be repeated several times before optimisation of the whole design is attained. Design change control begins as soon as the customer requirements document is authorised; full change control, which is different only in the extent of re-validation potentially required, begins immediately before design verification. All performance characteristics are obtained with product manufactured following finalized and authorised documentation and quality assurance (QA) parameters (known as “design lockdown”). Data generated throughout the design input and Research & Development phases is collected as the Design History File, the finalised specifications as the Device Master Record. Risk analyses are initiated as shown and reviewed regularly with direction from SOP XXX. Design control review meetings are also held regularly and the output of the meetings stored in the design history file. Training for manufacturing staff commences as soon as possible in the design phase, and always during Research & Development Phase 2 at the latest. Process SOPs are qualified in the factory by manufacturing staff under Research & Development Department supervision.

Any changes to the design, including to labelling, are controlled within the change control system and cascaded to all factories, with risk evaluations and re-qualifications as appropriate at each factory. Changes are notified in compliance with mandatory regulatory requirements.

1 Sourced from organizations such as the International Association of Conference Translators, International Federation of Translators, or the International Medical Interpreters Association.
6.1. Product design and manufacture

Figure 1: Simu Product Design Control System

Design Inputs (R+D Dept HQ)
- User requirements
- Regulatory requirements
- Manufacturing requirements & capabilities
- Management expectations

Customer Requirements Document (R+D Dept HQ)
- Design is validated against the identified requirements in this document.
- Design change control begins when this document is approved.

Product Specifications (R+D Dept HQ)
- Numeric design requirements for R&D.
- Product verified against these specifications.

R&D Phase 1 (R+D Dept HQ)
- (Under Design Change Control)
- Instrumentation identified and format developed. Processes developed and
  qualified manufacturing documentation commenced.
- Guard bands for all process parameters defined and developed.
- QA and QC parameters and materials defined, sourced and documented.
- Calibrators and internal controls developed and metrologically traceable.

R&D Phase 2 (R+D Dept HQ)
- Transition to Factory (Change Control begins)
- Instrument and material suppliers finalized and audited.
- Instrumental PQ, OQ in the factory.
- Pilot batches made, tested against putative QC.
- Interfering substances evaluated, efficacy of microbiocides proven
- Process documentation finalized and approved.
- All aspects of the cartridges and specimen stability investigated using approved
  cartridge design.
- IFU finalized and approved.
- QA and QC specifications finalized and approved.

R&D Phase 3 (R+D Dept HQ)
- Design VERIFICATION using material made in the factory to approved
documentation.
  (R&D evaluation of all aspects of product specification document e.g.
  performance, repeatability, reproducibility, lot to lot variability, all aspects of
  stability).

R&D Phase 4 (R+D Dept HQ)
- Design VALIDATION using material made in the factory AT SCALE to approved
documentation.
  (User evaluation of all aspects of product specification document and
customer requirements document)

Manufacture (Manufacturing Dept HQ)
- Regulatory approvals
- Full scale manufacturing under Change Control
- Post market surveillance
- Review of scientific literature for independent clinical performance studies.

Design and Development Plan written
Reader manufactured according to design inputs from R+D, by Imaginative Diagnostic Designers, Top
Street Industrial Estate, Some Country, Europe.

Design risk analysis
User, patient, manufacturing risk analysis started, re-evaluated regularly
Regular design reviews against the plan commence

Acronyms
HQ Headquarters
R+D Research and Development
QA Quality Assurance
QC Quality Control
PQ Performance Quality
OQ Operational Quality

Final risk analyses and production of Risk Declaration
6.1.1. Design overview

Design of the product is the responsibility of THE Manufacturing Company (987 Somewhere Street, Somewhere in Europe EU-1234) and is conducted under the Quality Management System (QMS). Changes to the design are also controlled under the QMS of THE Manufacturing Company. These processes are described in Figure 1, Section 6.1.

The SOP XXX Design Input Requirements for the Development of the Simu POC CD4 System was incorporated into and implemented in the development phase of the Simu POC CD4 System. ANNEX 7 is an excerpt from this SOP. Those parts not included are related to procedural aspects of developing the Design Inputs.

Certificates (ISO 13485) for the quality systems of each of the design and manufacturing sites are attached as part of Section 11.3.

The Simu POC CD4 System Cartridge

Elements of the design of the cartridge are discussed in Section 5.4. The principle of the assay is described in Section 5.2. The critical components are the two monoclonal antibodies, anti-CD4-phosphoresce (CDXXX) and anti-lymphocyte (refer Table 6.1.1 Critical Ingredients/ Reagents/Supplies/ Services.).

In this section, WHO would expect a rationale for the design and choice of critical components. For example:
These antibodies were chosen because........
Although external suppliers were available, the decision to manufacture the bodies in-house was taken because........
The critical reagents are listed in Table 6.1.1:

Table 6.1.1  CRITICAL INGREDIENTS/REAGENTS/SUPPLIES/SERVICES

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Supplier</th>
<th>Quality Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simu POC System Reader</td>
<td>Imaginative Diagnostic Designers, Top Street Industrial Estate, Some Country, Europe</td>
<td>ISO 9001 certification</td>
</tr>
<tr>
<td>Monoclonal anti-CD4-phosphoresce (CD4)</td>
<td>THE Manufacturing Company, 987 Somewhere Street, Somewhere in Europe EU-1234</td>
<td>ISO 13485 certification</td>
</tr>
<tr>
<td>Plastic (polyalkane) for cartridge mould</td>
<td>XYZ Chemo-plastics, <a href="http://www.xyz.chemoplastic.co.eu">www.xyz.chemoplastic.co.eu</a> S001 High St, Anytown, Anywhere, AY6700</td>
<td>ISO 9001 certification</td>
</tr>
<tr>
<td>General laboratory chemicals (SuperGrade)</td>
<td>SuperPure chemicals Inc <a href="http://www.cleanascanbe.com">www.cleanascanbe.com</a> Somewhere, 5600001</td>
<td>FDA GMP certified</td>
</tr>
<tr>
<td>Human whole blood for Control Cells</td>
<td>Dracula suppliers EastTown</td>
<td>GMP; Compliance with Council of Europe Blood Transfusion requirements</td>
</tr>
</tbody>
</table>

6.1.2. Formulation and composition

Cartridge Components

Table 6.1.2a  FORMULATION OF THE CARTRIDGE COMPONENTS

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Amount per litre or concentration</th>
<th>Line item number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal anti-CD4-phosphoresce (CDXXX)</td>
<td>5–100ng</td>
<td>34K789</td>
</tr>
<tr>
<td>Monoclonal anti-lymphocyte CD555</td>
<td>0.05–0.1 ng</td>
<td>34K790</td>
</tr>
<tr>
<td>Phosphate pH 7.9</td>
<td>50mM</td>
<td></td>
</tr>
<tr>
<td>(Bacteriostat) XXX</td>
<td>50 µg</td>
<td>120790</td>
</tr>
<tr>
<td>(Fungicide) XXX</td>
<td>50 µg</td>
<td>13D512</td>
</tr>
<tr>
<td>EDTA</td>
<td>20 µg</td>
<td>56P456</td>
</tr>
</tbody>
</table>
Control Cells

Table 6.1.2 b  FORMULATION OF THE CONTROL CELL

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Amount per litre or concentration</th>
<th>Line item number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate buffer pH5.1</td>
<td>100mM</td>
<td></td>
</tr>
<tr>
<td>Stabiliser 1</td>
<td>50mg</td>
<td>45E506</td>
</tr>
<tr>
<td>Modified human CD4+ T-cells</td>
<td>0.35 x 10E9 ± 0.9%</td>
<td>From SOP XXX</td>
</tr>
<tr>
<td>Gelatin (fish)</td>
<td>45g</td>
<td>31H000</td>
</tr>
</tbody>
</table>

1 active ingredients include fish proteins (XXX, XXXX) in a neutral pH buffer (pH 7.4) and proclin-300 (0.1%) as preservative.

6.1.3. Biological Safety

Monoclonal Antibodies
Produced by in-vitro continuous culture of modified mouse cells in a medium containing biological additives. The monoclonal antibodies are purified by affinity chromatography preceded by concentration and buffer exchange and then ion-exchange. Each culture is monitored to show freedom from bacterial, mycoplasmal and fungal contamination. The risk of any extraneous material being present is assessed as exceedingly low, see for example “ter Avest et al., Biologicals 20 (1992) 177–186”. Refer Residual Risk Report – Biological Safety Monoclonal Antibodies – DOC XXX, held on site.

Human CD4 cells
The source blood is certified as free from HIV, HCV, HTLV, HBV, TB, CMV. Testing is by laboratories certified for ISO 9001:2008 and accredited to ISO 17025:2005 (General requirements for the competence of testing and calibration laboratories) using state of the art nucleic acid detection in addition to serology. Cells are stabilised by our patented process, concentrated, purified, sterilized by UV treatment, diluted in a medium containing biostatins and biocides, then counted precisely using reference methods before packing. The probability of any infective agent passing through this system is extremely low (Refer Residual Risk Report – Biological Safety Control Cells – DOC XXX). However this residual risk is noted, balanced against the value of the Control Cell and judged appropriate with suitable notification in the IFU, as can be seen from the risk assessments to users and the risk declaration.

Bovine material
Bovine material is utilized in the production of the monoclonal antibodies. All bovine materials used are sourced from a manufacturer with certification of Transmissible Spongiform Encephalopathies (TSE) free status, with herds from a country declared free from Transmissible Spongiform Encephalopathies (TSE) (e.g. bovine spongiform encephalopathy and chronic wasting diseases of cervids).

Recombinant proteins
Recombinant proteins are used in the stabilisation process for the Control Cells where a recombinant from B. veryrarus is used. It is cloned from the immunodominant region of the membrane pXXX protein and cultured in a baculovirus system. It is purified by ion-exchange and continuous flow gel electrophoresis. A formal risk assessment of this process has been undertaken (Refer Residual Risk Report – Biological Safety Recombinants – DOC XXX) and demonstrates that when all factors are taken into account, the risk of human infectivity from either the purified recombinant or the final product is negligible.
Fish Components
All fish proteins used in the manufacture of this product are certified to pose minimal risk to human health. A formal risk assessment, indicated the most probable risk was from potential for an allergic reaction if the fish protein comes in contact with the skin. The cartridge has thus been designed to minimize the possibility of this outcome as very remote. (Refer Residual Risk Report – Biological Safety Fish Proteins – DOC XXX).

6.1.4. Documentation of design changes
Change control has been described in Section 6.0 above.
The design change control system notes the following changes:
   Reference: QMCC Report XXX
   This was a change to the customer requirement document and was evaluated in the patient risk analysis. It was found necessary from Research and Development work showing elevated imprecision above 3000 cells / µl.

2. Change of validation site 2. Change from site XYZ to site XYY. Date of change 2011 12 35 phase of work: Research and Development phase 4
   Reference: QMCC Report XXX
   This was a change in the approved validation plan. Site XYZ was found unable to perform the validation work to our requirements in the time available because of other commitments. The risks of performing the work at site XYY were evaluated in the manufacturing risk assessment and found negligible.

3. Change to IFU after validation during Research and Development phase 4 but before first release to market of the product. Date of change 2012 03 13.
   Reference: QMCC Report XXX
   It was found that the language of the detailed method instructions could be clarified by changing the spacing of the text and adding a small paragraph about disposal of the cartridge after use. This was assessed in the risks to users and the risk to patients FMEAs and judged an improvement in both cases. The changed text was revalidated in a small trial at Site XZY, the points having been suggested at centre XYY.

4. Change to the claimed shelf-life of the product. Phase of work – post first release to market. Date of change 2013 03 06.
   Reference: QMCC Report XXX
   On-going stability work with routinely manufactured kits showed that the life could be extended from 1 year to 2 years with no change to the performance of the product. This was verified in-house with end-of-life testing of all the performance factors (precision, range, effect of interferents, robustness …) using four routine manufactured lots two years and one month after their manufacture. This testing would have detected a 5% change in characteristics, which was not found. The performance was judged unchanged from the initial validation and verification work, the risk judged negligible.
6.2. Manufacturing processes

6.2.1. Overview of manufacture

The flow of product manufacture is shown below. The cartridge manufacture is shown as the main flow, the components manufactured on our behalf are shown separately. Quality control checks are indicated in green – the reason for each of these checks can be traced back either to a risk management document (Section 5.4) or is a normal technical measurement for the process concerned.
6.2.2. Sites of manufacture

The cartridges are made in our European factory: THE Manufacturing Company, 987 Somewhere Street, Somewhere in Europe EU-1234, Europe, in accordance with the process described above. A number of other Simu POC System products are manufactured at this site, using the same process. These are cartridges for the detection of

- Malaria
- HIV
- Hepatitis C
- Syphilis
- Hepatitis B surface antigen.

A site plan for the facility is included below.

Insert a diagram of the Site Plan here. It must be labelled with functions for each area.

The company has 96 staff. A structure chart is included in the Quality Manual, appended as ANNEX 8.

The instruments are made for us at the ISO 9001 certified facility listed in the key suppliers list below (Table 6.2.3).

6.2.3. Key suppliers

The Simu POC Reader is manufactured by Imaginative Diagnostic Designers, Top Street Industrial Estate, Some Country, Europe for THE Manufacturing Company according to THE Manufacturing Company specifications.

Release quality assurance for the reader is undertaken by an independent electrical testing house, to the specifications of THE Manufacturing Company.
The key suppliers are listed in Table 6.2.3

**Table 6.2.3 KEY SUPPLIERS**

<table>
<thead>
<tr>
<th>Material</th>
<th>Supplier</th>
<th>Address</th>
<th>Control of incoming goods (including purchasing and verification of ingredients/products/services)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Reader</td>
<td>Imaginative Diagnostic Designers</td>
<td><a href="http://www.IOD.eu">www.IOD.eu</a> Side street Somewhere, Europe</td>
<td>SOP XXX — Purchase control and full functional performance testing</td>
</tr>
<tr>
<td>QC services for Simu POC Reader</td>
<td>Electrical Testing House Services</td>
<td><a href="http://www.eths.eu">www.eths.eu</a> 24 Industry Park Industryville, Europe</td>
<td>SOP XXX — Lot acceptance Simu POC Reader Company provides quality control testing of all new lots of Simu POC reader. Certificate of Analysis</td>
</tr>
<tr>
<td>Routine chemicals</td>
<td>SuperPure Chemicals Inc</td>
<td><a href="http://www.cleaneascanbe.com">www.cleaneascanbe.com</a> Somewhere, 5600001</td>
<td>SOP XXX Certificates of analysis, routine check on samples taken as specified and performed in the SOP. Low level check on purity and identity, usually HPLC or GLC. Physical checks — conductivity per g/l etc.</td>
</tr>
<tr>
<td>IFU translations</td>
<td>Language specific</td>
<td>E to F West Africa Capital City</td>
<td>SOP XXX Review by local sales staff</td>
</tr>
</tbody>
</table>

All our suppliers are certified to ISO 9001:2008 (copies of certificates attached in Section 11), those providing analytical services are accredited by their local accreditation bodies to ISO 17025:2005 General Requirements for the Competence of Testing and Calibration Laboratories and where appropriate are certified to ISO 15189:2012 Medical laboratories – Requirements for quality and competence and/or ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.
WARNING: Please read the following important notes about the information provided in this section.

NOTE 1 For purposes of this Sample Product Dossier, Report Summaries have been provided. When providing a dossier for the WHO Prequalification Programme, the following should be provided as Annexes for EACH PERFORMANCE CLAIM:

- The complete study protocol
- The methods of data analysis
- The complete study report (signed and dated), including the study conclusion.

NOTE 2 The studies presented in this section do not represent the complete list of studies that are expected to be performed and submitted, but are a sample. For each claim, including but not limited to specimen type to be used, testing population, stability, performance characteristic, studies must be performed to support that claim.

NOTE 3 A number of references are made in superscript, sometimes without an associated text. These are added to emphasize the need for such references. Full details must be provided in a product dossier.

NOTE 4 The data provided in this section must be produced on the final version of the assay submitted for prequalification. Where this has not occurred, the version used should be stated and a justification for the inclusion of the data provided.
Section 7 Summary:

The results of all analytical and clinical performance testing, submitted in this dossier were conducted on the final version of the new Simu POC CD4 System. Earlier tests with prototype systems and procedures are not included, but the data are retained in design history files, held on site at THE Manufacturing Company.

For each study presented, the site(s) and principal investigator(s) are identified, the date each study was performed, the lot numbers used, and a description of the study design is given along with the statistical analysis, results and conclusions. All efforts were undertaken to eliminate potentials for bias, including but not limited to, blinding of known CD4 and HIV status, randomization of procedures that may unfairly influence the result outcome, and careful selection of reference testing. Additionally, validation studies were designed and executed in a manner to avoid the potentials for conflict of interest.

Where possible, internationally accepted standards were used to guide the design of each study and inform on the acceptance of the outcomes. These are comprehensively noted in the Essential Principle Checklist (Refer Section 5.3 of this dossier).

The results of both verification studies1 (performed by the manufacturer) and validation studies2 (performed on behalf of the manufacturer in the setting of intended use) have been submitted in support of the performance of the assay. The following performance studies were conducted in settings of intended use in order to examine the performance of the Simu POC CD4 System in these settings:

- Trueness of Measurement studies by comparison of CD4 values with results generated by a reference CD4 method on aliquots of the same samples from both normal and abnormal donors are presented from two sites.
- Repeatability studies presented from two sites.
- Between-instrument reproducibility is presented from one site.
- Reproducibility of samples with time from draw and between day-reproducibility of prepared samples are presented from two sites.
- Linearity studies were conducted at one site.

Please Note:

1. In the reproducibility and repeatability studies, a maximum coefficient of variation of 15% has been utilized, based on internationally accepted practice for CD4 technologies.3,4
2. In the lot to lot comparison studies, each different lot of cartridge has been manufactured using different batches of critical reagents to ensure maximum comparison.
3. In the studies undertaken by the manufacturer, the reference methods, single platform flow cytometric methods, were chosen according to proven reliability and reputation as state of the art for CD4 testing.5

no brackets required. Successful participation in international quality assessment programmes and consistent good performance as indicated in peer-reviewed journal articles informed the study designers in their choice.

1. ISO 9000:2005 Definition of Verification “confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.”
2. ISO 9000:2005 Definition of Validation “confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.”
3. FDA Guidance for Industry Bioanalytical Method Validation
7.1. Analytical studies

7.1.1. Specimen type

The Simu POC CD4 system has been evaluated with **venous whole blood** using EDTA as anticoagulant. Furthermore, it has been evaluated with **capillary blood** that was collected with safety lancets from finger sticks and transferred into the EDTA-coated reception chamber of the cartridge. The outcome of these studies can be found in Section 7.4 “Clinical Evidence” of this dossier. Use of whole blood collected in other anticoagulants has not been evaluated.

**Study Summary Report: Specimen Type Stability – Venous Whole Blood**

Full Report: AR XXX – refer ANNEX X.

Study Dates: 12–14 July 2012

Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company

Testing: Performed on site, Headquarters.

**Study Objective**

To determine requirements for specimen handling and specimen stability for two different storage temperature ranges, 23°C (+/-5°C) and 5°C (+/-3°C). This study investigated the stability of anticoagulated venous whole blood specimens.

**Methodology**

Specimens were categorized into 3 different CD4 levels (high >1200 cells/µL, normal 400–1200 cells/µL, and low <400 cells/µL). 4 patients were identified from each of these categories. Fresh venous blood specimens were freshly collected into EDTA collection tubes and stored for 12, 24, 36 and 48 hours at the 2 different temperature intervals, respectively. Before testing, all specimens were mixed and allowed to equilibrate to room temperature (18–28°C) for 15 minutes on a rolling apparatus. Each specimen was then loaded into the cartridge and measured at room temperature (18–28°C) on 4 different Simu POC CD4 systems in parallel. As a reference, the samples were measured within 1h after collection (T=0h).

**Reagents and Instruments:**

Simu POC CD4 Cartridge Lot Number: MPOC-1307 exp 07 2013

Simu POC System Reader Lot Number: MPR-11AGG

**Acceptance Criterion**

The overall CV value for replicate measurements for each sample/temperature range had to be below 15%.

**Statistical Analysis**

The association between CD4+ T cell counts and storage time was furthermore tested by Pearson’s product-moment correlation. A p value of <0.05 was considered to indicate a difference of statistical significance.

**Results**

Based on the determined CV values, specimen storage for up to 48 hours at room temperature prior to measuring on the Simu POC CD4 system had no significant influence on measured CD4+ T cell counts as shown for 3 different venous blood specimens (Refer Table 7.1.1).
Specimen incubation for up to 36 hours at 2 – 8 °C prior testing had no significant influence on measured CD4+ T cell counts as shown for 3 different venous blood samples (Refer Table 7.1.1) however performance was affected at 48 hours at this temperature. The CV for each specimen/each incubation temperature/all times of incubation and the averaged CV value of all specimens/incubation temperatures/time of incubations did not exceed 15%.

Table 7.1.1 Specimen Type Stability – Venous whole blood (EDTA)

<table>
<thead>
<tr>
<th>Storage Temp</th>
<th>Specimen CD4 count range (cells/µL)</th>
<th>12h</th>
<th>24h</th>
<th>36h</th>
<th>48h</th>
<th>P (R²)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–8°C</td>
<td>&lt;400</td>
<td>250</td>
<td>240</td>
<td>235</td>
<td>200</td>
<td>&gt;0.05</td>
<td>Fail at 48h Pass at 36h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Fail &gt;15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>400–1200</td>
<td>600</td>
<td>610</td>
<td>550</td>
<td>560</td>
<td>&gt;0.05</td>
<td>Pass at 48h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Pass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1200</td>
<td>1300</td>
<td>1250</td>
<td>1190</td>
<td>1230</td>
<td>&gt;0.05</td>
<td>Pass at 48h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Pass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–28°C</td>
<td>&lt;400</td>
<td>250</td>
<td>240</td>
<td>220</td>
<td>215</td>
<td>&gt;0.05</td>
<td>Pass at 48h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Pass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>400–1200</td>
<td>600</td>
<td>610</td>
<td>550</td>
<td>512</td>
<td>&gt;0.05</td>
<td>Pass at 48h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Pass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1200</td>
<td>1300</td>
<td>1250</td>
<td>1270</td>
<td>1110</td>
<td>&gt;0.05</td>
<td>Pass at 48h</td>
</tr>
<tr>
<td></td>
<td>Max %CV Pass Pass Pass Pass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
This study provides evidence that venous whole blood specimens collected in EDTA can be stored for a time period of up to 48 h between 18 and 28°C prior to testing on the Simu POC CD4 system without obvious effect on the measured CD4+ T cell count. Alternatively, these specimens can be stored refrigerated (2–8°C) for up to 36 h prior to testing using the Simu POC CD4 System.

7.1.2. Analytical performance characteristics

7.1.2.1. Accuracy of measurement
Accuracy of the new Simu POC CD4 System (including assessment of trueness and repeatability) to enumerate T-helper cells in venous and capillary whole blood of HIV-positive and HIV-negative individuals was evaluated in several clinical performance studies in Africa, Europe and US. The protocols and results of these studies are described in Section 7.4 of the product dossier.

7.1.2.1.1. Trueness of measurement
Trueness to enumerate T-helper cells in venous and capillary whole blood of HIV-positive and HIV-negative individuals was evaluated in several clinical performance studies in Africa, Europe and US. The protocols and results of these studies are described in Section 7.4 of the product dossier.
7.1.2.1.2. Precision of measurement

Repeatability:
Repeatability (intra-assay variation) to enumerate T-helper cells in venous and capillary whole blood of HIV-positive and HIV–negative individuals was evaluated in several clinical performance studies in Africa, Europe and US. The protocols and results of these studies are described in Section 7.4 of the product dossier.

Reproducibility:
Reproducibility of the results of the new Simu POC CD4 System was evaluated with venous blood samples, the day-to-day, reader to reader and lot-to-lot precision of this diagnostic device have to meet pre-defined acceptance criteria (CV<15%). Studies were performed at different sites in Africa, Europe, and USA by different users and are described in Section 7.4 of this product dossier.

7.1.2.1.2.1 Repeatability and reproducibility studies (Single Lot Number)

Study Summary Report: Assay precision (intra-and inter-assay), Assay reproducibility (Day to Day Variability) and Reader-to-Reader (inter-instrument) Variability

Full Report: AR XXX (refer ANNEX X).
Study Dates: 12–22 July 2012
Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company

Testing: Performed on site, Headquarters.

Study Objective
The study was designed to determine the Simu POC CD4 System precision (intra- and inter-assay variability), the reproducibility (day-to-day variability and reader-to-reader variability) of the Simu POC CD4 System according to the CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition (2004) with the indicated modifications. Measurements were performed daily on 4 consecutive days and on 6 different Simu POC CD4 Systems.

Methodology
Whole blood specimens from 2 healthy blood donors (established using a CD4 Reference Method Reference5) were collected in EDTA tubes and tested with a single lot of Simu POC CD4 System Cartridges to determine the absolute CD4+ T-cell counts over several hours on day 0 to establish the intra- and inter-assay variability. The day-to-day variability was assessed by determining the absolute CD4+ T-cell counts on the low count Simu POC CD4 System Control Cells on 12 consecutive days on the same Simu POC CD4 System. The assay reproducibility and inter-instrument variability were assessed by measuring the absolute CD4+ T-cell counts in a commercially available stabilized blood preparation (14 days in use stability) tested on 4 consecutive days and on 6 different Simu POC CD4 Systems. Data obtained from fresh blood specimens and from the Simu POC CD4 System Control Cells were analysed separately. The % CV of absolute CD4 counts/μL on day 0 were analysed on 10 replicates per specimen on day 0 after 1h (intra-assay), 3h and 6 h (inter-assay), over 4 days (day-to-day) per instrument (inter-instrument).

Reagents:
Simu POC CD4 System Cartridge Lot Number: Lot MPOC-1208 Exp 30 August 2012
Simu POC System Reader Lot Number: MPR-11AGG
Simu POC System Control Cells Lot Number: MPCC-1206 Exp 30 May 2013

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5 Full details of the reference method should be provided here
Acceptance Criteria
As an acceptance criterion for this study, the average CV% value as a measure for the precision of each aliquot had to be <15%.

Statistical Analysis
The repeatability and reproducibility were calculated using the mean CD4 results, the SD and the respective coefficient of variation (%CV) which were calculated for 2 fresh samples, 1 stabilized whole blood specimen and the Simu POC CD4 System Control Cells on 6 different instruments in total over a period of 4 consecutive days.

Results
Results of these studies are summarized in Tables 7.1.2.1.2.1-A, B and C.
The %CV for fresh whole blood samples was <15 % (intra-assay precision), <15% (inter-assay precision), <15% (reproducibility or day-to-day variation), and <15 % for reader-to-reader (inter-instrument) variability.

Results Table 7.1.2.1.2.1-A:
Assay repeatability (same specimen, same Simu POC CD4 System Cartridge lot, same Simu POC System Reader, day 0, same operator) (Simu POC System Reader Lot Number: MPR-11AGG)

<table>
<thead>
<tr>
<th></th>
<th>Specimen 1</th>
<th>Specimen 2</th>
<th>Simu POC CD4 System Control Cells (Low Count)</th>
<th>Simu POC CD4 System Control Cells (Normal Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 Reference MEAN</td>
<td>840</td>
<td>650</td>
<td>250</td>
<td>1000</td>
</tr>
<tr>
<td>CD4 Reference % CV</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>POC result 1</td>
<td>760</td>
<td>660</td>
<td>260</td>
<td>999</td>
</tr>
<tr>
<td>POC result 2</td>
<td>800</td>
<td>600</td>
<td>280</td>
<td>986</td>
</tr>
<tr>
<td>POC result 3</td>
<td>850</td>
<td>650</td>
<td>250</td>
<td>965</td>
</tr>
<tr>
<td>POC result 4</td>
<td>790</td>
<td>690</td>
<td>290</td>
<td>932</td>
</tr>
<tr>
<td>POC result 5</td>
<td>890</td>
<td>790</td>
<td>266</td>
<td>1023</td>
</tr>
<tr>
<td>POC result 6</td>
<td>960</td>
<td>690</td>
<td>245</td>
<td>998</td>
</tr>
<tr>
<td>POC result 7</td>
<td>795</td>
<td>590</td>
<td>245</td>
<td>1012</td>
</tr>
<tr>
<td>POC result 8</td>
<td>820</td>
<td>620</td>
<td>234</td>
<td>1023</td>
</tr>
<tr>
<td>POC result 9</td>
<td>877</td>
<td>677</td>
<td>256</td>
<td>996</td>
</tr>
<tr>
<td>POC result 10</td>
<td>864</td>
<td>664</td>
<td>256</td>
<td>943</td>
</tr>
<tr>
<td>POC Mean</td>
<td>841</td>
<td>663</td>
<td>258</td>
<td>988</td>
</tr>
<tr>
<td>POC SD</td>
<td>60</td>
<td>57</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>POC%CV</td>
<td>7</td>
<td>9</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>
Results Table 7.1.2.1.2.1-B:
Day-to-day variability, same specimen, same Simu POC CD4 System Cartridge lot, same Simu POC System Reader, same operator.

<table>
<thead>
<tr>
<th>Simu POC CD4 System Control Cells (Low Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Counts/µL</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Day 2</td>
</tr>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td>Day 4</td>
</tr>
<tr>
<td>Day 5</td>
</tr>
<tr>
<td>Day 8</td>
</tr>
<tr>
<td>Day 9</td>
</tr>
<tr>
<td>Day 10</td>
</tr>
<tr>
<td>Day 11</td>
</tr>
<tr>
<td>Day 12</td>
</tr>
<tr>
<td>POC Mean</td>
</tr>
<tr>
<td>POC SD</td>
</tr>
<tr>
<td>POC %CV</td>
</tr>
</tbody>
</table>

Results Table 7.1.2.1.2.1-C:
Reproducibility (different instruments, different operators, different days, same specimen, same Simu POC CD4 System Cartridge lot). (Simu POC System Reader Lot Numbers: MPR-10FWG, MPR-10LSA, MPR-10GJC, MPR-11AGG, MPR-11 DSQ NAD MPR-11TYP)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>MEAN</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument 1</td>
<td>255</td>
<td>299</td>
<td>255</td>
<td>222</td>
<td>258</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Instrument 2</td>
<td>256</td>
<td>296</td>
<td>299</td>
<td>212</td>
<td>266</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Instrument 3</td>
<td>222</td>
<td>266</td>
<td>299</td>
<td>256</td>
<td>261</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Instrument 4</td>
<td>231</td>
<td>277</td>
<td>222</td>
<td>288</td>
<td>255</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Instrument 5</td>
<td>253</td>
<td>250</td>
<td>233</td>
<td>287</td>
<td>256</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Instrument 6</td>
<td>220</td>
<td>231</td>
<td>278</td>
<td>266</td>
<td>249</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>MEAN</td>
<td>240</td>
<td>270</td>
<td>264</td>
<td>255</td>
<td>257</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
<td>26</td>
<td>33</td>
<td>32</td>
<td></td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
Assay variability (intra- and inter-lot), day-to-day reproducibility, and inter-instrument variability met the pre-defined acceptance criteria for both whole blood samples and Simu POC CD4 System Control Cells.
7.1.2.1.2 Lot-to-Lot Variability

Study Summary Report: Lot-to-Lot Variability
Full Report: AR XXX – refer ANNEX X.
Study Dates: 12 July 2012
Testing: Performed on site, Headquarters.

Study Objective

Methodology
Whole blood from 2 healthy blood donors was collected into EDTA tubes and CD4 counts established using Reference Method ZYX. From each specimen collected, 3 aliquots were prepared. To one of these, no manipulation of the specimen occurred. To the other two, artificially high and low counts were produced by the removal and addition of plasma. Each of three aliquots were then tested in replicate 10 times within 3 hours after collection on each of the three lot numbers. Testing was performed on lots of cartridges with different shelf lives remaining, to challenge the Simu POC CD4 system as much as possible.

Reagents and Instruments
Simu POC CD4 System Cartridge Lot MPOC-1203 Exp 30 August 2012
Simu POC CD4 System Cartridge Lot MPOC-1206 Exp 30 December 2012
Simu POC CD4 System Cartridge Lot MPOC-1305 Exp 30 September 2013

Acceptance Criteria
As an acceptance criterion for this study, the average CV% value as a measure for the precision of each aliquot replicate had to be <15%. Results are summarized in Table 7.1.2.1.2.2.

Statistical Analysis
The mean value of each duplicate test and the difference between the results of each duplicate test were taken for statistical analysis of variation. As a measure for precision, the duplicate SD and the respective duplicate coefficient of variation (CV in percent) were calculated for all samples in total.

Results
Replicate CVs between lots: Low CD4 count <15%, Normal CD4 count <15%, High CD4 count <15%.
### Results Table 7.1.2.1.2

Lot-to-lot variability assessment:

<table>
<thead>
<tr>
<th>Lot MPOC-1203</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spec 1</td>
<td>Low</td>
<td>10</td>
<td>250</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>10</td>
<td>650</td>
<td>90</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>10</td>
<td>1500</td>
<td>200</td>
<td>13</td>
</tr>
<tr>
<td>Spec 2</td>
<td>Low</td>
<td>10</td>
<td>150</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>10</td>
<td>800</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>10</td>
<td>2000</td>
<td>250</td>
<td>13</td>
</tr>
</tbody>
</table>

Lot MPOC-1206

<table>
<thead>
<tr>
<th>Spec 1</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10</td>
<td>280</td>
<td>35</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>690</td>
<td>90</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>1400</td>
<td>200</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Lot MPOC-1305

<table>
<thead>
<tr>
<th>Spec 1</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10</td>
<td>220</td>
<td>35</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>610</td>
<td>90</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>1700</td>
<td>200</td>
<td>12</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Spec 2</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10</td>
<td>120</td>
<td>19</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>850</td>
<td>120</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>10</td>
<td>1700</td>
<td>250</td>
<td>15</td>
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</tr>
</tbody>
</table>

Lot-to-lot

<table>
<thead>
<tr>
<th>Spec 1</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>250</td>
<td>10</td>
<td>30</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>650</td>
<td>10</td>
<td>40</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1533</td>
<td>10</td>
<td>153</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Spec 2</th>
<th>CD4</th>
<th>N</th>
<th>Mean Cell Count/µL</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>110</td>
<td>10</td>
<td>16</td>
<td>14</td>
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</tr>
<tr>
<td>Normal</td>
<td>853</td>
<td>10</td>
<td>55</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1866</td>
<td>10</td>
<td>153</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Average %CV: 13

**Conclusion:**

Precision of the CD4 measurements in lot-to-lot comparison met the pre-defined acceptance criterion for both whole blood samples and Simu POC CD4 Control Cells. Low CD4 %CV = 14.9; Medium CD4 %CV = 12 and High CD4 %CV = 12.25. Average %CV = 13.

7.1.2.2. Analytical sensitivity.

**Study Summary Report: Limit of Quantitation, Limit of Detection and Limit of the Blank.**

Full Report: AR XXX – refer ANNEX X.

Study Dates: 02 August 2012


Testing: Performed on site, Headquarters.
Study Objective
The study was designed to determine the sensitivity of the quantitative measurement procedure carried out with the Simu POC CD4 System including the determination of the corresponding statistical parameters according to the CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory measurement Procedures; Approved Guideline (2012) and the CDRH Class II Special Controls Guidance Document (2001).

Method
In this study, five different blood specimens with a CD4+ T cell concentration of approximately 200 cells/μL were used as the “high count” samples to generate 10 different lower levels of T-helper cell concentrations by dilutions with corresponding low count samples (diluents). Diluents were prepared from the corresponding blood specimen by CD45 cell depletion (a pan-leucogate antibody) (see linear range study protocol Chapter 7.1.2.5).

Four replicates of each test sample were measured with the Simu POC CD4 System. For all samples and per dilution step, a total of 5x4=20 CD4+ T cell measurements (dilution replicates) were conducted. For each dilution the mean and SD were determined.

3 parameters describing analytical sensitivity were assessed
1. Identify the Lower Limit of Quantification (LOQ) at an accepted maximal CV (coefficient of variation) value of 15%.
2. Define the Lower Limit of Detection (LOD) and
3. Limit of Blank (LOB).

Reagents and Instruments
Simu POC CD4 Cartridge Lot Number: MPOC-1307 exp 07 2013
Simu POC System Reader Lot Number: MPR-11AGG

Decision Criteria
The LOQ was defined as the lowest mean CD4+ T cell concentration at which the CV value did not exceed 15%. The LOD was defined as the mean CD4+ T cell count at which 95% of the counts of the dilution replicates are higher than the LOB. Limit of blank (LOB) was the mean CD4 cell count + 2SD calculated from the results measured for the CD45 depleted aliquots.

Results
The LOD for enumeration of CD4+ T cells by the Simu POC CD4 System and with proportions of false positives less than 5% and false negatives less than 5%; based on 40 determinations of 20 blank and 20 low samples is below 24 cells/μL.

The LOQ at a CV maximum value of 15% was assessed to be 30 cells/μL.

The LOB was determined to be 5 CD4+ T cells/μL.

Conclusion:
These results compare well with those published for known reference methods (References 7, 8, 9, 10).

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6 The following review was also used as a reference: “Limit of Blank, Limit of Detection and Limit of Quantitation” Clin Biochem Rev Vol 29 Suppl (1) August 2008 S49 Armbruster DA and Pry T.
7.1.2.3. Analytical specificity
The analytical specificity of each of the 2 antibodies utilized in the Simu POC System has been established based on the International Workshop on Human Leucocytes Differentiation Antigens. The specificity of the clones used is well-established (References 11, 12, 13, 14).

Antibody cross-reactivity (study No. 7.1.2.3.1), interference of hematocrit (study No. XXX), interference due to the presence of ART drugs and different diseases (study No. XXX) with the CD4+ T-cell enumeration by the Simu POC CD4 System were investigated in dedicated studies and are reported below. As shown by flow cytometry, the Simu POC CD4 reagent mix (containing anti-CD4-phosphoresce (CDXXX) and the anti-lymphocyte (CDXXX) monoclonal antibodies) showed the expected cross-reactivity with lymphocytes, monocytes and granulocytes, respectively. An elevated haematocrit (20 to 55%), a large number of anti-HIV treatments and other drugs as well as different diseases did not interfere with the Simu POC CD4 System.

7.1.2.3.1 Antibody Cross Reactivity
Study Summary Report: Antibody Cross Reactivity
Full Report: AR XXX – refer ANNEX X.
Study Dates: 27 February 2012
Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company
Testing: Performed on site, Headquarters.

Study Objective
To determine the cross reactivity of the anti-CD4-phosphoresce (CDXXX) and the anti-lymphocyte (CDXXX) monoclonal antibodies used in the Simu POC CD4 System with different blood cell sub-types.

Method
EDTA anti-coagulated whole blood samples from five healthy subjects were each stained with the two CD4 reagents utilized in the Simu POC CD4 System and analysed with a reference flow cytometer. Additional monoclonal antibodies labelled with a third fluorescent dye were used to additionally stain the monocyte population (using anti-CD14-PE) or all leucocytes of the sample, including the granulocyte and monocyte population (using anti-CD45-PECy5). The major white blood cell types, granulocytes, lymphocytes and monocytes from each sample were separately gated and analyzed to determine the percent of antibody positive cells according to the manufacturer’s instructions.

Reagents and Instruments
Reference instruments and reagent lots should be described here.

Results
In Table XXX, the percent positive cells, means, standard deviations (SD) and ranges for anti-CD4-phosphoresce monoclonal antibody and the anti-lymphocyte (CDXXX) monoclonal antibody are indicated for each blood cell type for the five normal donors studied. A total of 5,000 events were collected for the analysis of each blood component for each donor.

7,8,9,10, 11,12,13,14 The Manufacturer is expected to supply relevant references
Table XXX "Antibody Cross Reactivity" to be inserted here.

Conclusion:
This study shows the expected specificity of the anti-lymphocyte CDXXX monoclonal antibody for peripheral blood lymphocytes. It also shows the expected specificity of the anti-CD4-phosphoresce monoclonal antibody for peripheral blood lymphocytes. Additional components of the Simu POC CD4 System had no influence on the antibody reactivity result.

7.1.2.4. Metrological traceability of calibrators and control material values
Traceability with respect to the Simu POC CD4 System Control Cell falls under section 5.6 of ISO 17511:2003 In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials “Cases with manufacturer’s selected measurement procedure but neither international conventional reference measurement procedure nor international conventional calibrator and without metrological traceability to SI”.

Each lot of Simu POC CD4 System Control Cell is standardised against the median reading of five CD4 counting instruments (A, B, C, D and E), recognised internationally for their excellence\(^\text{15}\) (for use in large, well equipped and validated laboratories) by counting on those instruments and on 100 of the Simu POC CD4 System Cartridges taken from five manufacturing lots. The uncertainty of the value assigned to the Simu POC CD4 System Control Cell reagent is expressed according to ISO convention and takes into consideration differences between the reference instruments and the variability between our cartridges.

The signal from the Simu POC CD4 System Control Cell is intended to fall near the clinically significant value of 250–300 cells/µL (Refer User Risk 18 in ANNEX 4 Simu POC CD4 System User and Patient FMEA).

7.1.2.5. Measuring range of the assay

Study Summary Report: Measuring range of the assay
Full Report: QMCC Report XXX – refer ANNEX X.
Study Dates: 02 November 2010
Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company
Testing: Performed on site, Headquarters.

Study Objective:
To demonstrate the linearity of the quantitative measurement procedure carried out with the Simu POC CD4 System including the determination of the corresponding statistical parameters using the statistical process described in the CLSI EP6-A guideline Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guidelines (2003) and the CDRH Class II Special Controls Guidance Document (2001).

\(^{15}\) The Manufacturer is expected to supply relevant references
Methodology
Five different whole blood samples of known absolute CD4+ T cell counts:
- two specimens were artificially created from original samples to generate samples with high
  CD4+ T cell counts, 1501 and 2168 cells/μL, respectively
- one specimen from a hematologically normal donor (CD4+ T-cell count 690 cells/μL)
- two blood specimens with low CD4+ T cell counts <450 cells/μL.

Five dilution series were prepared by mixing the respective master sample and a CD45 depleted
aliquot of the same sample (i.e., CD4+ T cell counts close to zero) in predefined ratios. Each dilution
series consisted of 8–10 steps of different CD4+ T cell counts. The expected absolute CD4+ T cell
count of each aliquot was calculated using the known counts of the master sample, its CD45 depleted
aliquot and their respective mixing ratio. All aliquots were prepared in duplicate and a total of 16–20
aliquots per experiment measured. Observed values for absolute CD4+ T cell counts in each aliquot
were determined by measurement with the Simu POC CD4 System and compared to the expected
values.

Reagents
Simu POC CD4 System Cartridge Lot MPOC-130 Exp 30 September 2013

Acceptance Criteria
Acceptable data must be linear over the intended range according to the methods described in
CLSI EP6-A.

Statistical Analysis
Linear Regression

Results
The linear regression analyses of the expected versus observed values for absolute CD4+ T cell
counts with the Simu POC CD4 System are shown in the Table 7.1.2.5. The Simu POC CD4 System
measurement procedure for enumeration of CD4+ T cells has been demonstrated to be linear from
10 to 2000 cells/μL. All data meet the acceptance criterion of linearity by the methods described in
CLSI EP6-A and with a minimal R² of 0.95–0.99. The overall duplicate CV value was between 0.7 and
2.4% for the five experiments.
## Results Table 7.1.2.5

**Measuring Range**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET VALUE</strong></td>
<td>1501 CD4/µL</td>
<td>2168 CD4/µL</td>
<td>690 CD4/µL</td>
<td>300 CD4/µL</td>
<td>150 CD4/µL</td>
</tr>
<tr>
<td>Master</td>
<td>1501</td>
<td>1408</td>
<td>2168</td>
<td>2044</td>
<td>690</td>
</tr>
<tr>
<td>Dilution 1</td>
<td>1300</td>
<td>1200</td>
<td>2000</td>
<td>1800</td>
<td>600</td>
</tr>
<tr>
<td>Dilution 2</td>
<td>1100</td>
<td>1150</td>
<td>1800</td>
<td>1750</td>
<td>550</td>
</tr>
<tr>
<td>Dilution 3</td>
<td>900</td>
<td>850</td>
<td>1600</td>
<td>1499</td>
<td>500</td>
</tr>
<tr>
<td>Dilution 1</td>
<td>700</td>
<td>650</td>
<td>1400</td>
<td>1401</td>
<td>450</td>
</tr>
<tr>
<td>Dilution 4</td>
<td>500</td>
<td>550</td>
<td>1200</td>
<td>1198</td>
<td>400</td>
</tr>
<tr>
<td>Dilution 5</td>
<td>300</td>
<td>360</td>
<td>1000</td>
<td>1050</td>
<td>350</td>
</tr>
<tr>
<td>Dilution 6</td>
<td>100</td>
<td>120</td>
<td>800</td>
<td>780</td>
<td>300</td>
</tr>
<tr>
<td>Dilution 7</td>
<td>50</td>
<td>45</td>
<td>600</td>
<td>630</td>
<td>250</td>
</tr>
<tr>
<td>Dilution 8</td>
<td>10</td>
<td>22</td>
<td>400</td>
<td>350</td>
<td>200</td>
</tr>
<tr>
<td>R²</td>
<td>0.995</td>
<td>0.995</td>
<td>0.996</td>
<td>0.933</td>
<td>0.986</td>
</tr>
<tr>
<td>95% lower CI</td>
<td>0.982</td>
<td>0.978</td>
<td>0.983</td>
<td>0.736</td>
<td>0.940</td>
</tr>
<tr>
<td>95% upper CI</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
<td>0.984</td>
<td>0.997</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Conclusion

For enumeration of CD4+ T cells by the Simu POC CD4 System, the method has been demonstrated to be linear with a minimal $R^2$ of 0.99 within the tested assay range 10–2000 CD4+ T cells/µL.

7.1.2.6. Validation of assay cut-off

This is a quantitative measurement assay. Not applicable for CD4 testing. Analytical sensitivity of Simu POC CD4 System is described in Section 7.1.2.2.
7.2. Stability (excluding specimen stability)

Stability studies were performed per SOP XXX Reagent Stability Program. A summary of the claimed shelf life is given in the conclusion section of the accelerated studies (7.2.1.1) and the real-time stability studies (7.2.1.2) for the Simu POC CD4 System Cartridges.

Similar studies as those described below should be performed for the Simu POC CD4 System Control Cells.

7.2.1 Claimed Shelf-Life Simu POC CD4 System Cartridges and Simu POC CD4 System Control Cells.

Accelerated and preliminary real-time stability studies and stress tests were performed with Simu POC CD4 System Cartridges and Simu POC CD4 System Control Cells in order to determine shelf-life, storage and transport conditions. As a result, the shelf-life of Simu POC CD4 System Cartridges is 9 months whereas the Simu POC CD4 System Control Cells can be used for at least 6 months (recommended temperature range for long-term storage of these test cartridges is 2–40°C).

7.2.1.1 Accelerated Stability Study of Simu POC CD4 System Cartridges.

Study Summary Report: Accelerated Stability Studies
Full Report: SS XXX – refer ANNEX X.
Study Dates: 4 July 2012–8 September 2012
Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company
Testing: Performed on site, Headquarters.

Study Objective
To make a prediction of the shelf life, safe storing conditions and quality, based on application of the Arrhenius Equation in accordance with the requirements of CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline (2010).

Method
Simu POC CD4 System Cartridges from a single lot were stored at 4 different temperature ranges (2–8°C, 18–28°C, 43–48°C, 58–62°C). At weekly intervals over a period of 10 weeks (planned to continue longer if needed to observe significant product degradation), cartridges stored at each of these temperatures were each tested using 5 different fresh venous whole blood and 5 capillary blood specimens. Each set of specimens collected included specimens within the low cell count range (<350 cells/µL) and above.

CD4+ T cell counts for each sample were measured on the Simu POC CD4 System and on a reference single platform flow cytometer.

Reagents
1 lot of Simu POC CD4 System Cartridges produced under full production conditions using final approved product design.
Statistical Analysis
Use of the Arrhenius Equation by determining an estimate of the reaction constant through calculation of the linear regression. This is then used to estimate the reaction rate for product stored at the normal storage temperature, and from this an estimate of the stability duration.

Results

Results table/s to be inserted here.

Conclusion
The estimated shelf-life of the Simu POC CD4 System Cartridges is 9 months. The recommended temperature range for long-term storage is 2–40°C allowing for a safety interval of approximately 2°C beyond the upper temperature limit.

7.2.1.2 Real-time Stability Study of Simu POC CD4 System Cartridges
Full Report: SS XXX – refer ANNEX X.
Study Dates: 4 July 2012 – ongoing
Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company
Testing: Performed on site, Headquarters.

Overview:
The intention is to follow stability up for at least 36 months. Currently we have follow-up stability data for 9 months.

Three batches were used for real time stability testing at 4 different temperature ranges (2–8°C, 18–28°C, 43–48°C, 58–62°C). The samples represented 9 months of real time dating and were evaluated against a reference which had a 6 month shelf life (current shelf life). Results of the testing and evaluation of the aged versus reference indicated no significant difference for the 3 lower temperature ranges and meets product performance and usage requirements at 9 months of real time dating; as a result a 9 month shelf life was assigned at storage between 2–40°C and a shelf life of 3 months when stored at higher temperatures (43–48°C).

Results

Results table/s to be inserted here.

Conclusion:
The shelf-life of the CD4 cartridges is 9 months when stored between 2–40°C or 3 months when stored at higher temperatures 43–48°C. The recommended temperature range for long-term storage is 2–40°C allowing for a safety interval of approximately 2°C beyond the upper temperature limit. The real-time stability studies will continue until 36 months. The final shelf life will be established after the 3 year stability studies have been completed or sooner if product degradation is observed.
### 7.2.2. In use stability

#### Study Summary Report: In Use Stability
- **Full Report:** SS XXX (refer ANNEX X)
- **Study Dates:** 01 June 2012 – 21 August 2012
- **Conducted by:** A Blog, Research and Development Dept, THE Manufacturing Company
- **Testing:** Performed on site, Headquarters.

#### Study Objective
The study (No. XXX) was designed to determine the *Simu* POC CD4 System Cartridge stability once unsealed according to the CLSI EP05-A2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition* (2004) with the indicated modifications. Measurements were performed after 35, 40, 45, 50, 55, 60 and 90 minutes after breaking the seal.

#### Methodology
Whole blood specimens collected in EDTA tubes and finger-stick specimens from 2 hematologically normal donors (established using Reference Method XXX) were tested with one lot of *Simu* POC CD4 System Cartridges to determine the absolute CD4+ T cell counts over several cartridges in function of the time expired after breaking the seal. Data for cartridges used within 1 minute after breaking the seal were used as reference.

#### Reagents
*SIMU* POC CD4 System Cartridge Lot MPOC-123 Exp 30 December 2012

#### Acceptance Criteria
A deviation of <15 % is considered acceptable. A deviation of >15% will be considered as the end point.

#### Results
Refer Table 7.2.2. The % deviation for whole blood samples was <15% up to 60 minutes and >15% at 90 minutes after breaking the cartridge seals. The opened (unsealed) cartridges are considered to remain stable until 60 min after opening.

#### Conclusion
The in use stability of the unsealed cartridges is 60 minutes.

#### Table 7.2.2. In Use Stability *Simu* POC CD4 System Cartridges

<table>
<thead>
<tr>
<th>Minutes after seal break</th>
<th>Specimen 1</th>
<th>Specimen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MEAN</td>
</tr>
<tr>
<td>35</td>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>245</td>
</tr>
<tr>
<td>45</td>
<td>10</td>
<td>247</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>245</td>
</tr>
<tr>
<td>55</td>
<td>10</td>
<td>235</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>225</td>
</tr>
<tr>
<td>90</td>
<td>10</td>
<td>200</td>
</tr>
</tbody>
</table>
7.2.2.2 In Use Stability Study of Simu POC CD4 System Control Cells

Study Summary Report: In Use Stability of the Simu POC CD4 Control Cells

Full Report: SS XXX (refer ANNEX X)

Study Dates: 01 June 2012 – 01 December 2012

Conducted by: A Blog, Research and Development Dept, THE Manufacturing Company

Testing: Performed on site, Headquarters.

Study Objective

The study (No. XXX) was designed to simulate the use of Simu POC CD4 System Control Cells as routine QC specimens, used on a regular basis. The testing was according to the CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition (2004) with modifications. Several studies were undertaken: First, use of the Simu POC CD4 System Control Cells on a daily basis until all cells are used to simulate high volume usage, and secondly, use of a single opened bottle used on a regular basis over 7 months to represent low volume usage.

Methodology

Study 1: High Volume Usage: 3 bottles each of Count Simu POC CD4 Control Cells (Normal and Low Count), each representing different lots of the control cells, were tested daily according to the Instructions for Use until the control cell bottle was empty.

Study 2: Low Volume Usage (Use over 7 months). For both the Normal and Low Count Simu POC CD4 Control Cells, 3 bottles of control cells, each of a different lot number, were tested according to the Instructions for Use on a weekly basis for a period of 30 weeks.

Additionally, for this study, duplicate set of control cells from the same 3 lot numbers was opened and tested for bacterial contamination at the same intervals as the testing described above.

All reagents are stored between each testing occurrence according to the Instructions for Use.

Reagents

Control Cells: Lot CCPOC-XXX Exp 30 December 2012
Lot CCPOC-XXX Exp 30 March 2013
Lot CCPOC-XXX Exp 30 May 2013

Cartridge: Lot MPOC-XXX Exp 30 May 2013

Acceptance Criteria

A deviation of <15 % from the average value at Time 0 (day of opening bottle). A deviation of >15% was considered as the end point.

Results

Result tables to be inserted here.

Study 1 – results of testing on a daily basis
Study 2 – results of testing (for CD4) over 7 months, and results of microbiological analysis over the 7 month period.
Conclusion
For both studies, the overall %CV was <10% for the Normal count cells and <15% for the Low count
cells respectively, which is within the accepted range (≤15%). No bacterial contamination was
observed when open bottles were used regularly over a period of 7 months. Other possible influences
on aging effects of the Simu POC CD4 System Control Cells were not observed. The in use stability
of the opened Simu POC CD4 System Control Cells is determined to be 6 months.

Other stability studies should be included here, including in the case of the Simu POC CD4
System, stability studies to support the claim made in Section 5.2.3 of the dossier that “the
phosphorescent signal is unchanged over an ambient temperature incubation range of 10–40°C”.

7.2.3. Shipping stability
The following shipping studies, listed in Table 7.2.3, have been performed. Results held on site.

Table 7.2.3 Shipping Studies undertaken in support of the Simu POC CD4 System

<table>
<thead>
<tr>
<th>Document Number</th>
<th>Document Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>ShS-XXX</td>
<td>Shipping Study – Polyethylene Vials</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Shipping Dock Temperature Study</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Shipping Flight Temperature and Pressure Study</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Retrospective Validation of Shipping Conditions</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Package Performance Testing for the Simu POC CD4 System Shipping Container</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Ambient Packaging to withstand Higher/Lower Temperature Shipping Study</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Simu POC CD4 System and Control Cells Shipping Study</td>
</tr>
<tr>
<td>ShS-XXX</td>
<td>Simu POC Reader Packaging Vibration and Shipping Study</td>
</tr>
</tbody>
</table>

7.3. Software verification and validation
Software verification and validation was performed. Reference Software Verification and Validation
in ANNEX X.

TEST Report showing compliance with standard is required here
7.4. Clinical Evidence

For the purposes of this sample dossier, a detailed example with data and statistics, is given for one, representative study. REFER Study 7.4.2.1 Clinical Study Belgium.

All studies in this Section MUST utilise the final version of the developed product and the final approved Instructions for Use.

**Summary:** The accuracy of the *Simu* POC CD4 System to enumerate T-helper cells in venous whole blood and capillary blood is demonstrated in this dossier through the findings of three clinical studies in US, Belgium and Africa, respectively. Sites and specimen types vary to reflect the intended specimen type and a range of intended users and patient populations, in support of claims for intended use in the Instructions for Use.

In conclusion, performance of *Simu* POC CD4 System with both venous and capillary whole blood was shown to be equivalent to the reference method. The compatibility of the *Simu* POC CD4 System with external quality assurance schemes QASI and Streck CD4 Count and Immuno-Trol was demonstrated. An overview of completed clinical performance studies is given in below. Ongoing and planned clinical evaluation studies are summarized.

**7.4.1. Clinical evaluation – Manufacturer**

**Overview:** Clinical Study by the Manufacturer

This is a manufacturer controlled multi-center study designed to assess the accuracy of the *Simu* POC CD4 System to enumerate CD4+ T-cells in whole blood and in capillary blood over the measurement range expected for the intended population. The *Simu* POC CD4 System consists of the *Simu* POC CD4 System Cartridge and *Simu* POC System Reader to identify and determine the absolute counts of mature CD4+ T-lymphocytes in whole blood.

The accuracy of the *Simu* POC CD4 System was assessed by comparing the performance of the *Simu* POC CD4 System with that of 2 different well-established CD4 reference methods. Results from 120 patient specimens were included. Results are summarized in Table XXX. The resultant data obtained by the *Simu* POC CD4 System show a good correlation with the reference methods. The *Simu* POC CD4 System was shown to be compatible with Streck CD4 Count and Immuno-Trol EQAs.

**Conclusion:**

Based on the results of this study THE Manufacturing Company published a Memorandum on 8th December 2013 stating that: “When compared to reference CD4 enumeration assays, the *Simu* POC CD4 System provided accurate CD4 counts in whole blood and capillary blood with no measurable bias. The precision of the *Simu* POC CD4 System was within acceptable limits and comparable to a reference CD4 assay over a range of CD4 counts.”

A manufacturer-controlled multi-center study, designed to assess the accuracy of the *Simu* POC CD4 System to enumerate CD4+ T-cells in whole blood and in capillary blood over the measurement range expected for the intended population, was undertaken in October 2012. Sites were chosen specifically to challenge the validity of the System when used in intended countries of sale, and with operators with various levels of professional training (for example, health care clinic staff, trained laboratory personnel).
7.4.1.1 Agreement (Accuracy) (Independent studies)

1. Study Objective:
The purpose of this study was to demonstrate an agreement of the index test method (the Simu POC CD4 System) to the CD4 reference method (BD FACSCalibur flow cytometer) by using a comparative evaluation of the same specimens with the index test and the reference method.

2. Acceptance Criterion:
The 95% confidence interval (CI) of the mean difference between the index test and reference method must be within 10%.

3. Study Design
The design and analysis for the evaluation are based on recommendations given in the CLSI EP09-A2-IR Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Second Edition (Interim Revision) (2010). System agreement was determined through a comparative evaluation of the same specimens tested in parallel by the two methods. Specimens from HIV positive and negative patients and patients undertaking routine CD4 enumeration and/or immunophenotyping were obtained with Institutional Review Board approval from the National Reference CD4 laboratories in the US, Belgium and Uganda. Each site was required to submit to THE Manufacturing Company all hard copies and electronic data related to the investigation, including case report forms, list mode files (if applicable), and results of daily instrument setup (if applicable). All data from the evaluation studies are retained in the Clinical Operations Department files at THE Manufacturing Company.

The overview of the study design is summarized in the Table 7.4.1.1-A below:

Table 7.4.1.1-A – Study Design Summary

<table>
<thead>
<tr>
<th>Study site XXX</th>
<th></th>
</tr>
</thead>
</table>
| **System Configuration** | **Index Test**: Simu POC CD4 System and Simu Control Cells  
**Reference Method**: BD FACSCalibur flow cytometer with Multiset software with BD Tritest CD3/CD4/CD45 reagents with Trucount absolute count tubes. CD4 absolute count was enumerated with Trucount absolute count beads. |
| **Instrument Setup** | **Reference Method**: BD CaliBRITE 3 Beads using FACSComp software. |
| **Study Controls** | **Index Test**: Simu POC CD4 System Control Cells  
**Reference Method**: BD Multicheck Controls and BD Multi-check CD4 Low control |
| **Specimen Source** | Surplus specimens submitted for routine CD4 enumeration and/or immunophenotyping at tertiary care facilities. |
| **Specimen Collection** | Peripheral blood collected by venipuncture in EDTA tubes. |
| **Specimen Stain** | **Index Test**: Specimen applied to Simu POC CD4 System and 15 minute incubation time observed before reading. All specimens tested within 48 hours of collection.  
**Reference Method**: Specimen stained in duplicate after removal of aliquot for testing with index test. – The second tube is for QC purpose. Specimens stained within 24 hours of venipuncture and analyzed within 24 hours of staining. |
| **Sample Preparation Method** | **Index Test**: As described in the Specimen applied to Simu POC CD4 System IFU, specimen directly applied to the Simu POC CD4 System Cartridge.  
**Reference Method**: Lyse/no-wash |
| **Specimen Count (Reference Method)** | **Reference Method**: Four discrete bins were identified to provide an even distribution of data across the range for CD4. A minimum of 15 and a maximum of 30 specimens were collected per bin, with a target of 25 in each.  
Bin Range of CD4 absolute count  
1 >=50 to <= 250 cells/µL  
2 > 250 to <=750 cells/µL  
3 > 750 to <=1200 cells/µL  
4 > 1200 to <=5000 cells/µL |
After removal of an aliquot for testing with the index test, each specimen was stained in duplicate with BD Tritest CD3/CD4/CD45 reagent in BD Trucount tubes for the reference method according to the manufacturer’s instructions for use. The specimens were then analysed. Specimens were then grouped into Bin Ranges, until target numbers were obtained (refer Table 7.4.1.1-A). Matched unstained aliquots were then tested with the Index test according to the approved instructions for Use. The Simu POC CD4 System’s performance and linearity were confirmed using CD4 Controls. The BD FACSCalibur system was set up for acquisition using BD CaliBRITE setup beads and the Lyse/No-wash setup functionality in BD FACSComp software. The reported CD4 positive cells absolute counts (CD4 counts) were then compared between the Index test (Simu POC CD4 System) and reference method (BD FACSCalibur).

4. Statistical analysis
Statistical analyses were performed based on the recommendations of CLSI EP09-A2-IR.

5. Results and Discussion
All specimens were independently quality controlled. Specimens that did not meet quality control criteria, such as lacking test replicates, or lacking sufficient number of cells collected for analysis, were excluded from the analysis. Results that are “Outside of validated range” of the Reference Method were also excluded. Specimens exceeding the maximum bin requirement in the study protocol were excluded by the order they were acquired at each site. A summary of outcomes for all specimens rejected through the Specimen QC process is provided below in Table 7.4.1.1-B, followed by the mean bias results for the CD4+ absolute count (Table 7.4.1.1-C).

Table 7.4.1.1-B
Accuracy Study Specimen Outcome

<table>
<thead>
<tr>
<th>SPECIMEN ID</th>
<th>REASON FOR REJECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen 45</td>
<td>Blood was exposed to excessive (high) temperatures (&gt;50°C) for 2h</td>
</tr>
</tbody>
</table>

Table 7.4.1.1-C
Agreement (Accuracy) of Simu POC CD4 System to Reference Method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Relative Difference to Reference Method</th>
<th>Acceptance Criteria (95% Confidence)</th>
<th>Results (Pass/Fail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 Count</td>
<td>120</td>
<td>-3.6 (-1.0, 7.6)</td>
<td>Relative ±10%</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Results of the regression analysis for CD4+ absolute count were calculated. Results are provided graphically as regression plots, on which the BD Tritest CD3/CD4/CD45 with and without BD Trucount tubes on FACSCalibur (Reference Method) values are represented on the horizontal (x) axis, and the Simu POC CD4 System (Index test) values are on the vertical (y) axis.

6. Conclusion
The Simu POC CD4 System met the acceptance criteria of Method Comparison study and demonstrated acceptable agreement with the Reference Method.
7.4.1.2 Precision

1. Study Objective
The objective of the precision evaluation was to estimate the performance claims for precision of the Simu POC CD4 System using venous whole blood specimens collected into EDTA. Components of the precision estimates include: within-run, between-run precision, and between-day precision.

2. Acceptance Criterion:
The upper one-sided 95% confidence bound of the within-Device (Simu POC CD4 System Cartridge) precision for the absolute count of CD4+ T-cells shall be ≤15%.

3. Study Design
The design of this study was based on the CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition (2004). The within-run standard deviation (SD) and coefficient of variation (CV), and the Within-device SD and CV of the CD4 absolute count was calculated.

Precision of the CD4 absolute count and CD4 percentage was characterized as follows:
- Three new Simu POC CD4 Systems and three operators were used.
- For each set of duplicate patient specimens acting as CD4 Controls (including those with low counts), one of each set was stained with the CD4 reagents according to the requirements of the reference method.
- Two separate runs per day for a period of 21 days.
- Runs were separated by a minimum of 4 hours in accordance with the guideline.
- Daily quality control testing (using the Simu POC CD4 Control Cells) was performed for the study.
- Instruments and operators were randomized according to a schedule that was generated prior to beginning the study.

Specimen selection followed the recommendation of the CLSI guideline that the “test materials should be selected to simulate the characteristics of the appropriate clinical specimens. Stable pools are preferred when appropriate and possible. When necessary, stable, commercially available, protein-based materials may be used.”

4. Statistical analysis
The statistical analyses for this evaluation was based on the CLSI EP05-A2.

Each control specimen was analyzed separately.

Variance components included the following factors:
- Between-day
- Between-run
- Within-run (if applicable): e.g. not always possible with cartridges

Standard deviations with 95% confidence limits were calculated for the within-run precision and the within-device precision of the CD4 percentages.

Percent CVs with 95% confidence limits were calculated for the within-run precision and the within-device precision.

5. Results and Discussion
The within-device and within-run precision demonstrated by Simu POC CD4 System were reported at both sample concentrations of “Normal Control” and “Low Control” controls, and provided for each
parameter. For each parameter, precision results are summarized and corresponding coefficients of variation are compared to the study acceptance criteria (Table 7.4.1.2).

### Table 7.4.1.2

Precision Parameters – Results Comparison to Acceptance Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV (%)</th>
<th>95% CL</th>
<th>CV (%)</th>
<th>95% CL</th>
<th>Criteria (%)</th>
<th>Pass / Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within Run</td>
<td>4.04</td>
<td>4.77</td>
<td>3.46</td>
<td>4.09</td>
<td>&lt;15%</td>
<td>Pass</td>
</tr>
<tr>
<td>Within Device</td>
<td>4.82</td>
<td>5.44</td>
<td>4.28</td>
<td>4.84</td>
<td>&lt;15%</td>
<td>Pass</td>
</tr>
</tbody>
</table>

The new CD4 System + reagents demonstrate acceptable within-run and within-device precision.

6. Conclusion

The Simu POC CD4 System met acceptance criteria of the precision study and demonstrated acceptable precision performance.

### 7.4.2. Clinical evaluation – Independent studies

A summary of the two independent studies (No. 7.4.2.1 and 7.4.2.2) is given below. Both studies used venous and capillary blood samples from HIV-positive and HIV-negative individuals that were tested on the Simu POC CD4 system versus an accepted reference method for enumeration of CD4 positive T cells.

For a detailed protocol of the study, we refer to the publications of the studies in peer review journals (Journal of Clinical Cytometry Feb 201X and Journal of AIDS July 201X). The independent clinical studies focused on Accuracy and Precision of Measurement.

The above publications should be included for the convenience of the reviewer.

### 7.4.2.1 Clinical Study, Belgium – Summary Report

**Overview:** This is a single-center study designed to assess the diagnostic accuracy and precision of the Simu POC CD4 system to enumerate T-helper cells in capillary whole blood in comparison with an acknowledged state of the art reference method.

**Methods**

**Participants:** Clinical specimens from the outpatient clinic at the Institute of Tropical Medicine (ITM), Antwerp were collected during routine care for determination of CD4 T cells to monitor immune status in HIV infected patients. 105 HIV-positive patients were recruited from this clinic for the study. In addition, 50 HIV-negative patients were recruited from the Belgium Blood Bank. For each patient recruited, 2 specimens were simultaneously collected: venous whole blood collected into EDTA (for use with the reference method) and whole blood collected by fingerstick (for use with the index test).
**Test Methods:**

- To assess accuracy, all fingerstick whole blood specimens were tested using the *Simu* POC CD4 System. The results were compared with those obtained when the venous whole blood specimens were tested on the accepted reference instrument (BD FACSCalibur) flow cytometer.
- Reference method: The BD FACSCalibur flow cytometer was used with the BD CD3-FITC/CD4-PE/CD45-PerCP reagents with TruCOUNT Tubes, and MultiSET software (all from Becton Dickinson). The BD FACSCalibur was chosen due to its proven performance (reference to literature studies, EQAS results) which is why it is considered a gold standard method for CD4-T cell enumeration at ITM.
- Use of the methods was according to the respective instructions for use (IFU). Specimens were stored and tested according to each IFU.
- The CD4 index and CD4 reference tests were performed by different operators and results were not linked to specimen HIV status until data analysis.
- A single lot number of *Simu* POC CD4 System Cartridges was used (*Simu* POC CD4 System Cartridge Lot MPOC-1208 Exp 30 August 2012).
- To assess precision of the *Simu* POC CD4 System, 10 repeat measurements were made on 6 specimens representative for the following CD4+ cell count ranges: 0–200, 200–350, 350–500, and (BD FACSCalibur and *Simu* POC CD4 System).

**Results**

Patients were recruited and testing undertaken between April and May 2012. Measurements on *Simu* POC CD4 System and on BD FACSCalibur were performed on all specimens. All data generated from five HIV-positive patients were excluded from the analysis because specimens from these patients were not measured correctly on the *Simu* POC CD4 System (not read within 20 minutes as required). Data from the remaining 150 patients were included in the analysis.

**Performance Characteristics:**

**Trueness**

The results obtained from 100 HIV-positive and 50 HIV-negative individuals when tested by the *Simu* POC CD4 System and the reference method were compared using Passing-Bablok regression analysis. Results are described in **Figure 7.4.2.1-A** and **Table 7.4.2.1-A**. The Pearson correlation coefficient (95%CI) between the two measures was 0.97 (0.96 to 0.98).

**Figure 7.4.2.1-A**

Scatter Plot with Passing and Bablok Fit
Table 7.4.2.1-A
Passing & Bablok regression statistics

<table>
<thead>
<tr>
<th>N 150</th>
<th>Slope (95%CI)</th>
<th>1.023 (0.99 to 1.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept (95%CI)</td>
<td>-13 (-23 to -6)</td>
</tr>
<tr>
<td></td>
<td>Range x</td>
<td>2 to 1607</td>
</tr>
<tr>
<td></td>
<td>Range y</td>
<td>1 to 1543</td>
</tr>
</tbody>
</table>

Bland-Altman difference analysis (*Simu POC CD4 System vs BD FACSCalibur*) was also performed on the data and the results are shown in Figure 7.4.2.1-B and Table 7.4.2.1-B.

The mean bias (95% CI) across all 150 samples was -8 (-55 to +39) % which is not statistically significantly different from zero.

Figure 7.4.2.1-B
Bland-Altman difference analysis (*Simu POC CD4 System – BD FACSCalibur*)

Table 7.4.2.1-B
Distribution of Bias (*Simu POC CD4 System – Reference Method*) within Cell Count Ranges – Capillary Blood comparison.

<table>
<thead>
<tr>
<th>Range (cells/μL)</th>
<th>Entire Range</th>
<th>50–350</th>
<th>&gt;350</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>150</td>
<td>56</td>
<td>82</td>
</tr>
<tr>
<td>Mean Bias (%)</td>
<td>-8</td>
<td>-8.4</td>
<td>-0.1</td>
</tr>
<tr>
<td>95% lower CI</td>
<td>-55</td>
<td>-41</td>
<td>-21</td>
</tr>
<tr>
<td>95% upper CI</td>
<td>+39</td>
<td>+24</td>
<td>+21</td>
</tr>
</tbody>
</table>
Clinical Agreement

Clinical agreement between the methods was assessed at three different treatment decision points by computing a two-by-two contingency table. The results are illustrated in Table 7.4.2.1-C for the three decision points of 200 cells/μL, 350 cells/μL and 500 cells/μL, respectively. The agreement between the patient classification by the 2 systems was assessed using the inter-rater Kappa test. (Very good = 0.8–1; good = 0.6–0.8; moderate = 0.4–0.6). The discordance between the methods at each treatment decision point was assessed for differences in proportions using McNemar tests that show no statistically significant bias about the cutoffs. Sensitivity and specificity of the SimuPOC CD4 System to identify patients below the reference CD4 cutoff is given too and indicates that the performance of the SimuPOC CD4 System is excellent (>90%) at the cut-offs <200 cells/μL and <350 cells/μL and slightly less at <500 cells/μL (specificity <90%).

Table 7.4.2.1-C
Clinical Agreement using Capillary Blood (Fingerstick) at treatment decision points of 200, 350 and 500 CD4+ T-cells/μL

<table>
<thead>
<tr>
<th>Comparison about Cutoff &gt; 200 CD4+ T-cells/μL</th>
<th>Value</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement (Kappa)</td>
<td>0.87</td>
<td>0.74</td>
<td>1</td>
</tr>
<tr>
<td>CD4 Reference pos</td>
<td>29</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CD4 Reference neg</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2-sided McNemar test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94%</td>
<td>79%</td>
<td>99%</td>
</tr>
<tr>
<td>Specificity</td>
<td>95%</td>
<td>74%</td>
<td>99%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison about Cutoff &gt; 350 CD4+ T-cells/μL</th>
<th>Value</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement</td>
<td>0.95</td>
<td>0.87</td>
<td>1.02</td>
</tr>
<tr>
<td>CD4 Reference Pos</td>
<td>29</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CD4 Reference Neg</td>
<td>1</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>2-sided McNemar test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97%</td>
<td>83%</td>
<td>99%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
<td>89%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison about Cutoff &gt; 500 CD4+ T-cells/μL</th>
<th>Value</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement</td>
<td>0.81</td>
<td>0.70</td>
<td>0.92</td>
</tr>
<tr>
<td>CD4 Reference Pos</td>
<td>35</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CD4 Reference Neg</td>
<td>5</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2-sided McNemar test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88%</td>
<td>73%</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94%</td>
<td>86%</td>
<td>97%</td>
</tr>
</tbody>
</table>
WHO Prequalification - Sample Dossier

Precision
In total, 60 tests were performed on 6 samples to establish the precision of the method. All results were valid, none requiring exclusion. The results of within-method standard deviation and %CV of the Simu POC CD4 System measurements are illustrated in Table 7.4.2.1-D. MEAN is the mean of all replicate measurements within each range, SD is the root-mean-square of the standard deviations of the replicate measurements within each range (together with its 95% CI), and %CV is 100 times the SD divided by the MEAN.

Table 7.4.2.1-D
Precision Analysis based on replicate measurements

<table>
<thead>
<tr>
<th>Method</th>
<th>Range (cells/μL)</th>
<th>N</th>
<th>MEAN (cells/μL)</th>
<th>SD (cells/μL)</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simu POC CD4 System</td>
<td>&lt;200</td>
<td>10</td>
<td>50</td>
<td>7</td>
<td>40</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>Simu POC CD4 System</td>
<td>&lt;200</td>
<td>10</td>
<td>150</td>
<td>23</td>
<td>110</td>
<td>190</td>
<td>15</td>
</tr>
<tr>
<td>Simu POC CD4 System</td>
<td>200–350</td>
<td>10</td>
<td>250</td>
<td>35</td>
<td>200</td>
<td>300</td>
<td>14</td>
</tr>
<tr>
<td>Simu POC CD4 System</td>
<td>200–350</td>
<td>10</td>
<td>340</td>
<td>50</td>
<td>250</td>
<td>420</td>
<td>15</td>
</tr>
<tr>
<td>Simu POC CD4 System</td>
<td>350–500</td>
<td>10</td>
<td>410</td>
<td>50</td>
<td>400</td>
<td>500</td>
<td>12</td>
</tr>
<tr>
<td>Simu POC CD4 System</td>
<td>350–500</td>
<td>10</td>
<td>490</td>
<td>70</td>
<td>400</td>
<td>570</td>
<td>14</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>&lt;200</td>
<td>10</td>
<td>60</td>
<td>7</td>
<td>10</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>&lt;200</td>
<td>10</td>
<td>135</td>
<td>18</td>
<td>40</td>
<td>75</td>
<td>13</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>200–350</td>
<td>10</td>
<td>220</td>
<td>31</td>
<td>150</td>
<td>280</td>
<td>14</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>200–350</td>
<td>10</td>
<td>310</td>
<td>45</td>
<td>220</td>
<td>400</td>
<td>15</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>350–500</td>
<td>10</td>
<td>360</td>
<td>40</td>
<td>230</td>
<td>420</td>
<td>11</td>
</tr>
<tr>
<td>Reference Standard</td>
<td>350–500</td>
<td>10</td>
<td>470</td>
<td>48</td>
<td>380</td>
<td>590</td>
<td>10</td>
</tr>
</tbody>
</table>

Conclusion
Data from this study show that the performance of the Simu POC CD4 System satisfied the performance of criteria and is also equivalent to that of the CD4 reference methods when fingerstick specimens are used.

Conflict of Interest
This study was conducted using Simu POC CD4 system provided free of charge to the investigators. However, records are available that confirm the non-interference or influence in the testing and subsequent analysis and publishing by THE Manufacturing Company.

7.4.2.2 Clinical Study, Uganda Africa – Summary Report

Overview
The accuracy of the Simu POC CD4 System to measure absolute CD4+ T-cell counts was assessed by comparison to the cell counts measured with the BD FACSCalibur system as the CD4 reference method. The testing was performed at a busy health clinic in Uganda. Capillary and patient-matched venous whole blood specimens collected in EDTA venipuncture tubes were used.

Study Population
Matched capillary blood and venous whole blood samples collected in EDTA, from 149 HIV-positive individuals presenting to a health care facility in Entebbe, Uganda were collected and analyzed in duplicate using the Simu POC CD4 system and in the reference standard (single measurement).
Test Methods
Staff using the index test were trained in basic laboratory skills, including venous blood collection. Simu training was conducted by the principle investigators who had been trained with the IFU and the job aid, by the Ugandan representative for THE Manufacturing Company. Testing of the index test occurred after collection, but specimens were batch tested using the reference method. Results of either test were not matched until time of result correlation and analysis.

Reagents and Instruments

Identify all reagent lot numbers and instruments here.

Statistical Analysis
Correlation of the methods was calculated using two statistical formulae: the Passing-Bablok regression and the Pearson correlation coefficient.

Results
The results of the Passing-Bablok regression are illustrated in Figure 7.XXX and Table 7.XXX. (Results were expressed as per example Tables XXX above). The Pearson correlation coefficient (95%CI) between the two measures was 0.96 (0.94 to 0.97).

Figure 7.XXX: Simu POC CD4 System accuracy analysis: Passing&Bablok regression analysis.
Table 7.XXX: Passing&Bablok regression statistics
Figure 7.XXX: Bland-Altman difference analysis (Simu POC CD4 System – BD FACSCalibur).
Table 7.XXX: Distribution of Bias

Clinical Agreement:
Clinical agreement between the methods was assessed about a diagnostic cutoff by computing a two-by-two contingency table. The results are illustrated in Table 7.xx below for three diagnostic cutoffs, 200 cells/μL, 350 cells/μL and 500 cells/μL, respectively.

Discordance between the methods at each diagnostic cutoff was assessed for bias using a McNemar test and the bias was shown to be insignificant.

Table 7.XXX: Clinical Agreement about cutoffs 200, 350 and 500 cells/μL

Insert table/s here
Insert figure/s here
Precision
The within method standard deviation and %CV of the Simu POC CD4 System measurements was calculated based on repeat measurements made on all 5 samples and for subsets of samples in the cell count ranges of <200, <350, <500 and overall, as illustrated in Table 7.XXX. MEAN is the mean of all replicate measurements within each range, SD is the root-mean-square of the standard deviations of the duplicate measurements within each range (together with its 95% CI), and %CV is 100 times the SD divided by the MEAN.

Table 7.XXX: Precision Analysis based on duplicate measurements

| Insert table here |

Errors:
From the total 304 measurements (venous and capillary blood) with Simu POC CD4 system, 4.3% (n=13) delivered an error message. No further testing was possible to further explore reasons for the errors (e.g. further training required).

Conclusion
Data from this study show that the performance of Simu POC CD4 system is equivalent to that of CD4 reference standard when venous whole blood specimens (EDTA anticoagulant) are used.

Conflict of Interest
This study was conducted using Simu POC CD4 System provided free of charge to the investigators. However, records are available that confirm the non-interference or influence in the testing and subsequent freedom from conflict of interest of the study investigators.
8. LABELLING

8.1 Labels

Figure 8.1 below depicts the convention of terms for the front-view of a Simu POC CD4 System box containing the Simu POC CD4 cartridges.

Next, the requirements with regard to materials, design and labeling are listed.

Orientation:

Figure 8.1: Front view of the Simu POC CD4 System box used to package the cartridges.

Material
• Type of cardboard: standard “folding cardboard” internally reinforced with corrugated cardboard.
• Water resistant by lamination.
• Closing system: by folding and a sticker to avoid tampering of the box. No information is printed on the tape/sticker itself, since it becomes unreadable when the tape/sticker is broken.

Design
• Dimensions: \( L = 18 \text{ cm}, W = 12.5 \text{ cm}, H = 7 \text{ cm} \) (100 Test Cartridge Pack).

Labeling
• Only internationally recognized symbols are used (ISO 15223-1:2012).
• Well-fixed water-resistant label (applied with water resistant glue) and permanent printing are utilized.
• Temperature tags included on the box. This allows THE Manufacturing Company to monitor shipments and storage as well as to trace and remediate errors.
**Figure 8.2** label fixed to the top side of the box.
- Please note, that the labelling for the larger kit size (250 test cartridge pack) is in all cases identical except for the Product Code reference, being X1235-ROW.

**Figure 8.2. Label for top side of the box.**

<table>
<thead>
<tr>
<th>IVD</th>
<th>Simu POC CD4 System</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑️</td>
<td>X1234-ROW 100 Test Cartridge Pack</td>
</tr>
</tbody>
</table>

**Rapid point of care testing for the enumeration of CD4 cells in whole blood.**

<table>
<thead>
<tr>
<th>LOT</th>
<th>YYYYY-MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>🕒</td>
<td>☑️</td>
</tr>
</tbody>
</table>

**Temperature tag to be placed here**

The Manufacturing Company 987 Somewhere Street, Somewhere in Europe EU-1234

For Technical Support please contact your local distributor or call Europe: +99.1234.5678-999, Africa: +27.12.34.56.78, or email: enquiries@themanufacturingcompany.com

**Figure 8.3: Labeling of right and left lateral sides, and the front of the box.**

<table>
<thead>
<tr>
<th>The Manufacturing Company Simu POC CD4 System</th>
</tr>
</thead>
<tbody>
<tr>
<td>REF X1234-ROW (100 Test Cartridge Pack)</td>
</tr>
</tbody>
</table>

**Rapid point of care testing for the enumeration of CD4 cells in whole blood.**

<table>
<thead>
<tr>
<th>Content</th>
<th>Simu POC CD4 System: Cartridges Instructions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>🕒</td>
<td>☑️</td>
</tr>
</tbody>
</table>

**Needed but not provided**

Simu POC Reader Gloves Sharps container Specimen collection devices and specimen transfer devices

<table>
<thead>
<tr>
<th>LOT</th>
<th>YYYYY-MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>🕒</td>
<td>☑️</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature tag</th>
<th>2°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑️</td>
<td>🕒</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature tag</th>
<th>40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑️</td>
<td>🕒</td>
</tr>
</tbody>
</table>
Simu POC CD4 System Cartridge - Sealed Packaging (Figure 8.4)

Material
- Waterproof material is used.
- An indentation is present to allow easy opening of the device packaging without the need for scissors.

Labeling

Figure 8.4 Simu POC CD4 System Cartridge - Sealed Packaging

8.2 Instructions for use
The Intended Use section explains that the Simu POC CD4 System is a quantitative in vitro assay for enumeration of CD4+ T-cells in whole blood. Results are automatically calculated and can be printed, stored or transmitted via a USB portal or the wireless transmitter. The System has been designed for use in all health care settings including point of care, with testing to be performed by health care workers only. The assay is intended as an aid to management of patients with pre-diagnosed HIV infection. The CD4 cell count is utilized in the determination of ART initiation and monitoring therapeutic response. It can also be used to determine the need for prophylaxis for opportunistic infections. The Simu POC CD4 System is validated for use on capillary or venous whole blood collected into EDTA. It has not been validated for use in children less than six years of age.

The Test Principle section describes the immunophosphorescent method for the enumeration of CD4 cells. A dual monoclonal antibody system is housed in the Simu POC CD4 System Cartridge. These detect markers on the surface of CD4 cell populations in the whole blood specimen. One of the monoclonal antibodies binds to T-cells. The other monoclonal antibody is labelled with reagents that phosphoresce when the antibody binds to the CD4 protein but only when both monoclonal antibodies are bound to the same cell. The technology ensures that only one labelled monoclonal antibody can bind to any one CD4 cell. Thus the degree of phosphorescence is relative to the number of CD4+ T cells present in the specimen.

The Package Contents and Storage section lists the materials provided and required. Each Simu POC CD4 System box contains: Individually pouching Simu POC CD4 Cartridges with humidity indicator, (100 tests Product Code X1234-ROW or 250 tests Product Code X1235-ROW). Instructions for Use with Job Aid. Store at 2–40 °C until date of expiry.

The Warning for Users section includes safety precautions for users, such as for in vitro diagnostic use, professional use only, use of the assay with specimens other than specifically nominated may result in inaccurate test results, single use cartridge only, open cartridge immediately before use, wear protective clothing, including lab coat, eye/face protection and disposable gloves while handling assay and clinical specimens, wash hands thoroughly after performing the test, do not pipette by mouth, patient specimens may contain infectious agents, handle with caution, dispose of all sharps (needles, lancets) in a sharps hazard container, and dispose of all wastes in accordance with all local, regional and rational regulations.
Precautions
- Do not open the foil pouch containing the cartridge until ready to proceed.
- Do not use the cartridge if the humidity indicator shows any purple colouring.
- Do not use cartridges if the foil pouch has been damaged.
- Do not use cartridges beyond the expiration date printed on the pouch label.

Specimen Collection, Preparation and Storage
- Only venous whole blood collected into EDTA coated tubes, as well as finger stick collected blood, have been evaluated and found to give acceptable results.
- No clinically significant effect has been detected in assay results of specimens with increased levels of protein, lipids or bilirubin.
- Do not use grossly haemolysed specimens.
- Do not use clotted specimens.
- Ensure that there is clear identification and traceability of the patient specimen throughout the testing process.

Whole Blood Collection By Fingerstick
1. Prepare patient for fingerstick specimen collection.
2. The best locations for fingersticks are the 3rd and 4th fingers of the non-dominant hand. Do not use the tip of the finger or the centre of the finger pad. Avoid the side of the finger where there is less soft tissue, where vessels and nerves are located, and where the bone is closer to the surface. The 2nd (index) finger tends to have thicker, calloused skin. The fifth finger tends to have less soft tissue overlying the bone. Avoid puncturing a finger that is cold or cyanotic, swollen, scarred, or covered with a rash. Avoid fingers with rings on.
3. Warm up the fingers if needed. Have the patient hold their hand downwards to increase blood flow to the finger.
4. Wipe the tip of the appropriately selected finger with an alcohol swab and let the alcohol air dry.
5. Remove one Simu POC CD4 System Cartridge from its foil pouch.
6. Use a sterile lancet to make a skin puncture just off the center of the finger pad. The puncture should be made perpendicular to the ridges of the fingerprint so that the drop of blood does not run down the ridges. It is important to press the lancet firmly onto the finger and maintain contact while ejecting the lancet. Do not squeeze or apply strong repetitive pressure (milking) to the site; this may result in hemolysis or tissue-fluid contamination of the specimen. If necessary, gentle massaging of the finger may be conducted in order to ensure a steady blood flow.
7. Wipe off the first drop of blood with a dry cloth or gauze. Ensure steady blood flow that generates large enough drops of blood. If necessary, wipe off another drop, until blood flows freely.
8. Hold the fingertip and blood drop facing downward.
9. Collect blood in the specimen transfer device and transfer directly into the specimen collection slot in the Simu POC CD4 System Cartridge.
10. Insert the loaded cartridge into the Simu POC System Reader and ensure it is activated (a message will appear). Follow the instructions on the screen.

Whole Blood Collection By Venipuncture
1. Collect blood aseptically by venipuncture into a sterile EDTA (ethylenediaminetetraacetic acid) blood collection tube.
2. Collect the specimen according to the instructions provided by the manufacturer to avoid improper dilution.
3. Invert collection tube 8–10 times.
4. Use a specimen transfer device to apply blood specimen into the specimen slot of the Simu POC CD4 System Cartridge.
5. Continue as described from point 10 of the previous section.

Quality Control – Validation of Results
System validation: The stability of the Simu POC CD4 System can be validated by routine use of the Simu POC CD4 System Control Cells. Expected ranges are recorded on the labels of each batch of Control Cells.

Built-in Quality Control Features
The Simu POC CD4 System Cartridge contains built-in control features to check Simu POC System Reader and reagent functionality. The following checks are performed automatically once the cartridge is inserted into the Simu POC System Reader:

Expiry date: The linear barcode on the Simu POC CD4 Cartridge contains expiry
Specimen volume: The Simu POC System Reader records whether sufficient specimen has been loaded onto the Simu POC CD4 System Cartridge. If insufficient specimen has been loaded onto the test cartridge the analysis will not start and the cartridge must be rejected. A fresh specimen must be collected and a new cartridge used.

Interpretation of Results

Reference Range

Studies performed by THE Manufacturing Company on healthy adults in Europe and in Africa indicate the following reference range for the Simu POC CD4 System.

Absolute CD4 95% Reference Range 360–1959 cells/µL (Mean = 875.36, n = 485).

According to the 2013 WHO HIV treatment Guidelines "Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendation for a Public Health Approach. June 2013", as a priority, ART should be initiated in the following instances, based on the CD4 count.1

In Adults and Adolescents

- in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³.
- ART should be initiated in all individuals with HIV with CD4 count >350 cells/mm³ and ≤500 cells/mm³ regardless of WHO clinical stage.

Clinical Agreement

Clinical agreement between The Simu POC CD4 System and the Reference Method was assessed at three different treatment decision points. The agreement between the patient classification by the 2 systems was assessed using the inter-rater Kappa test. (Very good = 0.8–1; good = 0.6–0.8; moderate = 0.4–0.6). The discordance between the methods at each treatment decision point was assessed for differences in proportions using McNemar tests that show no statistically significant bias about the cutoffs. Sensitivity and specificity of the Simu POC CD4 System to identify patients below the reference CD4 cutoff indicates that the performance of the Simu POC CD4 System is >90% at the cut-offs <200 cells/µL and <350 cells/µL and slightly less at <500 cells/µL (specificity <90%).

Trueness

The results obtained from 100 HIV-positive and 50 HIV-negative individuals when tested by the Simu POC CD4 System and the reference method were compared using Passing-Bablok regression analysis. Results are described in Figure 1 and Table 1. The Pearson correlation coefficient (95%CI) between the two measures was 0.97 (0.96 to 0.98).

The mean bias (95% CI) across all 150 samples was -8 (-55 to +39) cells/µL which is not statistically significantly different from zero.

Performance Characteristics

Performance of the Simu POC CD4 System was established at THE Manufacturing Company, Europe, and in Belgium, the US and Africa.

Limitations

1. The results of a Simu POC CD4 System should be evaluated in the context of all the clinical and laboratory data available. In those instances where the laboratory results do not agree with the clinical evaluation, additional tests should be performed accordingly.

2. The Simu POC CD4 System has been evaluated with capillary whole blood and venous whole blood using EDTA as anti-coagulant. Serum, plasma and whole blood obtained using other anti-coagulants have not been evaluated and should not be used.

3. Absolute CD4 T cell counts may differ between laboratories using different manufacturer’s equipment.

4. Product performance has not been established on subjects undergoing monoclonal antibody chemotherapy.

Trueness

The results obtained from 100 HIV-positive and 50 HIV-negative individuals when tested by the Simu POC CD4 System and the reference method were compared using Passing-Bablok regression analysis. Results are described in Figure 1 and Table 1. The Pearson correlation coefficient (95% CI) between the two measures was 0.97 (0.96 to 0.98).

The mean bias (95% CI) across all 150 samples was -8 (-55 to +39) cells/µL which is not statistically significantly different from zero.
In total, 60 tests were performed on 6 specimens with differing clinically relevant CD4 counts. The same experiment using the same specimens was repeated with the Reference Method. In all cases the CV for each specimen was not greater than 15% by both methods.

Table 1 Distribution of Bias (Simu POC CD4 system - BD FACSCalibur) within Cell Count Ranges

<table>
<thead>
<tr>
<th>Range (cells/μL)</th>
<th>Entire</th>
<th>0-350</th>
<th>&gt;350</th>
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<tr>
<td>N</td>
<td>150</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>Mean Bias (cells/μL)</td>
<td>-8</td>
<td>-4</td>
<td>-22</td>
</tr>
<tr>
<td>95% lower Cl</td>
<td>-55</td>
<td>-22</td>
<td>-50</td>
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<tr>
<td>95% upper Cl</td>
<td>39</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

References


Symbols

For Technical Support please contact your local distributor or call Europe: +99.1234.5678-999, Africa: +27.12.34.56.78, or email: enquiries@themanufacturingcompany.com


IFU v 04 2013 ROW

1 http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf
How To Do the Simu POC CD4 System
for the enumeration of CD4 cells in whole blood

Collect:
A NEW unopened test packet
B NEW unopened alcohol swab
C NEW unopened lancet
D NEW pair of disposable gloves
E Sharps box
F Marker pen
G Specimen Transfer Device
H SIMU POC Reader

READ THESE INSTRUCTIONS CAREFULLY BEFORE YOU BEGIN.

1. Check the expiry date on the test packet.
2. Put on the gloves. Use new gloves for each patient.
3. Open the packet and remove the Simu POC CD4 Cartridge:
4. Ensure there is no purple colouring in the sachet. Discard Simu POC CD4 Cartridge if any beads have turned purple. DO NOT USE if any beads are purple.
5. Write the patient’s name on the test.
6. Open the alcohol swab. Grasp the 4th finger on the patient’s left hand. Clean the finger with the alcohol swab. Allow the finger to dry before pricking. Keep the hand below the heart level of the patient.
7. Open the lancet. Prick patient’s finger to get a drop of blood. Do not allow the tip of the lancet to touch anything before pricking the patient’s finger.
8. Discard the lancet in the Sharps Box immediately after pricking finger. Do not set the lancet down before discarding it.
9. Use the specimen transfer device to collect the drop of blood. Do not transfer blood directly from the finger tip.
10. Use the specimen transfer device tube to put the drop of blood into the slot marked “A.”
11. Discard the specimen transfer device tube in the Sharps Box.

12. INSERT SIMU POC CD4 CARTRIDGE INTO SIMU POC SYSTEM READER.
This will activate the reader. Follow the instructions on the display.

13. A result will be displayed 15 minutes after insertion of the Cartridge into the Simu POC System Reader. Record results or transmit as required.

14. Dispose of the cartridge, gloves, alcohol, desiccant sachet and packaging in a non-sharps waste container.

Each test can be used ONLY ONE TIME. Do not try to use the test more than once.

Adapted from generic training material produced jointly by the Foundation for Innovative New Diagnostics (FIND) the World Health Organization (WHO), United States Agency for International Development (USAID), University Research Co., LLC (URC), Special Programme for Research and Training in Tropical Diseases (TDR), Malaria Consortium and Zambia National Malaria Control Centre. Support for developing this training manual was provided by the United States Agency for International Development (USAID), the Special Programme for Research and Training in Tropical Diseases (TDR) and the Australian Agency for International Development (AusAID). The materials do not necessarily reflect the views or policies of the initial funding entities or development partners. The initial funding entities does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.
9. COMMERCIAL HISTORY

9.1. Countries of supply

The ROW version of the Simu POC CD4 System has been supplied in South Africa, Nigeria, Kenya and Zambia since late 201X.

A total of 560,000 test kits have been supplied. The price per unit varies between 1.5 USD and 2.5 USD. The majority of units sold have been at the 1.5 USD price. A number of units (approximately 20,000) were donated to Nigeria for performance evaluation.

No formal training programmes have been implemented. The Instruction for Use (IFU) incorporate a Job Aid which can, on request to THE Manufacturing Company, be printed in local language (noting that a fee may apply). The utility of both these instructions have been subjected to intense testing by THE Manufacturer, as part of our risk analysis for instructions to users. The goal was that these instructions would prove sufficient to a range of users with varying skills levels, acknowledging the fact that the product will be used in a variety of settings. A report of this testing is held at Headquarters (refer DOC XXX). Technical support is provided by the local distributor as required.

9.2. Adverse events and field safety corrective actions

No field safety corrective action has been required since any version of the product has been marketed.

A table of adverse event reports is provided below.

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Country of Event</th>
<th>Determined Cause</th>
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</tbody>
</table>
10. REGULATORY HISTORY

The ROW product currently has no regulatory approvals.

The version with CE marking has been supplied since July 2011. As the product is self-certified under the IVD Directive (98/79/EC) no conformity assessment certificates accompany this product. However, a certified copy of the relevant ISO certification is provided for the CE marked version and the ROW version (including Reader and Control Cells) in ANNEX X. Certified copies of the Import Medical Device Registration Certificate, issued by the China Food and Drug Administration, and the Korea Licence Holder Certificate, are also provided in ANNEX X.
11. QUALITY MANAGEMENT SYSTEM

11.1. Quality manual
Refer ANNEX 8

11.2. Quality manual system documents

This subsection is still to be developed by WHO.

11.3. Quality manual system certificates
Refer ANNEX X
## ANNEX 1
### ESSENTIAL PRINCIPLES CHECKLIST

| Check list of Essential Principles of GHTF/SG1/N068 for the Simu CD4 POC System |
|-----------------------------------|-----------------------------------|-----------------------------------|
| Simu POC CD4 System               | THE Manufacturing Company         | Product Codes X1234, X1235, INS 1234 and CONTC 1234 |
| Document version # 02             | Document date:                    |                                   |
| Written by:                       | Approved by:                      | Agreed by:                        |
| signatures date                   | QA                                | R&D                              |
| Signature date                    | date                              | signature date                    |
| Regulatory affairs                | signature date                    | Manufacturing                      |
| Signature date                    | date                              | signature date                    |

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<th>Changes from earlier versions:</th>
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<th>Modification</th>
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<td>Modification</td>
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<tr>
<td>02</td>
<td>Date 2011 09 15</td>
<td>B C 3.1</td>
</tr>
<tr>
<td>03</td>
<td>Date 2011 09 15</td>
<td>B A1</td>
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Please Note. The checklist submitted to WHO must include dates and signatures.
<table>
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<tr>
<th>Essential Principles</th>
<th>Applicable/Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
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<tbody>
<tr>
<td><strong>A. GENERAL PRINCIPLES</strong></td>
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<tr>
<td>**A.1 Medical devices should be designed and manufactured in such a way that, when</td>
<td>A</td>
<td>Application of recognised Standards:</td>
<td></td>
</tr>
<tr>
<td>used under the conditions and for the purposes intended and, where applicable, by</td>
<td></td>
<td>- ISO 13485:2003 Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes.</td>
<td>ISO 13485 certificate held by QA department section,</td>
</tr>
<tr>
<td>virtue of the technical knowledge, experience, education or training and the</td>
<td></td>
<td>- ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>certificed copy submitted for section 11.3 of this dossier.</td>
</tr>
<tr>
<td>medical and physical conditions of intended users, they will perform as intended by</td>
<td></td>
<td>- EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic medical devices.</td>
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<tr>
<td>the manufacturer and not compromise the clinical condition or the safety of patients,</td>
<td></td>
<td>- IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment</td>
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<td>or, where applicable, other persons, provided that any risks which may be</td>
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<td>associated with their use constitute acceptable risks when weighed against the</td>
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<td>benefits to the patient and are compatible with a high level of protection of health</td>
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<td>and safety.</td>
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<td>**A.2 The solutions adopted by the manufacturer for the design and manufacture of</td>
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<td>Application of recognised Standards:</td>
<td></td>
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<tr>
<td>the devices should conform to safety principles, taking account of the generally</td>
<td></td>
<td>- ISO 13485:2003 Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes.</td>
<td></td>
</tr>
<tr>
<td>acknowledged state of the art. When risk reduction is required, the manufacturer</td>
<td></td>
<td>- ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td></td>
</tr>
<tr>
<td>should control the risks so that the residual risk associated with each hazard is</td>
<td></td>
<td>- ISO 18113:2009 In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) – Parts 1,</td>
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<tr>
<td>judged acceptable. The manufacturer should apply the following principles in the</td>
<td></td>
<td>2 and 3.</td>
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<td>priority order listed:</td>
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<tr>
<td>- identify known or foreseeable hazards and estimate the associated risks arising</td>
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<td>from the intended use and foreseeable misuse;</td>
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<td>- eliminate risks as far as reasonably practicable through inherently safe design</td>
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<td>and manufacture;</td>
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<td>- reduce as far as reasonably practicable the remaining risks by taking adequate</td>
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<td>protection measures, including alarms; and</td>
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<tr>
<td>- inform users of any residual risks.</td>
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</tr>
</tbody>
</table>
## Essential Principles Checklist

### THE Manufacturing Company

<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
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<tbody>
<tr>
<td>A.3</td>
<td>A</td>
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<td>• Risk management policy document &quot;Policy XXX&quot; and risk analysis SOPs &quot;SOP XXX&quot; &quot;SOP XXXX&quot; held by QM Department.</td>
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<tr>
<td></td>
<td></td>
<td>Verification and Validation Studies</td>
<td>• Risk analysis output documents &quot;Simu POC CD4-risk-design&quot;; &quot;Simu POC CD4 risk - processes&quot;, &quot;Simu POC CD4 risk-users&quot;.</td>
</tr>
<tr>
<td></td>
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<td>• Section 7 ISO 13485:2003 Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes.</td>
<td>• &quot;Simu POC CD4 System Risk Management and Control Report&quot; held by QA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>• All verification and validation studies (refer Section 7 of this dossier).</td>
</tr>
<tr>
<td></td>
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<td>• EN 13612:2002 Performance evaluation of in vitro diagnostic medical devices.</td>
<td>• Traceability of Simu POC CD4 Control Cells.</td>
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<td>• GHTF/SGS/N8:2012 Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices.</td>
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<tr>
<td>A4</td>
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<td>Application of recognised standards.</td>
<td>• All verification and validation studies (refer Section 7 of this dossier) including Stability studies (Section 7.2).</td>
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<tr>
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<td></td>
<td>Stability and (user) Validation Studies</td>
<td>• Risk management policy document &quot;Policy XXX&quot; and risk analysis SOPs &quot;SOP XXX&quot; &quot;SOP XXXX&quot; held by QM Department.</td>
</tr>
<tr>
<td></td>
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<td>• ISO 18113:2009 In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) – Parts 1 and 2.</td>
<td>• Risk analysis output documents &quot;Simu POC CD4-risk-design&quot;; &quot;Simu POC CD4 risk - processes&quot;, &quot;Simu POC CD4 risk-users&quot;.</td>
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<td>• ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>• &quot;Simu POC CD4 System Risk Management and Control Report&quot; held by QA.</td>
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<tr>
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<td>A</td>
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<td>Stability Studies</td>
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<td>• ISO 18113:2009 In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) – Parts 1 and 2.</td>
<td>• Risk analysis output documents &quot;Simu POC CD4-risk-design&quot;; &quot;Simu POC CD4 risk - processes&quot;, &quot;Simu POC CD4 risk-users&quot;.</td>
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<td>• ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>• &quot;Simu POC CD4 System Risk Management and Control Report&quot; held by QA.</td>
</tr>
</tbody>
</table>

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**Simu CD4 POC System**

**Product Codes.** X1234, X1235, INS 1234 and CONTC 1234

**Application of recognised standards.**

**Stability Studies**

- ISO 18113:2009 In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) – Parts 1 and 2.

**Verification and Validation Studies**

- GHTF/SGS/N8:2012 Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices.

**Stability and (user) Validation Studies**

- ISO 18113:2009 In vitro diagnostic medical devices – Information supplied by the manufacturer (labeling) – Parts 1 and 2.
<table>
<thead>
<tr>
<th>THE Manufacturing Company</th>
<th>Simu CD4 POC System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential Principles</strong></td>
<td><strong>Product Codes.</strong> X1234, X1235, INS 1234 and CONTC 1234</td>
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</tbody>
</table>

<p>| <strong>A6</strong> | All known and foreseeable risks, and any undesirable effects, should be minimised and be acceptable when weighed against the benefits of the intended performance of medical devices during normal conditions of use. |</p>
<table>
<thead>
<tr>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
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<td>• GHTF/S65/N8:2012 Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices.</td>
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<tr>
<td>• ISO 14971:2007 Medical devices — Application of risk management to medical devices.</td>
<td>• Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”.</td>
</tr>
<tr>
<td>• Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
<td></td>
</tr>
</tbody>
</table>

| **C** | DESIGN AND MANUFACTURING PRINCIPLES |
| **C1** | Chemical, physical and biological properties |

| **C1.1** | The IVD medical devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Section A. Particular attention should be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens and/or analyte (measurand) to be detected (such as biological tissues, cells, body fluids and micro-organisms), taking account of its intended purpose. |
| **Method(s)** | Application of recognised standards. |
| **Reference to Supporting Controlled Documents** | Verification and Validation Studies |
| **Section 7 of this dossier** | • All verification studies (refer Section 7 of this dossier) |
| • ISO 14971:2007 Medical devices — Application of risk management to medical devices. | • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. |
| • ISO 18113:2009 In vitro diagnostic medical devices — Information supplied by the manufacturer (labeling) – Parts 1 and 2. | • ”Simu POC CD4 System Risk Management and Control Report” held by QA. |
| • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. | • Simu POC CD4 System Instructions for Use ("Warnings for Users", "Specimen Collection, Preparation and Storage"). |

| **C1.2** | The IVD medical devices should be designed, manufactured and packaged in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the device. |
| **Method(s)** | Application of recognised standards. |
| **Reference to Supporting Controlled Documents** | • ISO 14971:2007 Medical devices — Application of risk management to medical devices. |
| • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. | • Simu POC CD4 System Risk Management and Control Report” held by QA. |
| • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. | • Packing and Shipping SOP XXX. |
| • Simu POC CD4 Cartridge Robustness Studies (held on site). | • Simu POC CD4 System Risk Management and Control Report” held by QA. |
| • Package Robustness Studies (held on site). | • Simu POC CD4 Cartridge Robustness Studies (held on site). |

| **C1.3** | The IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks posed by substances that may leach or leak from the IVD medical device. Special attention should be given to substances which are carcinogenic, mutagenic or toxic to reproduction. |
| **Method(s)** | Application of recognised standards. |
| **Reference to Supporting Controlled Documents** | ISO 14971:2007 Medical devices — Application of risk management to medical devices. |
| • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. | • Simu POC CD4 System Risk Management and Control Report” held by QA. |
| • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-CD4 risk - processes”; “Simu POC CD4 risk-users”. | • Simu POC CD4 Cartridge Robustness Studies (held on site). |
## ANNEX 1 – ESSENTIAL PRINCIPLES CHECKLIST

### THE Manufacturing Company

<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/ Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1.4 IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risk of infection to user, professional or lay, or, where applicable, other person. The design should:</td>
<td>A</td>
<td>Application of recognised standards. Verification and Validation Studies • ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>• Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-risk-users”. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
</tr>
<tr>
<td>C2 Infection and microbial contamination</td>
<td></td>
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<tr>
<td>C2.1 The IVD medical devices and manufacturing processes should be designed in such a way as to eliminate or to reduce as far as reasonably practicable and appropriate any microbial leakage from the IVD medical device and/or microbial exposure during use; and prevent microbial contamination of the IVD medical device or specimen where applicable, by the user, professional or lay, or other person.</td>
<td>A</td>
<td>Application of recognised standards. Verification and Validation Studies • Section 7 ISO 13485:2003 Medical Devices – Quality Management Systems-Requirements for Regulatory Purposes. • ISO 14971:2007 Medical devices – Application of risk management to medical devices. • EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic medical devices.</td>
<td>• All verification studies (refer Section 7 of the dossier). • Risk analysis output documents “Simu POC CD4-risk-design”; “Simu POC CD4-risk-users”. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA. “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
</tr>
<tr>
<td>C2.2 IVD medical devices labelled either as sterile or as having a special microbiological state should be designed, manufactured and packaged to ensure they remain so when placed on the market and remain so under the transport and storage conditions specified by the manufacturer, until the protective packaging is damaged or opened.</td>
<td>NA</td>
<td>Not provided in a sterile state</td>
<td></td>
</tr>
<tr>
<td>C2.3 IVD medical devices labelled either as sterile or as having a special microbiological state should have been processed, manufactured and, if applicable, sterilized by appropriate, validated methods.</td>
<td>NA</td>
<td>Not provided in a sterile state</td>
<td></td>
</tr>
<tr>
<td>Essential Principles</td>
<td>Applicable/Not Applicable (A/NA)</td>
<td>Method(s) and References Used to Demonstrate Conformity</td>
<td>Reference to Supporting Controlled Documents of Manufacturer</td>
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<tr>
<td>C2.4 IVD medical devices intended to be sterilized should be manufactured in appropriately controlled (e.g. environmental) conditions.</td>
<td>NA</td>
<td>Not provided in a sterile state.</td>
<td></td>
</tr>
<tr>
<td>C2.5 Packaging systems for non sterile IVD medical devices should maintain the integrity and cleanliness of the device.</td>
<td>A</td>
<td>- Sections 68.7 ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.</td>
<td>• Robustness studies (results available in R&amp;D Department).</td>
</tr>
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<td></td>
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<td>• ISO 14001 Environmental management systems — Requirements with guidance for use</td>
<td>• Control Specimen Antimicrobial Effectiveness study (results available in R&amp;D Department).</td>
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<td></td>
<td>• Application of recognised standards.</td>
<td>• Environmental Control SOP XXX.</td>
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<td>Verification and Validation Studies</td>
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<td></td>
<td>- EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic medical devices.</td>
<td></td>
</tr>
<tr>
<td>C3 IVD medical devices incorporating materials of biological origin</td>
<td>A</td>
<td>Application of recognised standards.</td>
<td>Applicable to BSA and other products of animal origin in the Simu Cartridge</td>
</tr>
<tr>
<td>C3.1 Where IVD medical devices include tissues, cells and substances originating from animals, the processing, preservation, testing and handling of tissues, cells and substances of animal origin should be carried out so as to provide optimal safety for user, professional or lay, or other person.</td>
<td></td>
<td>- Risk analysis output documents “Simu POC CD4 risk-design”, “Simu POC CD4-CD4 risk – processes”, “Simu POC CD4 risk-users”.</td>
<td>• Control materials contain potentially infectious components. Policy reflects requirements to source materials that pose the least possible risk of transmission of infection.</td>
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<td></td>
<td></td>
<td>- “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
<td>• Document control policy requires on-going review of risk posed by scientific methods used to reduce or eliminate potential infectious agents in components for Systems already on the market.</td>
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<td></td>
<td></td>
<td>- National regulations may require that the manufacturer and/or the Regulatory Authority retain information on the geographical origin of the animals.</td>
<td>• Material specification sheets</td>
</tr>
<tr>
<td>Essential Principles</td>
<td>Applicable/ Not Applicable (A/NA)</td>
<td>Method(s) and References Used to Demonstrate Conformity</td>
<td>Reference to Supporting Controlled Documents of Manufacturer</td>
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| C3.2 Where IVD medical devices include human tissues, cells and substances, the selection of sources, donors and/or substances of human origin, the processing, preservation, testing and handling of tissues, cells and substances of such origin should be carried out so as to provide optimal safety for user, professional or lay, or other person. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This may not apply to certain IVD medical devices if the activity of the virus and other transmissible agent are integral to the intended purpose of the IVD medical device or when such elimination or inactivation process would compromise the performance of the IVD medical device. | A Application of recognised standards. Verification and Validation Studies  
• ISO 14971:2007 Medical devices — Application of risk management to medical devices  
• EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic medical devices  
• Section 4.2.4 ISO 13485:2003 Medical Devices — Quality Management Systems -Requirements for Regulatory Purposes. | Applicable to control cells (human origin)  
• Risk analysis output documents “Simu POC CD4-risk design”, “Simu POC CD4 risk - processes”, “Simu POC CD4-risk-users”.  
• “Simu POC CD4 System Risk Management and Control Report” held by QA.  
• Materials management requirements and policy kept in R&D:  
  o Control materials contain potentially infectious components. Policy reflects requirements to source materials that pose the least possible risk of transmission of infection.  
  o Document control policy requires on-going review of risk posed by scientific methods used to reduce or eliminate potential infectious agents in components for Systems already on the market.  
  • Material specification sheets |

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<th>Reference to Supporting Controlled Documents of Manufacturer</th>
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</thead>
</table>
| C3.3 Where IVD medical devices include cells and substances of microbial origin, the processing, preservation, testing and handling of cells and substances should be carried out so as to provide optimal safety for user, professional or lay, or other person. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This may not apply to certain IVD medical devices if the activity of the virus and other transmissible agent are integral to the intended purpose of the IVD medical device or when such elimination or inactivation process would compromise the performance of the IVD medical device. | A Application of recognised standards. Verification and Validation Studies  
• ISO 14971:2007 Medical devices — Application of risk management to medical devices  
• EN 13641:2002 Elimination or reduction of risk of infection related to in vitro diagnostic medical devices  
• Section 4.2.4 ISO 13485:2003 Medical Devices - Quality Management Systems -Requirements for Regulatory Purposes. | Applicable to monoclonal antibodies (microbial origin) in the Simu POC CD4 Cartridge  
• Risk analysis output documents “Simu POC CD4-risk design”, “Simu POC CD4-risk-design”, “Simu POC CD4 risk - processes”, “Simu POC CD4-risk-users”.  
• “Simu POC CD4 System Risk Management and Control Report” held by QA.  
• Materials management requirements and policy kept in R&D:  
  o Control materials contain potentially infectious components. Policy reflects requirements to source materials that pose the least possible risk of transmission of infection.  
  o Document control policy requires on-going review of risk posed by scientific methods used to reduce or eliminate potential infectious agents in components for Systems already on the market.  
  • Material specification sheets |
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<tr>
<td>C4</td>
<td>Application of recognized standards. Validation Studies</td>
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<td></td>
<td>• Section 7 ISO 13485:2003 Medical Devices – Quality Management Systems-Requirements for Regulatory Purposes.</td>
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<td>• ISO 14971:2097 Medical devices – Application of risk management to medical devices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Risk analysis output documents “Simu POC CD4-risk-design”, “Simu POC CD4 CD4-risk – processes”, “Simu POC CD4 risk-users”.</td>
<td></td>
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<tr>
<td></td>
<td>• “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
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<td></td>
<td>• Design specifications (held on site).</td>
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<td></td>
<td>• “Simu POC CD4 System Instructions for use, Simu POC Reader Users’ Manual, Simu POC CD4 System job aid.</td>
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<td></td>
<td>• All validation data (refer Section 7.4 of this dossier).</td>
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</table>

**C4.1** If the IVD medical device is intended for use in combination with other devices or equipment, the whole combination, including the connection system should not impair the specified performance of the devices. Any restrictions on use applying to such combinations should be indicated on the label and/or in the instructions for use.

**C4.2** IVD medical devices should be designed and manufactured in such a way as to remove or reduce as far as reasonably practicable and appropriate:

**C4.2.1** the risk of injury to user, professional or lay, or other person in connection with their physical and ergonomic features;

**C4.2.2** the risk of use error due to the ergonomic features, human factors and the environment in which the IVD medical device is intended to be used;
<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/ Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
</table>
| **C4.2.3** | - risks connected with reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, pressure, humidity, temperature or variations thereof; | A | Application of recognised standards.  
Validation and Stability Studies  
- **Section 7.4 ISO 13485:2003 Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes.**  
- **ISO 14971:2007 Medical devices — Application of risk management to medical devices.**  
- Routine audits of subcontractor’s compliance to required specifications, including safety testing.  
- Risk analysis output documents “Simu POC CD4-risk-design”, “Simu POC CD4-CD4 risk – processes”, “Simu POC CD4-risk-users”.  
- “Simu POC CD4 System Risk Management and Control Report” held by QA.  
- Design specifications (held on site).  
- Simu POC CD4 System Instructions for use, Simu POC Reader Manual, Simu POC CD4 System Job Aid.  
- All validation data (refer Section 7.4 of this dossier).  
- Stability studies (refer Section 7.2 of this dossier). |
| **C4.2.4** | - the risks associated with the use of the IVD medical device when it comes into contact with materials, liquids, and gases to which it is exposed during normal conditions of use; | A | Application of recognised standards.  
Validation Studies  
- **Section 7.4 ISO 13485:2003 Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes.**  
- “Simu POC CD4 System Risk Management and Control Report” held by QA.  
- Design specifications (held on site).  
- All validation data (refer Section 7.4 of this dossier). |
| **C4.2.5** | - the risk associated with the possible negative interaction between software and the environment within which it operates and interacts; | A | Application of recognised standards.  
The software is built into the Simu POC CD4 reader.  
The Simu POC CD4 reader software can detect hardware failure.  
- **IEC 62304 Medical device software — Software life cycle processes.**  
- **IEC 62366 Medical devices — Application of usability engineering to medical devices standard.** | - Refer to subcontractor’s “Software performance testing — Robustness study” (held on site).  
- Refer to joint study  
- THE Manufacturer and subcontractor’s “Usability Testing Report”. |
<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/ Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4.2.6  • the risks of accidental penetration of substances into the IVD medical device;</td>
<td>A</td>
<td>Application of recognised standards. Validation Studies  • Section 7150 13485:2003 Medical Devices – Quality Management Systems-Requirements for Regulatory Purposes.  • ISO 14971:2007 Medical devices – Application of risk management to medical devices</td>
<td>Risk analysis output documents “Simu POC CD4-risk-design”, “Simu POC CD4 risk – processes”, “Simu POC CD4 risk-users”. “Simu POC CD4 System Risk Management and Control Report” held by QA. Design specifications (held on site). All validation data (refer to Section 7.4 of this dossier).</td>
</tr>
<tr>
<td>C4.2.7  • the risk of incorrect identification of specimens/samples;</td>
<td>A</td>
<td>Application of recognised standards. Validation Studies  • Section 7150 13485:2003 Medical Devices – Quality Management Systems-Requirements for Regulatory Purposes.  • ISO 14971:2007 Medical devices – Application of risk management to medical devices</td>
<td>Risk analysis output documents “Simu POC CD4-risk-design”, “Simu POC CD4 risk – processes”, “Simu POC CD4 risk-users”. “Simu POC CD4 System Risk Management and Control Report” held by QA. Design specifications (held on site). All validation data (refer Section 7.4 of this dossier).</td>
</tr>
<tr>
<td>C4.2.8  • the risks of reasonably foreseeable interference with other devices such as carry over between IVD medical devices.</td>
<td>NA</td>
<td>Single use device only. No chance of carry over.</td>
<td>Simu POC CD4 System Instructions for use, Simu POC Reader Manual, Simu POC CD4 System Job Aid.</td>
</tr>
<tr>
<td>Essential Principles</td>
<td>Applicable/ Not Applicable (A/NA)</td>
<td>Method(s) and References Used to Demonstrate Conformity</td>
<td>Reference to Supporting Controlled Documents of Manufacturer</td>
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<tr>
<td>C4.3</td>
<td>A</td>
<td>Application of recognised standards.</td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2006/95/EC (held on site).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Section 7.4 ISO 13485:2003 Medical Devices – Quality Management Systems - Requirements for Regulatory Purposes.</td>
<td>• Routine audits of subcontractor’s compliance to required specifications, including safety testing.</td>
</tr>
<tr>
<td>C4.4</td>
<td>A</td>
<td>Application of recognised standards.</td>
<td>• Refer to Simu POC CD4 System Instructions for Use, Simu POC Reader User Manual “Section XYZ Calibration and Maintenance”.</td>
</tr>
<tr>
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<td></td>
<td>• Section 7.4 ISO 13485:2003 Medical Devices – Quality Management Systems - Requirements for Regulatory Purposes.</td>
<td>• Routine audits of subcontractor’s compliance to required specifications, including safety testing.</td>
</tr>
<tr>
<td>C4.5</td>
<td>A</td>
<td>Application of recognised standards.</td>
<td>• Risk analysis output documents “Simu POC CD4-risk-design”, “Simu POC CD4-CD4 risk – processes”, “Simu POC CD4-risk-users”.</td>
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<tr>
<td></td>
<td></td>
<td>• ISO 14001:2004 Environmental management systems. Requirements with guidance for use.</td>
<td>• “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
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<tr>
<td></td>
<td></td>
<td>• ISO 14971:2007 Medical devices – Application of risk management to medical devices.</td>
<td>• Design specifications (held on site).</td>
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<td>• Simu POC CD4 System Instructions for use, Simu POC CD4 System Job Aid.</td>
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</table>
C5.1 IVD medical devices should be designed and manufactured in such a way that the performance characteristics support the intended use, based on appropriate scientific and technical methods. In particular, where appropriate, the design should address sensitivity, specificity, accuracy which is trueness and precision (repeatability and reproducibility), control of known relevant interference and limits of detection.

These performance characteristics need to be maintained during the lifetime of the IVD medical device as indicated by the manufacturer.

<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5.1</td>
<td>Performance characteristics</td>
<td>Application of recognised standards</td>
<td>Design specifications (held on site).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Performance Studies and Stability Studies</td>
<td>All validation and verification studies, and stability studies (refer to all of Section 7 of this dossier).</td>
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<td></td>
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<td>• Section 7 ISO 13485:2003 Medical Devices – Quality Management Systems—Requirements for Regulatory Purposes.</td>
<td>• Lot release procedures “SOP QC xxx”.</td>
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<td>• ISO 23640:2011 In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents.</td>
<td>• Traceability of the Simu CD4 Control Cells (refer to Records QC Control Cells and Traceability Policy, held on site).</td>
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<td>• ISO 15193:2009 In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures.</td>
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<td>• ISO 17511:2003 In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials.</td>
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<td>• CLSI EP15-R Metrological Traceability and Its Implementation; A Report.</td>
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<td>• CLSI ILA 30-A Immunoassay Interference by Endogenous Antibodies; Approved Guideline.</td>
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<td>• FDA Guidance for Industry – Analytical Procedures and Methods Validation Chemistry, Manufacturing, and Controls Documentation.</td>
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<td>• FDA Guidance for Industry and FDA Staff — Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.</td>
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<td>• FDA Guidance for Industry – Bioanalytical Method Validation.</td>
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<td>• FDA CDRH Class II Special Controls Guidance Document (2001).</td>
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<td>• EN 13975:2003 Sampling procedures used for acceptance testing of in vitro diagnostic medical devices — Statistical aspects.</td>
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<td>• All relevant ISO standards of ISO TC 69 SC6 (Measurement Measures and Results).</td>
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<td>Essential Principles</td>
<td>Applicable/Not Applicable (A/NA)</td>
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</tbody>
</table>
| **C5.2** Where the performance of devices depends on the use of calibrators and/or control materials, the traceability of values assigned to such calibrators and/or control materials should be assured through available reference measurement procedures and/or available reference materials of a higher order. | A | Application of recognised standards.  
• ISO 15193:2009 In vitro diagnostic medical devices — Measurement of quantities in samples of biological origin — Requirements for content and presentation of reference measurement procedures  
• ISO 17511:2003 In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials. | • Refer to subcontractor’s “Software Validation and Verification Studies” (held on site). |
| **C5.3** Wherever possible values expressed numerically should be in commonly accepted, standardised units, and understood by the users of the device. | A |  |
| **C6.1** IVD medical devices should be designed, manufactured and packaged in such a way that exposure of user, professional or lay, or other person to the emitted radiation (intended, unintended, stray or scattered) is reduced as far as reasonably practicable and appropriate. | NA | No radiation utilized in the design of the Simu POC CD4 System. |  |
| **C6.2** When IVD medical devices are intended to emit potentially hazardous, visible and/or invisible radiation, they should as far as reasonably practicable and appropriate be:  
• designed and manufactured in such a way as to ensure that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted;  
• and fitted with visual displays and/or audible warnings of such emissions. | NA |  |
| **C7.1** For IVD medical devices which incorporate software or for standalone software that are IVD medical devices in themselves, the software must be validated according to the state of the art taking into account the principles of development life cycle, risk management, verification and validation. | A | Application of recognised standards.  
The software is built into the Simu POC CD4 reader.  
• IEC 62304 Medical device software — Software life cycle processes.  
• IEC 62366 Medical devices — Application of usability engineering to medical devices standard.  
• ISO 14971, Medical devices — Application of risk management to medical devices. | • Refer to subcontractor’s “Software Validation and Verification Studies” (held on site).  
• Refer to subcontractor’s “Software Risk Management Report” (held on site). |
<p>| <strong>C8.1</strong> IVD medical devices where the safety of the patient depends on an internal power supply in the IVD medical device should be equipped with a means of determining the state of the power supply. | A |  | Design of the Simu POC Reader includes a screen that provides instructions, allowing confirmation it is turned on. A LED turns on when the Simu Reader is “ON”. |</p>
<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8.2 IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks of creating electromagnetic interference which could impair the operation of this or other devices or equipment in the usual environment.</td>
<td>A</td>
<td>Application of recognised standards. IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment</td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C8.3 IVD medical devices should be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity to electromagnetic disturbance to enable them to operate as intended.</td>
<td>A</td>
<td>Application of recognised standards. EMC Testing for Medical Devices IEC 60601-1-2:2007 Electromagnetic Compatibility (EMC) Testing.</td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C8.4 IVD medical devices should be designed and manufactured in such a way as to avoid, as far as reasonably practicable, the risk of accidental electric shocks to the user, professional or lay, or other person both during normal use of the device and in the event of a single fault condition in the device, provided the IVD medical device is installed and maintained as indicated by the manufacturer.</td>
<td>A</td>
<td>The Simu POC CD4 reader is battery-operated (sealed lead acid or Li-ion rechargeable battery). Application of recognised standards. - IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control and laboratory use – Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment</td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C9 Protection against mechanical and thermal risks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C9.1 IVD medical devices should be designed and manufactured in such a way as to protect the user, professional or lay, or other person against mechanical risks connected with, for example, resistance to movement, instability and moving parts.</td>
<td>NA</td>
<td>Simu POC CD4 System does not incorporate moving parts. The Simu POC CD4 reader and rechargeable batteries are manufactured in accordance with the EC EMC standards.</td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C9.2 Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means must be incorporated.</td>
<td>A</td>
<td>Application of recognised standards. Refer to C3.1, C3.2 and C3.3</td>
<td></td>
</tr>
<tr>
<td>C9.3 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.</td>
<td>NA</td>
<td>Simu POC CD4 System does not generate vibrations.</td>
<td></td>
</tr>
<tr>
<td>Essential Principles</td>
<td>Applicable/ Not Applicable (A/NA)</td>
<td>Method(s) and References Used to Demonstrate Conformity</td>
<td>Reference to Supporting Controlled Documents of Manufacturer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>C9.4 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source.</td>
<td>NA</td>
<td>Simu POC CD4 System does not generate noise.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C9.5 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user, professional or lay, or other person has to handle should be designed and constructed in such a way as to minimize all possible risks.</td>
<td>A</td>
<td>The Simu POC CD4 reader is battery operated (sealed lead acid or Li-ion rechargeable battery). Application of recognised standards.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IEC 62333 Electromagnetic compatibility (EMC) — Part 6-3: Generic standards — Emission standard for residential, commercial and light-industrial environments.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
<td></td>
</tr>
<tr>
<td>C9.6 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level, the risk of error when certain parts within the device are intended to be connected or reconnected before or during use.</td>
<td>A</td>
<td>The Simu POC CD4 reader is battery operated (sealed lead acid or Li-ion rechargeable battery). Application of recognised standards.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IEC 62333 Electromagnetic compatibility (EMC) — Part 6-3: Generic standards — Emission standard for residential, commercial and light-industrial environments.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IEC 61010-2-101: Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
<td></td>
</tr>
<tr>
<td>C9.7 Accessible parts of the IVD medical devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings should not attain potentially dangerous temperatures under normal use.</td>
<td>NA</td>
<td>Simu POC CD4 System does not generate heat.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C10 Protection against the risks posed by IVD medical devices for self-testing</td>
<td>NA</td>
<td>This device is for professional use only. However a broad range of user skills have been considered in the design.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C11 Labels and Instructions for Use</td>
<td>NA</td>
<td>This device is for professional use only. However a broad range of user skills have been considered in the design.</td>
<td>- Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
</tr>
<tr>
<td>C11.1 Users should be provided with the information needed to identify the manufacturer, to use the device safely and to ensure the intended performance, taking account of their training and knowledge. This information should be easily understood.</td>
<td>A</td>
<td>Application of recognised standards.</td>
<td>- Risk analysis output documents “Simu POC CD4 risk-design”, “Simu POC CD4 risk – processes”, “Simu POC CD4 risk-users”.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ISO 14971:2007 Medical devices — Application of risk management to medical devices.</td>
<td>- “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ISO 18113-1:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) – Part 1: Terms, definitions and general requirements.</td>
<td>- Simu POC CD4 System Instructions for Use, Simu POC Reader User Manual, Simu POC CD4 System Job Aid.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EN ISO 18113-3:2011 In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) – Part 3: In vitro diagnostic reagents for professional use.</td>
<td>- “Simu POC CD4 System Risk Management and Control Report” held by QA.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).</td>
<td></td>
</tr>
</tbody>
</table>

**Table Notes:**
- The table in the document details essential principles for IVD medical devices, including the applicability of standards, methods, and supporting documents.
- Each principle is accompanied by a description of the device’s design, operational requirements, and regulatory compliance.
- The table also includes references to specific standards and guidelines used to demonstrate conformity to regulatory requirements.
- Additional documents and manuals provided for the device, such as user manuals and risk management reports, are referenced to ensure comprehensive user training and risk management.

**Example Entry:**
- **C9.4** IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source.
  - **Method(s) and References Used to Demonstrate Conformity:**
    - The Simu POC CD4 reader is battery operated (sealed lead acid or Li-ion rechargeable battery).
    - Application of recognised standards:
  - **Reference to Supporting Controlled Documents of Manufacturer:**
    - Copy of subcontractor’s Declaration of Conformity (Annex IV) to DIRECTIVE 2004/108/EC (held on site).
<table>
<thead>
<tr>
<th>Essential Principles</th>
<th>Applicable/Not Applicable (A/NA)</th>
<th>Method(s) and References Used to Demonstrate Conformity</th>
<th>Reference to Supporting Controlled Documents of Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C12 Performance evaluation including analytical performance and, where appropriate, clinical performance</td>
<td></td>
<td>Application of GHTF Guidance.</td>
<td>- Performance Evaluation Summary (refer Section 7 of this dossier).</td>
</tr>
<tr>
<td>C12.1 For an IVD medical device a performance evaluation should be conducted in accordance with GHTF guidance. The performance evaluation should review analytical performance data and, where appropriate, clinical performance data in the form of any:   • literature,   • performance study reports; and   • experience gained by routine diagnostic testing.   • to establish that the IVD medical device achieves its intended performance during normal conditions of use and that the known, and foreseeable risks, and any undesirable effects, are minimised and acceptable when weighed against the benefits of the intended performance.</td>
<td>A</td>
<td>- Application of GHTF Guidance.</td>
<td>- Documentation of all ethics committee approval (held on site).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GHTF/SG5/N8:2012 Clinical Evidence for IVD Medical Devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices.</td>
<td></td>
</tr>
<tr>
<td>C12.2 Clinical performance studies using specimens from human subjects should be carried out in accordance with the spirit of the Declaration of Helsinki. This includes every step in the clinical performance study from first consideration of the need and justification of the study to publication of the results. In addition, some countries may have specific regulatory requirements for informed consent.</td>
<td>A</td>
<td>Ethics committee approval of all prospective clinical performance studies.</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 2
THE MANUFACTURING COMPANY DOC XXX
RISK MANAGEMENT POLICY

Please Note: The following DOC XXX Risk Management Policy has been prepared for the purposes of this sample dossier, and is not a complete document. It is to provide an example of some aspects to be considered in such a document and must reflect the internal policies of the company.

<table>
<thead>
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<th>Document version</th>
<th>Document date: 2011 09 15</th>
</tr>
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<tbody>
<tr>
<td>Written by:</td>
<td>Approved by:</td>
</tr>
<tr>
<td>signatures</td>
<td>Head of QA</td>
</tr>
<tr>
<td>date</td>
<td>signature date</td>
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<tr>
<td></td>
<td>Head of manufacturing</td>
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<td></td>
<td>signature date</td>
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Changes from earlier versions:

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<td>02</td>
<td>20110915</td>
<td>Main text</td>
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<td></td>
<td></td>
<td>Reference to the proposed European in-vitro diagnostic regulation added</td>
</tr>
<tr>
<td>03</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

NOTE: Documents submitted must be signed and dated.

1. Introduction

1.1. The company is committed to the effective management of risk at every level:
1.1.1. Reducing as far as possible any risks associated with any product developed or manufactured by the company, at every stage of the product life-cycle from design to in-use surveillance.
1.1.2. Ensuring a safe environment for its employees and customers.
1.1.3. Training to enable its employees to undertake their work effectively, efficiently and safely.
1.1.4. Enhancing and protecting the local environment.
2. The company will achieve these objectives

2.1. By ensuring company management fully accepts the need for risk control, which cannot be balanced against financial profit.
   2.1.1. The Head of Quality Assurance will be responsible for risk management and control throughout the company, subject to this.
   2.1.2. The Head of Research & Development will be responsible for risk management and control in the design of product and process.
   2.1.3. The Head of Manufacturing will be responsible for risk management and control related to supply of product, safety in the facility, and respect for the environment. These responsibilities cannot be passed to subordinates.

2.2. By following the guidelines of the GHTF/SG3/N15R8 and 98/79/EC in a hierarchy of control methods:
   2.2.1. Inherent safety by design of any items we develop or manufacture, and their manufacturing processes, including risks related to security of supply.
   2.2.2. Protective measures for the user and patient in the device, and for our employees in the manufacturing processes.
   2.2.3. Information for safety, such as warnings, as a last resort for risks that cannot be removed by design of the products or the processes.

2.3. By ensuring that risk management is integrated into the quality management system of the company, to include risk management planning and plans for all aspects of our work and product development.

2.4. By training of all employees in the importance of safe practices in all aspects of their work.

2.5. By training specific employees in the regulations and methods of risk analysis and control.
   2.5.1. ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes ISO 14971:2007, Medical Devices. Application of risk management to medical devices documentation, GHTF and IMDRF guidelines, FDA and ICH Q9 and Q10 guidance,
   2.5.2. Standard methods for the tools of risk analysis, including Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis, Preliminary Risk Analysis, Risk Ranking and Filtering and Hazard and Operability Studies.

3. The company will ensure consistent application of risk control methods through a set of standard operating procedures (SOP) directed by this policy. The SOPs will include, but are not limited to:

3.1. SOP and template for FMEA – who, how, when
3.2. SOP for training in the use of risk management tools.
3.3. SOP for estimation of degrees of hazard and control measures

This is not intended to be a complete policy document.
# ANNEX 3

*Simu* POC CD4 SYSTEM DESIGN INPUT FMEA

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**Product Codes X1234 and X1235 (taking into account *Simu* POC System Reader)**

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<thead>
<tr>
<th>Version</th>
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<th>Changes</th>
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<td>1.0</td>
<td>2011/10/19</td>
<td>Initial</td>
</tr>
<tr>
<td>2.0</td>
<td>2012/11/14</td>
<td>After first project review, more details from literature searches added and considered, hazards 15 - 18</td>
</tr>
</tbody>
</table>

The manufacturing company FMEA design input template version 1

Controlling SOP: Design input risk analysis SOP 00967

The manufacturing company FMEA design input template version 1

Controlling SOP: Design input risk analysis SOP 00967

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<th>Present at second FMEA</th>
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<tr>
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<td>Department</td>
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<tr>
<td>1</td>
<td>Manufacturing factory</td>
<td>Marketing</td>
</tr>
<tr>
<td>2</td>
<td>Manufacturing suppliers</td>
<td>R&amp;D</td>
</tr>
<tr>
<td>2a</td>
<td>QA - customer support</td>
<td>QA - customer support</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Hazard</th>
<th>Known or suspected likely problem</th>
<th>Potential Effects of Problem</th>
<th>Severity</th>
<th>Occur</th>
<th>Risk Index</th>
<th>Recommended Action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monocytes have CD4</td>
<td>Over count of T4 cells</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>Design so that monocytes do not interfere</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>specimens likely to be HIV positive and have other diseases</td>
<td>Health risk to user</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>Design to minimise specimen handling, safety in handling,</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>specimens likely to be HIV positive</td>
<td>Disposal risk</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>Design to contain all specimen during and after reading</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>specimens likely to be HIV positive</td>
<td>Disposal risk</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>Ensure easy decontamination of reading device</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Patients likely to be TB positive</td>
<td>Increase of monocytes</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>See hazard 2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Monoclonal antibodies from external suppliers are variable</td>
<td>Variability of failure of product supply</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>Control by either supplier audit and strong incoming goods controls or make own monoclonal antibodies</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Free CD4 in blood, not cell bound</td>
<td>Inappropriately high values presented, treatment not started</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>Design to be independent of free CD4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Manual assembly of Control Cells packaging process not adequate for needs</td>
<td>Product goes out of stock, loss of market, patient threat</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>Automate as soon as possible</td>
<td>Switching from semi-automated to full automation will require a complete revalidation</td>
</tr>
<tr>
<td>7</td>
<td>Malarial infection affects lysis of red cells, can interfere</td>
<td>Failure to flow into the instrument, incorrect readings</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>Design so red cells are not required to be haemolysed; design so volume is evaluated by the instrument</td>
<td>High occurrence in malaria areas, not elsewhere</td>
</tr>
<tr>
<td>8</td>
<td>anti BSA in areas of high raw meat eating</td>
<td>Agglutination prevents smooth flow, gives low counts</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>Design so volume is evaluated by the instrument</td>
<td>Rare but known</td>
</tr>
<tr>
<td>9</td>
<td>HIV infection lowers CD4 protein on cells, might lower countability if signal level is important</td>
<td>Improperly lower CD4 values presented, treatment initiated too early</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>Design so that cells are counted, not dependent on signal level</td>
<td>Frequent issue</td>
</tr>
<tr>
<td>10</td>
<td>Leukaemia increase B-cells so % values are strangely low</td>
<td>Loss of confidence in the device if the leukaemia status is not known</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>Warning in IFU</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Collection of blood requires anticoagulants, especially on capillary devices for collecting capillary blood</td>
<td>Blood clots and does not flow, low counts or no counts, inappropriate treatment</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>Avoid need for special measuring tubes for capillary blood</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Human materials might cause infections if not properly sourced</td>
<td>Health problems for users</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>Controls on source blood, warning in IFU to wear gloves</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Storage of specimens at 2-8°C affects many cell counters</td>
<td>Incorrect values presented, early or late treatment</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>Design system to avoid this problem, fully evaluate storage conditions for specimens, warnings and statements in IFU</td>
<td></td>
</tr>
</tbody>
</table>
### Simu POC CD4 System Product Codes X1234 and X1235

#### Design input FMEA

<table>
<thead>
<tr>
<th>Probability of Occurrence</th>
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<th>3 Occasional</th>
<th>2 Rare</th>
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<td>Minimal</td>
<td>Negligible</td>
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<tr>
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<td>High</td>
<td>Med</td>
<td>Low</td>
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<td></td>
<td>Occasional</td>
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<td>Med</td>
<td>Low</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Improbable</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

All items must be addressed

- **High**: Redesign, and/or improve, or add another mode of control and/or gain approval of program management and PDMRB
- **Med**: Redesign, and/or improve, or add another mode of control if possible Review with program management and QA to proceed.
- **Low**: Complete a team level QA review

See SOP for definitions of probabilities and severities
**ANNEX 4**

*Simu POC CD4 SYSTEM USER AND PATIENT FMEA*

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>2011/11/08</td>
<td>Initial: from design input FMEA</td>
</tr>
<tr>
<td>2.0</td>
<td>2012/10/19</td>
<td>New input hazards from customer support: problems found on similar products from other companies</td>
</tr>
<tr>
<td>3.0</td>
<td>2012/12/10</td>
<td>At transition to factory, with RED completed: new issues from monoclonal production interacting with users</td>
</tr>
</tbody>
</table>

---

**The manufacturing company FMEA user and patient template version 1**

Controlling SOP: User and patient risk analysis SOP ~ 23456

<table>
<thead>
<tr>
<th>SOP Version</th>
<th>1</th>
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</thead>
</table>

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<th>Signature</th>
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<th>Department</th>
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<th>Signature</th>
<th>Department</th>
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<td></td>
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<td>Customer support</td>
<td>Customer support</td>
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<td>Sales</td>
<td>Customer support</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td>R&amp;D</td>
<td>Customer support</td>
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<td>Manufacturing</td>
<td>R&amp;D</td>
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<td>R&amp;D</td>
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<td>Regulatory affairs</td>
<td>Manufacturing</td>
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<td>R&amp;D</td>
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<td>Sales</td>
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</tr>
</tbody>
</table>
## Simu POC CD4 System Product Codes X1234 and X1235

### User and Patient FMEA

<table>
<thead>
<tr>
<th>Status at initial FMEA</th>
<th>Status after risk minimisation method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard #</strong></td>
<td><strong>Activity</strong></td>
</tr>
<tr>
<td><strong>Patient 1</strong></td>
<td>Blood taking</td>
</tr>
<tr>
<td><strong>User 1</strong></td>
<td>Blood taking</td>
</tr>
<tr>
<td><strong>User 2</strong></td>
<td>Pipetting</td>
</tr>
<tr>
<td><strong>User 2a</strong></td>
<td>Pipetting</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td>Labeling</td>
</tr>
<tr>
<td><strong>Patient</strong></td>
<td>General Safety</td>
</tr>
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</table>
### Severity Rating

<table>
<thead>
<tr>
<th>Severity Rating</th>
<th>Severity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>CATASTROPHIC: Results in Patient Death</td>
</tr>
<tr>
<td>4</td>
<td>CRITICAL: Results in permanent impairment or life-threatening injury</td>
</tr>
<tr>
<td>3</td>
<td>SERIOUS: Results in injury or impairment requiring professional medical intervention.</td>
</tr>
<tr>
<td>2</td>
<td>MINOR: Results in temporary injury or impairment not requiring professional medical intervention.</td>
</tr>
<tr>
<td>1</td>
<td>NEGLIGIBLE: Inconvenience or temporary discomfort.</td>
</tr>
</tbody>
</table>

#### Effect Severity Supporting Information

<table>
<thead>
<tr>
<th>Effect Number</th>
<th>Rationale / Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Patient would be affected for a short time-until the next CD4 measurement but would require physicians attention at that time</td>
</tr>
</tbody>
</table>

### Occurrence Rationale

#### FMEA Occurrence Probability of Failure

<table>
<thead>
<tr>
<th>FMEA Occurrence Probability of Failure</th>
<th>Failure Rates</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY HIGH: Failure is almost inevitable</td>
<td>&gt;1 in 2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1 in 3</td>
<td>4</td>
</tr>
<tr>
<td>HIGH: Generally associated with activities similar to previous activities that have often failed.</td>
<td>1 in 8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1 in 20</td>
<td>4</td>
</tr>
<tr>
<td>MODERATE: Generally associated with activities similar to previous activities which have experienced occasional failures but not in major proportions.</td>
<td>1 in 80</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1 in 400</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1 in 2000</td>
<td>3</td>
</tr>
<tr>
<td>LOW: Isolated failures associated with similar activities.</td>
<td>1 in 15,000</td>
<td>2</td>
</tr>
<tr>
<td>VERY LOW: Only isolated failures associated with almost identical activities</td>
<td>1 in 150,000</td>
<td>1</td>
</tr>
<tr>
<td>REMOTE: Failure is unlikely. No failures ever associated with almost identical activities.</td>
<td>&lt;1 in 1,500,000</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Rationale / Support

- User 1
### Simu POC CD4 System Product Codes X1234 and X1235
#### User and Patient FMEA

| Risk Grid |
|---|---|---|---|
| **Severity of Effect** | 4 | 3 | 2 | 1 |
| Major | Probable | High | High | Med | Low |
| Moderate | Occasional | High | Med | Low | Low |
| Minimal | Rare | Med | Low | Low | Low |
| Negligible | Improbable | Low | Low | Low | Low |

**Probability of Occurrence**
- 4: Probable
- 3: Occasional
- 2: Rare
- 1: Improbable

All items must be addressed:
- High: Redesign, and/or improve, or add another mode of control and/or gain approval of program.
- Med: Redesign, and/or improve, or add another mode of control if possible. Review with program management and QA to proceed.
- Low: Complete a team level QA review.

---

### Simu POC CD4 System Product Codes X1234 and X1235
#### User and Patient FMEA

**Outputs from FMEA User and Patient: Impact on Instructions for Use**

This diagram is to be updated as the FMEA evolves and when the IFU is revised (reference SOP XXX).

Ensure IFU is read and understood
Ensure device is at room temperature
Ensure protective clothing available and worn
Ensure battery from Reader is charged

- **Step 1**
  - Action 1.1
  - Action 1.2
  - Action 1.3
  - Ensure patient in correct position for bleeding
  - Ensure wipes and lancets prepared
  - Ensure cartridge is ready to use

- **Step 2**
  - Action 2.1
  - Action 2.2
  - Action 2.3
  - ****

- **Step 3**
  - Action 3.1
  - Action 3.2
  - Action 3.3
  - ****

---

**IFU Activity**

Links to Hazard 5a
Hazard 2C
Hazard 2. Design Inputs
Hazard 5C: POC SYSTEM READER FMEA
Who Prequalification - Sample Dossier

Annex 5
Simu POC CD4 System Process FMEA

This FMEA would be included in the dossier as part of the risk management documentation.

Annex 6
Simu POC CD4 System Supplier Management FMEA

This FMEA would be included in the dossier as part of the risk management documentation.
ANNEX 7
DESIGN INPUT REQUIREMENTS

Excerpts from SOP XXX Design Input Requirements for the Development of the Simu POC CD4 System

THE Manufacturing Company
Design Input Requirements for the Development of the Simu POC CD4 System

The inputs and outputs of this document will be the responsibility of the following departments of THE Manufacturing Company: Research and Development Department, Marketing Department, Manufacturing Department, and Quality Assurance Department.

The outcome of this process will be approved by Senior Management on completion.

Document Key:
- Orange and blue – template of a minimum set of factors to be considered.
- Black – design inputs that will be converted to numerical specifications when all the “customers” inputs have been collected.

Document Appendices: policy documents related to design input and references

1. Functional requirements
   1.1 What is the kit supposed to do?
      1.1.1 Quantitative measurement of CD-4 T-cells in Europe, Asia and in major hospitals, medical facilities and remote and resource restricted locations with performance equivalent to that obtained in European doctor’s offices.

   1.2 What inputs and what outputs?
      1.2.1 Output of a hard-copy of an individual patient’s CD-4 count given a blood specimen compatible with 1.1.1. Physical inputs to the device to be compatible with 1.1.1, especially in terms of user training, access to power, water, medical hardware supplies

2. Management requirements
   2.1 Financial including staff allocation
      2.1.1 Staffing in R&D to be kept within budget constraints, no new staff to be taken on except as replacements
      2.1.2 Total costs to be less than $100,000 per staff member per year

   2.2 Administration and control structure
      2.2.1 The usual R&D, QA and manufacturing control systems, administered by the HIV team

   2.3 Reporting methods and intervals
      2.3.1 By the normal project management group, with reporting to senior management through the design control committee at a minimum of 2 monthly intervals
3. Format
   3.1.1 All to be decided following customer and expert reviews, note target intended use in 1.1.1

3.2 Interfaces to other systems (measurement system – fluorescence, OD, by eye only; patient tracking and identification, result recording)

3.3 Methodology – flow, single use device, ... open or closed system

3.4 Presentation of the product

4. Operating requirements
   4.1 Expected physical environment – temperature, power availability, equipment, materials available (distilled water, pipette tips), transport capability, physical stability ...

   4.2 Expected technological environment (nature of the working area), educational level of operators.
      4.2.1 Data reduction systems, LIMS

5. Performance requirements
   5.1.1 To be decided and documented following customer and expert review, Quality Function Deployment and conversion of requirements, suggestions and needs into a design specification agreed by R&D and manufacturing. All prior to substantial work

5.2 Safety critical

5.3 Specimen types
   5.3.1 anti-coagulant types if plasma

5.4 Operating temperatures for the assay in users labs

5.5 Sensitivity, specificity, precision at the cut-off, degree of confidence in these values, definition of populations

5.6 Precision, trueness and accuracy: if quantitative
   5.6.1 LoD, LoQ, precision at various concentrations or clinical decision points

5.7 Interfering factors

5.8 Internal QA requirement (“run controls”)

5.9 Stability of device
   5.9.1 Shelf-life after manufacture under stated conditions
   5.9.2 Transport stability
   5.9.3 Stability after first use
   5.9.4 Stability on-board
   5.9.5 Stability once opened if kept in sachets
   5.9.6 Stability of result after assay – time allowed prior to reading
5.10 Stability of specimens
   5.10.1 Time at ambient or cold
   5.10.2 Time frozen

5.11 Robustness or fault tolerance, “ruggedness”, “guard band studies”, “flex studies”

5.12 Speed to result and batching of assays

5.13 Capacity – assays per technician or instrument per hour or per day

6. Manufacturing requirements
   6.1.1 To be decided and documented in the early stages of R&D in agreement with manufacturing and marketing

6.2 Where to be made

6.3 Equipment, staff, space available or to be obtained
   6.3.1 Qualification of work-space, instruments, services

6.4 Cost of production

6.5 Cost of materials

6.6 Constraints on materials to be used – safety, storage, environmental

6.7 Sourcing of raw materials
   6.7.1 Supplier qualification and monitoring processes

6.8 Storage, in-process stability of intermediates, product

6.9 Packaging

6.10 QA factors – “manufacturing capability” in the statistical sense

6.11 In-process and release QA values

7. Maintainability and support requirements
   7.1.1 Documented in discussions with marketing and purchasing bodies in accord with 1.1.1

7.2 Maintenance requirements

7.3 Supportability requirements

7.4 Installation requirements
8. Cultural and political requirements
8.1 Cultural requirements – bovine, porcine materials

8.2 Political requirements

9. Regulatory requirements
9.1 The product will be CE marked as it is intended to be used in Europe in addition to resource restricted areas

9.2.1 Environmental ISO 14001, safety, performance, registration
9.2.2 Material safety data sheets

9.3 Standards requirements – if quantitative: ISO 17511

9.4 Clinical trials requirements ISO 14155: 2009 (not IVD but relevant)
9.4.1 Helsinki protocols

10. Usability and “human factors” requirements
10.1 Ease of use

10.2 Ease of learning – training – staff technical ability

10.3 Accessibility requirements – colour blindness

10.4 Power sources

Minimum aspects of performance that need to be evaluated during a feasibility study using predefined plans and criteria derived from the device specification documents

1) Sensitivity
2) Range
3) High dose hook
4) Intra- and inter-assay precision
5) Lot to lot consistency, precision and trueness if quantitative
6) Interferents (Haemoglobin, bilirubin, lipaemia …)
7) Cross-reactivity (of structurally similar proteins)
8) Anticoagulants
9) Stability of samples / reagents
10) Assay drift due to addition of specimen across several devices before reading, if appropriate
11) Clinical study: choice of reference method – clinical and/or an existing test, if possible should be a suitable reference test c.f. a comparator (refer FDA Guidance “Statistical guidance on reporting results from studies evaluating diagnostic tests”).
12) Definition of statistical methods, power studies, regression studies, treatment of “outliers”

US FDA QSR:
(y) Specification means any requirement with which a product, process, service, or other activity must conform.
ISO 8402 1995 Quality management and quality assurance vocabulary

10.14 **specification**
10.4.1 document stating requirements

**NOTES**
1. A qualifier should be used to indicate the type of specification, such as product (1.4) specification, ‘test specification’.
2. A specification should refer to or include drawings, patterns or other relevant documents and indicate the means and the criteria whereby conformity (2.9) can be checked.

**FDA on “Design control guidance for medical device manufacturers”**

**Design input**
- Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient.
- The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements.
- The design input requirements shall be documented and shall be reviewed and approved by designated individual(s).
- The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

§ 820.3(f) Design input means the physical and performance requirements of a device that are used as a basis for device design.

Design input is the starting point for product design. The requirements which form the design input establish a basis for performing subsequent design tasks and validating the design. Therefore, development of a solid foundation of requirements is the single most important design control activity.
ANNEX 8
THE MANUFACTURING COMPANY QUALITY MANUAL

The Manufacturing Company®
Simu POC Tests for Developing Markets

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1. Scope 3
2. Quality System Requirements 3
3. Definitions and Abbreviations 3
4. Quality Management System 3
5. Management Responsibility 6
6. Resource Management 12
7. Product Realisation 13
8. Measurement, Analysis and Improvement 21
1. **Scope**


1.2. **Company Background**

THE Manufacturing Company is a venture capitalist supported ISO 9001-, ISO 13485- certified manufacturing company founded in 2001 and based in Europe.

2. **Quality System Requirements**


3. **Definitions and Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BPIC</td>
<td>Inventory Control System</td>
</tr>
<tr>
<td>DHF</td>
<td>Design History File</td>
</tr>
<tr>
<td>DMR</td>
<td>Device Master Record</td>
</tr>
<tr>
<td>IVDD</td>
<td>In-vitro Diagnostics Medical Devices Directive 98/79/EC</td>
</tr>
<tr>
<td>OEM</td>
<td>Original Equipment Manufacturer</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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</table>
4. **Quality Management System**

4.1. **General Requirements**

The Quality Manual and SOPs describe the processes for the quality

4.2. **Documentation Requirements**

4.2.1. General

The Quality Management System Documentation includes the documents shown below:-Policy Documents are generated by individual Departments to give more detailed guidance of activities carried out by or managed by the particular Department.

SOPs are written for systems and processes which may affect product quality or the quality of service. SOPs are controlled by the central Documentation Group and circulation is usually across departments. SOPs are technical or administrative instructions intended to provide standard methods and/or procedures for conducting scientific tests, processes, manipulations or administrative procedures. The writing and departmental control of SOPs is described in SOP XXX & SOP XXX and the authorisation, approval and change control of SOPs is described in SOP Production Documents are controlled by the central Documentation Group.

Work Instructions/Local Procedures are written for tasks which are only used within a single working group. The control of Work Instructions and Local Procedures is detailed in SOP XXX.

Technical Specifications are written for raw materials and packaging items which are manufactured specifically by a supplier for THE Manufacturing Company and/or where specific additional testing is required by either THE Manufacturing Company or the supplier, and also, if the item is manufactured from materials of human or animal origin, to ensure compliance with the Essential Principles.

Technical Specifications are agreed with and authorised by the supplier together with representatives of THE Manufacturing Company. Writing, authorisation and Control of Technical Specifications is defined in SOP XXX.

Product Structure & Routing Specifications are a document set for a reagent or finished pack which includes the bill of materials for a manufacturing operation and the associated department instructions. Product Structure & Routing Specifications are used in filtration, filling and freeze drying, plate or cartridge coating, labelling and final packing of product. The relevant SOPs describing writing, authorisation and control of these documents are SOP XXX.

Quality Assurance Product Release Specifications detail the testing that is carried out by Product Quality Assurance team to ensure that the claims for the product detailed in the Instruction for Use (IFU) are met. Writing and authorisation of these documents is detailed in SOP XXX.

Device Master Records (DMRs) reference the location of all documents containing the design specifications, manufacturing procedures, quality assurance requirements and labelling of THE
Manufacturing Company manufactured and marketed products. The preparation, authorisation and maintenance of DMRs is described in SOP XXX. Manufacturing activities are conducted in accordance with these documents.

Quality Policies, Procedures and Processes define Quality System requirements.

Technical Documentation/Technical File/Design Dossiers form the total documentary evidence that a product conforms with the appropriate requirements of the various regulatory bodies as well as the Essential Principles. Technical Files and Design Dossiers provide a summary of the Technical Documentation. Preparation and maintenance of Technical Files and Design Dossiers is described in SOP XXX.

4.2.2. Quality Manual
The Quality Manual is maintained according to SOP XXX.

4.2.3. Control of Documents

A list of documents held under the QMS should be appended here.

documents are authorised and issued following the appropriate SOPs. The distribution and revision of most controlled documents is controlled by the central Documentation Group. The Planning Department is responsible for the control and maintenance of Product Structure and Routing Specifications.

Changes are proposed, processed, authorised and implemented using the procedure known as the THE Manufacturing Company Change Management System. This includes changes to a production process, production documentation, technical documentation, QA specification, Instruction for Use, other printed material, labels, or other documentation which may affect either the performance claim of the product, the manufacturing process, product presentation or Declaration of Conformity. The change procedure is defined in SOP XXX.

Certain changes to THE Manufacturing Company products and THE Manufacturing Company Quality System must be notified to the various Competent Authorities or their recognized assessment body (for example, the Notified Body under the provisions of the IVD Directive (98/79/EC) for CE marked products). The process for determining and notifying of ‘significant changes’ is outlined in SOP XXX.

In addition, copies of applicable national or international standards/regulations are controlled by Regulatory Affairs.

4.2.4. Control of Records
Records are maintained to provide evidence of conformity to requirements and of the effective operation of the quality management system. Records are completed according to SOP XXX, and must be legible and readily identified.

The major record types and retention times are defined in SOP XXX. Quality records are maintained in such a way that they are readily retrievable and unlikely to deteriorate.
5. Management Responsibility

5.1. Management Commitment
The senior managers demonstrates its commitment to the development and implementation of the quality management system requirements by
• Establishing and maintaining a quality system
• Defining the quality policy and quality objectives (quality plan) and communicating these throughout the organization
• Ensuring the availability of resources
• Conducting management reviews (SOP)

5.2. Customer Focus
The senior managers ensures that customer requirements are defined throughout all stages of product realisation. Performance against these is reviewed to improve customer satisfaction via the Complaint Handling process (SOP), Customer Requirements (SOP), Design Reviews, Post Market Surveillance (SOP) and CAPA Oversight / Management Review (SOP). In addition THE Manufacturing Company Marketing Executive communicates within the company and with customers to provide further definition of customer needs.

5.3. Quality Policy
The Quality Policy of THE Manufacturing Company Biotech Limited (THE Manufacturing Company) is to improve health care by providing high quality, safe and effective diagnostic products.

This is achieved
a) Through the processes of design, development, manufacture and distribution carried out by competent and empowered staff.
b) by striving for continuing quality improvement.
c) by recognising that the involvement and commitment of all THE Manufacturing Company personnel is essential.
d) by providing appropriate training and an organisational structure which promotes empowerment.
e) by assessment of and effective communication with OEM suppliers
f) by ensuring appropriate investment in technology and systems

effectiveness is measured by

  g) customer feedback through the enquiry and complaint system.
  h) product availability.
  i) quality metrics
  j) employee feedback.

The Quality Policy is communicated to all employees via the Annual Quality System Training, the policy is reviewed at management Review Meetings (SOP XXX).

5.4. Planning

5.4.1. Quality Objectives
The requirements for quality are defined within the relevant Quality System Procedures, including POIs, Technical Specifications, POIs and QA Product Release Specifications and the Design & Development Plan for new products. The activities include identification and acquisition of resources and skills to achieve the required quality.
Senior managers establish Quality objectives as part of the Quality Plan for each year. Each employee has a job description which includes the quality accountabilities of the position. In addition an employee may have specific quality goals.

5.4.2. Quality Management System Planning
Senior managers review data relating to the Quality System requirements and objectives at the six-monthly Management Review and at the monthly meetings of the CAPA Oversight Review Board and Europe Site Management Team. This includes identification and acquisition of resources and skill to achieve the Quality Policy. Key metrics of the Quality System are reviewed at these meetings. SOP XXX details the aspects of the quality system that are reviewed.

5.5. Responsibility, Authority and Communication

5.5.1. Senior managers are responsible for ensuring that responsibilities and authorities are defined and communicated.

5.5.2. Senior managers and their responsibilities are defined following:

Site Director
This position has overall responsibility for the site

Functional Managers in R&D, QA and Finance
These positions report into their respective directorates within the company but also report to the Site Director on a day to day operational basis.

The position holder has overall responsibility for THE Manufacturing Company Quality Policy and for the quality of all products produced by THE Manufacturing Company, and is chairman of the CAPA Oversight Review Board and Management Review Board.

Operations Manager
The prime accountability of the Operations Manager is to ensure that the manufacturing laboratories meet their cost, quality and service level goals and that the facilities and HS&E functions are effectively managed. This is achieved through delegated responsibilities to line reports.

Financial Controller
The principal responsibilities of this position are to provide the executive and line management of THE Manufacturing Company and other Companies managed from the site with accurate and timely financial information on which informed business decisions can be made. The position holder is also responsible for safeguarding the Companies’ assets through the maintenance of a system of internal accounting controls and ensuring that the Companies are at all times compliant with all statutory financial requirements.

The Financial Controller is responsible to the Site Director for the operation and development of electronic information systems. This includes the purchase and maintenance of hardware; systems security; data security; software licensing; and software development. Basic user training is provided in the use of systems. The position holder is also responsible for the development of improved business processes, in collaboration with other managers.

Quality Assurance (QA) Manager
The position holder is responsible for ensuring that THE Manufacturing Company Quality System is in compliance with regulations and is operating to assure quality in all products and services.
It is the responsibility of this position holder to ensure that THE Manufacturing Company Quality Systems requirements are communicated to all THE Manufacturing Company managers and employees and that the actions required to maintain compliance with ISO 9001:2008, ISO 13485:2003 and the requirements of the IVDD and other relevant regulations are highlighted to appropriate personnel.

The QA Manager is responsible for ensuring that the performance of THE Manufacturing Company Quality System is reviewed in order to improve its effectiveness.

Other responsibilities include the Internal Audit System, training personnel on the Quality Policy and Quality System, defining criteria for release of products, assessment and release of incoming raw materials and packaging items, issuing Quality Holds and Recalls due to internal failure and/or customer complaints; and authorisation of the IVDD Declaration of Conformity.

The QA Manager reports to the senior managers.

Regulatory Affairs Manager
The Regulatory Affairs Manager is responsible to the QA Manager for ensuring that site management is aware of legal and regulatory requirements, which affect the company and its products.

The Regulatory Affairs Manager has defined regulatory responsibilities for labelling and product safety including defining the products already on the market to which the IVDD applies, and the classification of these products according to the various regulations in country of export. The position holder has sign off authority for non-conformances and all changes to THE Manufacturing Company products.

The position holder facilitates any changes in processes and procedures, which are needed in order to meet new regulatory requirements.

It is the responsibility of the Regulatory Affairs Manager to ensure the knowledge of national and international regulatory requirements affecting THE Manufacturing Company's products is maintained up-to-date within the Regulatory Affairs Department. This includes ensuring the requirements are met for both existing and new products. Where appropriate, new requirements are incorporated into THE Manufacturing Company quality system documentation.

The Regulatory Affairs Manager is responsible for Product Support and has vigilance responsibilities under the various regulations.

Services QA Manager
The Services QA Manager reports to the QA Manager. This position holder is responsible for the management of the documentation systems and administration of systems such as change management. The position holder is also responsible for the environmental quality through the use of effective sampling and monitoring, and the assessment and release of incoming goods using appropriate sampling and test methods. These responsibilities are met through the management of accountable teams.

Product QA Manager
The Product QA Manager reports to the QA Manager and is responsible for the management of the trend analysis process which ensures that production departments carry out effective trend reviews and that appropriate action is taken. Other responsibilities include ensuring that Test Method Validation is completed according to plans and approving all product related validation plans and reports.
Human Resources Manager
Reporting to the Site Director, the Human Resources Manager has responsibility for manpower resourcing, training, development and education, employee relations and reward.

Manufacturing Services Manager
Reporting to the Site Director, the Manufacturing Services Manager is responsible for all manufacturing operation.

Supply Chain Manager
Reporting to the Site Director, the Supply Chain Manager is responsible for ensuring that all the Manufacturing areas know what to manufacture; for planning orders on OEM suppliers and for the availability of purchased materials and other items to support the forecasted demands.

The Supply Chain Manager is supported by a team of Planners and Purchasing staff. Responsibility for the different aspects of planning and procurement are allocated to these staff. These responsibilities extend to include the control and design of Packaging Materials. Plans include both quantities and due dates, and consist of both short- and mid-term requirements. Short-term requirements include specific lots with priorities and expediting requirements. Longer-term requirements are aimed at ensuring overall capacity requirements for both labour and plant are communicated in a timely manner to the manufacturing area Managers and OEM suppliers. Procurement activities aim to optimise quality and costs whilst maintaining high service level performance.

Health, Safety and Environmental Manager
Reporting to the Operations Manager, the Health, Safety & Environmental Manager is responsible for providing a comprehensive health and safety service to all functions of the company. The job holder is responsible for ensuring that the demands of relevant national and international legislation are met, taking into consideration what is reasonably practicable in relation to the level of risk.

In addition to the above responsibilities the job holder advises on environmental issues which affect the company’s operation.

The position holder is also the Dangerous Goods Safety Advisor for the company and advises on the shipping of items which are classified as dangerous under the various mandatory codes and regulations.

Research & Development Department Manager
The Research and Development Manager is responsible or all aspects of assay projects within Research and Development including:

a. The development of new products.

b. The introduction and approval of new and improved materials and processes to be used for the manufacture of existing products.

c. Approval of changes to manufacturing processes.

d. The authorisation of production documentation relating to these projects.

e. The content of the instructions for use.


g. Management of THE Manufacturing Company Marketing Executive who is the company’s principle customer contact for developing customer requirements and Marketing Plans.

h. In addition the position holder has responsibility to the Site Director for the resolution of technical problems related to the performance of products already on the market.

Facilities Manager
Reporting to the Operations Manager, the Facilities Manager is responsible for installation, service,
maintenance and repair of all manufacturing machinery, building services, utilities, environmental control equipment and qualification of equipment, utilities and facilities.

The position holder is also responsible for the calibration policy of quality critical devices and for providing traceable primary reference devices. The Facilities Manager is responsible for ensuring that the Company complies with all legal and statutory requirements in respect of electrical, mechanical and building services.

5.5.3. Internal Communication
The senior managers are responsible for communicating customer, statutory and regulatory requirements to all members of the company. This is achieved by means of All-Employee Meetings, Team Briefs, Communication Meetings and annual Quality System training.

5.6. Management Review

5.6.1. General
Monitoring and review of the THE Manufacturing Company Quality System is performed by the Management Review Board (SOP XXX), which includes the Site Director and senior managers from Operations, R&D and Quality.

At least twice per calendar year the Management Review Board reviews the adequacy and effectiveness of the THE Manufacturing Company Quality System, and reviews opportunities for improvement and the need for changes to the quality management system, including the Quality Policy and Quality objectives.

5.6.2. Review Input
Inputs to Management Review includes review of Internal Audits, Complaint Issues, review of process and product conformance, Post Market Surveillance Reviews, issues from Corrective and Preventive Action, Supplier issues, review of training and Regulatory issues and other changes that could Affect the Quality System.

5.6.3. Review Output
Outputs of the Management Review Board are documented including summaries of data evaluation, analyses and recommendations and actions relating to the effectiveness of the Quality System and its processes.

6. Resource Management

6.1. Provision of Resource
THE Manufacturing Company identifies resources required through the budgeting process, and inputs from the senior managers to maintain the Quality System and ensure Customer and Regulatory requirements are met.

6.2. Human Resource

6.2.1. General
All staff have a Job Description, describing the primary objective of the position, major accountabilities, supervisory responsibilities, education and background experience required for the job and an outline training plan (SOP XXX).
6.2.2. Competence, Awareness and Training
All staff will receive the necessary training to enable them to perform their job effectively and safely (SOP XXX). It is a THE Manufacturing Company policy that all personnel take responsibility for the quality of their work. This training will be both formal and informal and will be provided by the Human Resources Department, external trainers or local area supervisors as appropriate.

It is the responsibility of individual managers to assess whether their staff require re-training following changes to procedures.

Direct job related training will be supplemented by educational and developmental opportunities in line with the business needs.

Job related, functional training of all critical operating tasks will be provided by a formal system in accordance with SOP XXX. This system also covers other non-critical operating tasks, which are of a functional nature.

Training on the processes and procedures is completed by reading SOPs and signing off on the Electronic Training Management System (ETMS). If competency assessment is required this is documented by means of a Training Assessment Form as described in SOP XXX.

All Departments identify individual training needs on an annual basis via the performance appraisal process and these are consolidated by the Human Resources Department into a company training plan.

Annual Quality System training is given to all employees and includes consideration of how they can contribute to the achievement of the quality objectives.

6.3. Infrastructure and Work Environment

Systems have been established to provide an infrastructure to ensure conformity to product requirements. Where special arrangements are required e.g. Category III working these are defined in specific SOPs and training is given.

Equipment is qualified and is maintained to ensure continuing process capability. Monitoring the requirement for maintenance is carried out either locally according to SOP XXX for the equipment concerned or by the Engineering Department.

Environmental monitoring is carried out, according to SOP XXX, to ensure that product performance is not impacted by the environment.

Facility cleaning is defined by the Cleaning Contract specification for Contract Cleaners, and cleaning of work surfaces by SOP XXX. The monitoring of facility cleaning is described in SOP XXX.

Clothing procedures for staff working in manufacturing areas are detailed in SOP XXX.

7. Product Realisation

7.1. Planning of Product Realisation

Stock and work in progress is considered before determining the net requirements. Firm orders for finished goods are raised on the system and become the driver for the manufacture of lower local components, bulks and the purchase of raw materials. Purchase orders are also placed for OEM products.
The Design Control Procedures and responsibilities of personnel within the system are described in SOP XXX. Projects are approved and design goals set within the budgeting process. Products are then developed according to a procedure which ensures that the product has been designed to meet, the design inputs. A Design History File (DHF) is compiled during the development of a product, and is updated throughout the life cycle of the product. The methods of how product is manufactured and released for sale are detailed in SOPs and POIs for the processes used.

7.2. Customer-related processes

7.2.1. Determination of requirements related to the product
Customer Requirements Document (CRD) and Product Requirement Document (PRD) are written for new or redeveloped products (SOP XXX). The CRD defines the physical and performance requirements of a device based on input from internal and external customers. The PRD translates customer requirements into a technical product description that is measurable and verifiable. These include statutory and regulatory requirements.

7.2.2. Determination of requirements related to the product
The ongoing review of requirements to ensure customer needs and customer satisfaction are meet is through the Product Co-Ordination Group, chased by THE Manufacturing Company Marketing Executive and through annual Post Market Surveillance Reviews (SOP XXX).

At each Design Review, and for changes made during the product life cycle, the appropriate requirements of the IVDD will be considered. Risk Analysis (User, Patient) is carried out according to SOP XXX.

7.2.3. Customer communication
Customers are provided with information relating to the products through THE Manufacturing Company Marketing Executive. Information on products is also communicated to customers through Product Information Letters, follow up of complaint investigations, Technical Bulletins and communication to the customer where product requirements are not met.

7.3. Design and Development

7.3.1. Design and Development Planning
The design and development activities fall into the key project stages listed below. These are defined in the Design and Development Plan (SOP 5/199). At each stage there may be several organisational functions involved.

During the course of the project there will be regular reviews of the development activities against Design Input requirements.

The Design and Development Template is developed into the project plan by the Project Manager and is circulated to Project Group Members. As the project progresses, the plan is updated/revised as necessary and re-issued. Progress with the relevant parts of the Design and Development Plan are noted as the project progresses.

During the initial planning stage, appropriate and adequate resource is assigned to each activity and this also is reviewed during the course of the project.

Having received the approval to develop a product, the Project Group is the controlling body for a project. Regular meetings (normally monthly) are held, chaired and minuted by a Project Manager; copies of these minutes are distributed to Project Group members and appropriate members of the Site Management Team. Review of progress against the plan is made by this group.
Detailed issues are addressed outside the Project Group at R&D Technical meetings and Operations meetings. Technical Meetings run by R&D are normally held monthly and include members from Operations.

Minutes of these meetings form part of the DHF and are circulated appropriately. The functional leader for a specific area will report back to the next Project on resulting issues.

7.3.2. Design and Group meeting Development Inputs
The Design Inputs are defined according to SOP. The product requirements (SOP) are documented and agreed by Marketing and R&D. The needs of the user and patient are considered during this process.

A summary of the regulatory requirements relevant to the product in the countries into which it will be sold is prepared according to SOP XXX.

The conformity assessment route to be followed will be determined according to the risk class that the product falls into (Refer GHTF/SG1/N045:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification). Where a product may, according to the risk classification rules, fall into several classes, the conformity assessment route must be determined by the highest risk class that may apply.

Products are then designed and developed to meet the specification, with regular reviews of the product against the Design Inputs.

Current statutory safety requirements are addressed by performing COSHH assessments, providing Material Safety Data Sheets and in the “Warnings & Precautions” section in the package inserts. Each of these activities are covered by the Design and Development Plan or project minutes.

7.3.3. Design and Development Outputs
The design output is routinely monitored through Design Review and Technical and Project Group meetings to ensure that it meets the requirement of the Design Inputs.

Design output in the form of documentation and data such as POIs, QA Specifications, SOPs and stability reports is reviewed before release.

7.3.4. Design and Development Review
An independent review of the design output against the Design Input Requirements takes place at various stages during product development including design input, design verification, design validation.

Prior to release for sale the product is reviewed by Division and appropriate Site Management (SOP XXX).

For products which will be CE marked under the IVD Directive, Product QA cannot release the first batch for sale until the Declaration of Conformity is signed.

7.3.5. Design and Development Verification
During the development process R&D undertake evaluations using materials of clinical origin and if available appropriate external standards to ensure that the product meets the Product Specification (SOP XXX). A Design Verification review is performed according to SOP XXX.

7.3.6. Design and Development Validation
Design validation is carried out by performing Performance Evaluation Trials under the direction of the Project Manager. The new product is evaluated against the Customer Requirements Document.
using clinical samples (SOP XXX). Results are analysed and assessed by R&D Scientist. Details of how the evaluation is planned and carried out can be found in SOP XXX.

For products classified by the IVDD as Annex II List A, the requirements of the Common Technical Specifications are met as part of the Design Validation.

7.3.7. Control of Design and Development changes
During the development phase of a new product any changes which are proposed are reviewed, agreed by all signatories and incorporated into the Product Specification.

The Design Change Control Procedure is defined in SOP XXX.

Once Design Validation has been undertaken changes are managed through a controlled procedure for the review, approval and implementation of change which is detailed in SOP XXX.

The correct transfer of product design into POIs is checked by R&D and Manufacturing personnel during the Pre-Production Phase (SOP XXX).

Process validation is a key part of design and development in order to ensure quality critical processes are sufficiently well defined and controlled.

The DHF (SOP XXX) is completed throughout the Design Phase. It is a compilation of records which describe the design history of the finished device and includes the Design and Development Plan, the Product Specification and the dossier from each review meeting.

7.4. Purchasing

7.4.1. Purchasing Process
Materials which form part of the manufacturing process for THE Manufacturing Company products are identified by means of an item coding system. Ad hoc purchases for R&D purposes, facilities maintenance and administration are dealt with separately. Where possible THE Manufacturing Company item codes are linked to supplier catalogue codes and both are stated on purchase orders. Where this combination is not possible, technical specifications are agreed with suppliers and referenced to THE Manufacturing Company item code. These specifications define the dimensional and quality requirements together with any other parameters critical to the performance and acceptability of the item being purchased.

Where a finished product is purchased from an OEM supplier, the process for evaluation and approval of the product is defined in SOP XXX.

Suppliers are selected on the basis of ability to supply the required items or services at the right quality in the most timely and economic manner.

Suppliers are the subject of a rating/approval scheme (SOP XXX) which assesses either the suitability to supply (for a new supplier) or the effectiveness of supply (for existing suppliers). Ratings are regularly reviewed and updated and the results of the review process determine the priority of the requirement to audit.

Suppliers are approved following assessment of their Quality System (SOP). A list of Approved Suppliers is maintained.
7.4.2. Purchasing Information
Requirements are communicated to suppliers by means of authorised Purchase Orders. Purchasing documents are controlled by Standard Operating Procedures.

Purchase Orders will contain references, as appropriate, to THE Manufacturing Company Item Codes, Supplier Catalogue Codes, agreed Technical or Purchasing Specifications or legal agreements between THE Manufacturing Company and the Supplier. If necessary, copies of specifications, drawings etc. will be referenced in the Purchase Order document and that document will be annotated accordingly. Review and authorisation of Purchase Orders is carried out as described in SOP XXX. Purchase orders are quality records and are retained for traceability purposes.

7.4.3. Verification of Purchased Product
Inspection and verification of incoming goods, including raw materials, packaging components and instrumentation is carried out according to documented procedures.

Testing is only performed at THE Manufacturing Company when quality critical material is involved and it is not possible to be sure that adequate controls are exercised at source.

If components are required urgently for production, there are systems to allow production to progress before testing has been completed, but the final product cannot be released before the testing has been completed satisfactorily.

7.5. Production and Service Provision

7.5.1. Control of Production and Service Provision
Manufacturing processes are controlled in accordance with Process Operating Instructions (POIs) or Production Specifications. Some processes, such as filling, are monitored and controlled using statistical process control techniques throughout the operation.

Product structure and routing information to support the production of products is defined by Product Structure & Routing Specifications which are controlled by the Planning Section.

Products are manufactured using software, facilities, utilities, equipment, materials and processes that have undergone appropriate validation (SOP XXX).

All materials from Incoming Goods through intermediate manufacturing stages to final product are handled in accordance with written, approved specifications and Standard Operating Procedures.

The intention of THE Manufacturing Company is that premises are as far as possible suited to their intended use, being secure, of adequate size and design to allow product security by minimising the risk of mix-up occurring. Safety, ease of cleaning and adequate pest control receives high priority.

Procedures are followed to maintain labelling integrity and to prevent labelling errors.

The packing process, including the information printed by THE Manufacturing Company on the labels and packaging, is controlled by Product Structure & Routing specifications.

Final product can only be picked for distribution if it has been approved for issue by Product QA.

Product packaging and shipping containers are designed to protect the products from damage during normal conditions of storage, handling and distribution. Records relating to the identification and quantity of product shipped and the identity of the consignee are retained.
Installation and Servicing Activities are not undertaken by THE Manufacturing Company.

7.5.2. Validation of Processes for Production and Service Provision.

The approach to validation is defined in SOP XXX.

Equipment qualification is performed to ensure that equipment used in the manufacture of quality critical processes has been designed to meet the needs of that function and will operate consistently to meet the needs of the intended process (SOP XXX).

Process validation is performed to establish a high level of confidence that quality critical processes are sufficiently well controlled so as to ensure a consistently high level of quality in terms of efficacy and product stability (SOP XXX).

Test Method Validation is performed to establish that the performance characteristics of the method meet the requirements of the intended use of the test (SOP XXX).

Software validation is completed according to SOP XXX.

7.5.3. Identification and Traceability

Materials used as part of the manufacturing process for products are identified by a part code and the manufacturer's lot number or the THE Manufacturing Company allocated batch number. All intermediate products and bulks are identified by unique THE Manufacturing Company lot numbers assigned by Manufacturing.

Final components and kits are labelled with the component or kit product code together with individual batch numbers. The Batch Histories which are maintained by the Quality Assurance Department can be used to trace the history of the product or component batch to the Production Records kept by Manufacturing.

Material/component/product status is computer driven and under the control of Purchasing Quality Services/Product QA. Product release for sale is the responsibility of the respective Product QA Manager, but may be delegated to appropriate authorised personnel from within Quality Assurance.

Inspection and testing activities which verify that the specified requirements for that product are met are defined in the relevant Quality System Procedure.

In-Process inspection and testing of THE Manufacturing Company products is carried out by manufacturing personnel following procedures described in Production Specifications. Quality Assurance personnel also perform in-process inspection and testing following QA Specifications.

Depending on the results of the inspection and testing, products may be passed, referred or rejected.

Final inspection, and testing where appropriate, of THE Manufacturing Company products is carried out by Quality Assurance personnel following QA Specifications.

For CE marked products classified as Annex II List A products, the Product QA Manager is responsible for ensuring that the verification of manufactured product by the Notified Body is received before the batch is released for sale (SOP XXX).

Production records containing the results of inspection and testing by Manufacturing personnel are held within the Manufacturing area before archiving.
Batch Histories (Secondary Manufacturing records and Quality Assurance testing of each product batch) are held accessible as original hard copy for up to 3 months beyond the expiry of the product. Beyond that point QA records are archived in the form of microfiche. The personnel responsible for the release of product are defined in appropriate SOPs and indicated on the Batch Histories.

7.5.4. Preservation of Product
Storage areas preclude adverse environmental effects on stored materials and allow orderly stock control by providing effective separation of different materials and materials of different status.

Appropriate facilities are available for the storage and handling of materials that are potentially infectious.

7.6. Control of Monitoring and Measuring Devices

All quality influencing equipment is subject to regular calibration and is traceable to national standards.

The management of routine calibration work will, for the most part, be the responsibility of the Facilities Manager. This responsibility will be shared by responsible personnel in each area who ensure that only properly calibrated equipment is in routine use.

The frequency with which equipment is calibrated and the tolerances that are allowed before adjustments are made will be as recommended in manufacturer’s user guides and/or service manuals. In deciding on the optimum retest cycle and adjustment limits the Engineering Department will take account of the reliability and criticality of the relevant equipment.

Calibration records will be kept adjacent to the relevant equipment in the various operating areas and/or centrally by the Engineering Department as appropriate.

Implementation of this policy is controlled in SOP XXX.

Where products contain calibrators or quantified controls, traceability to an independent standard where available is ensured through Design Input and the QA Release Specifications.

8. Measurement, Analysis and Improvement

8.1. General

Procedures have been designed / developed and implemented to monitor
- if customers requirements for products and service delivery have been met,
- the effectiveness of the Quality Management System,
- and the ongoing improvement of the Quality Management System.

8.2. Monitoring and Measurement

8.2.1. Customer Satisfaction
Procedures have been developed and implemented, which define the process for the determination of product and service quality levels.
End-user satisfaction is monitored by the country organisations. The country organisations provide feedback through the complaint management system. A review is held annually for each product (SOP XXX) as part of Post Market Surveillance.

8.2.2. Internal Audit
Internal audits are co-ordinated by the Audit Co-ordinator within QA and are performed by trained internal auditors from a range of Departments. Audits are performed by personnel independent of the process or area being audited.

Audits are performed of specified activities (e.g. Hold/Corrective Action, Control of Change, Calibration) and of specific areas, to cover all relevant aspects of ISO 9001, ISO 13485 and the IVDD. The procedure followed is described in SOP XXX.

The progress with corrective actions arising from internal audits involves visits to the appropriate area. Failure to meet agreed dates is highlighted to the CAPA Oversight Review Board.

8.2.3. Monitoring and Measurement of Processes and Product
Processes have been designed and implemented to ensure that the data on records relating to the Quality Management System, and product quality are gathered, evaluated and analysed for trends. This trend data is then used to implement corrective and/or preventive actions.

In-process materials are sampled, inspected and tested by trained personnel in accordance to documented standardised and validated test procedures. Requirements are stated in the applicable testing procedures and sampling plans.

Material conformance is based on test and/or inspection results and work order review. Disposition is assigned by trained personnel. Materials are held until all tests and inspections have been completed and approved. Any non-conforming in-process materials are controlled, segregated, where practicable, and the non-conformity documented.

Final sampling, testing, inspection and disposition of product are done by trained quality personnel in accordance to documented standardised and validated test procedures. Requirements are stated in the applicable testing procedures and referenced sampling plans.

Final product test records, certifying that all required tests have been satisfactorily completed, are required prior to disposition by authorised personnel.

Appropriate statistical techniques are used for packaging materials inspection, and in-process inspection and testing during manufacture. These are defined in the relevant SOPs.

Where appropriate, sampling methods are reviewed in the light of non-conformances in product or processes or other appropriate information.

Assessment of product performance for Design Verification is performed using techniques which are the accepted norm in the IVD industry.

Product trend are reviewed according to SOP XXX.

Product is released to distribution upon final approval or, in cases where regulatory requirements have to be met upon regulatory approval or consent (e.g. in case of notifications). The stability of products is monitored after release for sale (SOP XXX).
8.3. Control of Nonconforming Product

The control of non-conforming raw material or components and non-conforming final product is the responsibility of appropriate Quality Assurance personnel. The procedures followed are described in SOP XXX. The procedure for quarantining non-conforming material is detailed in SOP XXX.

Appropriate corrective action following a product failure after release is initiated and co-ordinated by the Quality Assurance Manager. The procedures followed are described in SOP XXX.

The review and disposition of non-conforming product is carried out according to SOP XXX.

If product is reworked, the specific requirements of SOP are followed. It is the responsibility of the Regulatory Affairs Manager or agreed deputy to ensure regulatory requirements are met before authorising a non-conformance report. The procedure for the complete rejection of product and subsequent disposal is described in SOP XXX.

8.4. Analysis of Data

Procedures have been implemented to collect and analyse appropriate data. Data is evaluated for the reviews by Site Management.

8.5. Improvement

Post Market Surveillance and related activities to meet the requirements of the IVDD (Annex III (5), Annex IV (3.1) or Annex VII (3.1)) is carried out according to SOP XXX for ALL products, regardless of the regulatory version.

8.5.1. Continual Improvement
Data on trends in non-conformances related to the Quality Management System, suppliers, product and processes are input to the Management Review Meeting to determine that appropriate corrective / preventive action is taken.

8.5.2. Corrective Action
Customer complaints are received, investigated, reported, and replied to by the Product Support Group. SOP XXX describe the procedures followed and include the requirements for Vigilance reporting under the various regulations.

The investigation of the cause of non-conforming product following customer complaints is detailed in SOP XXX if action is required for products with customers.

The procedure for investigations and defining of Corrective Action following a non-conformance or a Customer Complaint is detailed in SOP XXX. Subsequent to implementation of that Corrective Action Plan, the effectiveness of the action is reviewed.

8.5.3. Preventive Action
A variety of sources of information are reviewed in order to detect, analyse and eliminate potential causes of non-conformities. The information reviewed includes Non-Conformance reports, Investigations and Corrective Actions, reports of internal and external audits, Change Notes, trend analysis and complaints.

Preventive action is progressed or monitored by the Management Review Board (SOP XXX).