

**WHO Prequalification Team - Inspection services**  
**WHO PUBLIC INSPECTION REPORT (WHOPIR)**

| <b>Inspected site</b>                         |                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of Manufacturer                          | Diagnostics for the Real World Ltd.                                                                                                                                                                                                                                                                                                                                                      |
| Address of inspected manufacturing site       |                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Inspection details</b>                     |                                                                                                                                                                                                                                                                                                                                                                                          |
| Dates of inspection                           | 21-22 November 2019                                                                                                                                                                                                                                                                                                                                                                      |
| Type of inspection                            |                                                                                                                                                                                                                                                                                                                                                                                          |
|                                               |                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Introduction</b>                           |                                                                                                                                                                                                                                                                                                                                                                                          |
| Brief description of manufacturing activities | The manufacturing activities take place at two Diagnostics for the Real World sites (one in San Jose, California and one in Little Chesterford, Essex, United Kingdom) and at the premises of a critical contract manufacturer (Barric Ltd, Diss, Norfolk, UK). The San Jose site manufactures the consumables for the SAMBA I and II qualitative tests and semi quantitative HIV tests. |
| General information about the manufacturer    |                                                                                                                                                                                                                                                                                                                                                                                          |
| History                                       |                                                                                                                                                                                                                                                                                                                                                                                          |

| <b>Brief report of inspection activities undertaken – Scope and limitations</b> |                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Areas inspected                                                                 | Quality management system<br>Management responsibility<br>Purchasing<br>Production and Service Controls<br>Measurement, analysis and improvement<br>Adverse Events and Advisory Notices Reporting<br>WHO pre-qualification-specific requirements                    |
| Scope                                                                           |                                                                                                                                                                                                                                                                     |
| Criteria                                                                        | ISO 13485:2016 and WHO Prequalification specific requirements                                                                                                                                                                                                       |
| Objective(s)                                                                    | <ul style="list-style-type: none"> <li>Review the effectiveness of the implementation of corrective actions implemented following the previous WHO inspections</li> <li>Establish whether the applicable requirements to ISO 13485:2016 and WHO were met</li> </ul> |
| Limitations                                                                     |                                                                                                                                                                                                                                                                     |
| Out of scope                                                                    | Exclusions and non-applications from ISO 13485:2016:<br>7.5.5 Particular requirements for sterile medical devices<br>7.5.9.2/8.2.4.2 Requirements for implantable and active medical devices                                                                        |
| <b>Abbreviations</b>                                                            | <b>Meaning</b>                                                                                                                                                                                                                                                      |
| CoA                                                                             | Certificate of analysis                                                                                                                                                                                                                                             |
| IQ                                                                              | Installation qualification                                                                                                                                                                                                                                          |
| IVD                                                                             | In vitro device                                                                                                                                                                                                                                                     |
| MR                                                                              | Management review                                                                                                                                                                                                                                                   |
| MSDS                                                                            | Material safety data sheet                                                                                                                                                                                                                                          |
| NC                                                                              | Non-conformity                                                                                                                                                                                                                                                      |
| PPE                                                                             | Personal protective equipment                                                                                                                                                                                                                                       |
| OOS                                                                             | Out-of-specifications test result                                                                                                                                                                                                                                   |
| OQ                                                                              | Operational qualification                                                                                                                                                                                                                                           |
| PM                                                                              | Preventive maintenance                                                                                                                                                                                                                                              |
| PQ                                                                              | Performance qualification                                                                                                                                                                                                                                           |
| PW                                                                              | Purified water                                                                                                                                                                                                                                                      |
| QA                                                                              | Quality assurance                                                                                                                                                                                                                                                   |
| QC                                                                              | Quality control                                                                                                                                                                                                                                                     |
| QCL                                                                             | Quality control laboratory                                                                                                                                                                                                                                          |
| QMS                                                                             | Quality management system                                                                                                                                                                                                                                           |
| QRM                                                                             | Quality risk management                                                                                                                                                                                                                                             |
| RA                                                                              | Risk assessment                                                                                                                                                                                                                                                     |
| RCA                                                                             | Root cause analysis                                                                                                                                                                                                                                                 |
| SOP                                                                             | Standard operating procedure                                                                                                                                                                                                                                        |

**Summary of the findings and comments**

The inspection findings are listed below, following the numbering of the clauses of the ISO 13485:2016 standard for easy reference.

**4. Quality management system****4.2. Documentation requirements****4.2.2. *Quality manual***

The manufacturer's Quality Manual was found appropriate and reflected the intended practices of the manufacturer. Non-applicable clauses of ISO13485:2016 ("the standard") were listed/excluded with appropriate justification.

**4.2.3. *Medical device file***

The manufacturer established and maintained documents demonstrating conformity to the requirement of the standard. These included descriptions of the labelling requirements. Labelling of the finished product was verified. The required information (e.g. the content, number of tests, preservation temperature, product codes, batch number and expiry dates) was clearly visible and would not smudge.

**4.2.4. *Control of documents***

The manufacturer updated its documented procedures for document control, which broadly met the requirements of the standard. A hybrid paper-electronic system was used.

**4.2.5. *Control of records***

Record retention was at least equivalent to the lifetime of the device. At the time of the inspection, the requirements for the retention of records and documents (3 years) well exceeded the less than 12 months long shelf life of the product.

**5. Management responsibility****5.1. Management commitment**

There was evidence of top management's commitment to the development and implementation of the quality management system and maintenance of its effectiveness. Top management had established an adequate Quality Policy including a commitment to comply with regulatory requirements and to maintain the effectiveness of the QMS.

**5.3. Quality policy**

The manufacturer had established an adequate quality policy, including a commitment to comply with regulatory requirements and to maintain the effectiveness of the quality management system. The quality policy was applicable to the purpose of the organization and related to quality objectives.

#### 5.4. Planning

##### 5.4.1. *Quality objectives*

Quality objectives were established, measurable and had defined targets and were consistent with the quality policy.

##### 5.4.2. *Quality management system planning*

The manufacturer had documented the organizational structure and defined designated responsibilities and authorities for staff undertaking or verifying work affecting quality. Reporting lines for quality and production were independent of the other.

#### 5.5. Responsibility, authority and communication

##### 5.5.2. *Management representative*

There was continuity in the role of the management representative, with the responsibilities and authorities as defined in the standard.

#### 5.6. Management review

##### 5.6.1. *General*

Documented requirements for management review were implemented and the review meetings were held at least annually. The manufacturer monitored and measured the ability of the quality management system processes to meet planned results, as indicated in the records of Management Review.

### 6. Resource management

#### 6.1. Provision of resources

The manufacturer had determined and continued to provide the resources needed to implement the quality management system, to maintain its effectiveness, and to a great extent to meet regulatory and customer requirements.

#### 6.2. Human resources

The manufacturer had a strong research background and employed highly qualified researcher scientists.

#### 6.4. Work environment and contamination control

##### 6.4.1. *Work environment*

Manufacturing activities remained in the premises located in a light industry area of San Jose. The premises were only a few years old, spacious and allowed for a generally acceptable work flow. The premises were maintained satisfactorily and had an appearance of being clean and tidy. The manufacturer had previously determined and continued to maintain the work environment suitable for the type of product manufactured. The deficiencies that were initially identified during the onsite inspection had been satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

#### 6.4.2. *Contamination control*

Environmental monitoring was performed once per year. The air pressure in the manufacturing areas was higher than that of the warehouse, although the pressure difference appeared rather small.

### 7. **Product realization**

#### 7.1. Planning of product realization

The manufacturer's approach to planning of product realization followed the requirements of the standard and the procedures and work instructions reviewed indicated that they included all relevant production processes. The requirements for risk management were documented in relevant procedures. The deficiencies that were initially identified during the onsite inspection had been satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

#### 7.3. Design and development

##### 7.3.9. *Control of design and development changes*

The change control procedure included adequate provisions for informing WHO of planned changes to the product, processes, facility and/or equipment.

#### 7.4. Purchasing

##### 7.4.1. *Purchasing process*

The manufacturer maintained documented requirements for purchasing controls and supplier management that largely followed the requirements of the standard. Criteria for selection, evaluation and re-evaluation of suppliers of products and services included provisions for the approval of new suppliers of critical materials.

##### 7.4.3. *Verification of purchased product*

Inwards goods testing was performed in accordance with documented specifications. The incoming QC standard operating procedures and specifications reviewed were found in compliance with the standard.

#### 7.5. Production and service provision

##### 7.5.1. *Control of production and service provision*

Several manufacturing activities were observed, including packaging of spheres in cartridges, buffer vial filling and sealing and quality control. Deficiencies initially identified during the inspection were satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

##### 7.5.6. *Validation of processes for production and service provision*

The manufacturer had procedures and corresponding records for the validation of processes for production and service provision demonstrating the ability of these processes to achieve planned results consistently. The manufacturer had documented procedures for the validation of the application of an Excel spreadsheet used in production. Deficiencies initially identified during the inspection were satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

#### *7.5.9. Traceability*

The manufacturer had documented provisions to ensure traceability and status identification of products at all stages of manufacturing, including during quality control testing. Deficiencies initially identified during the inspection were satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

#### *7.5.11. Preservation of product*

The manufacturer had documented the procedures for preserving the conformity of the product to the requirements of the standard during processing, storage, handling, and distribution. The deficiencies related to provisions for ensuring preservation of product that were initially identified during the onsite inspection had been satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan. Prescribed preservation conditions were based on studies investigating real-time stability, including temperatures outside the recommended temperature range.

### **8. Measurement, analysis and improvement**

#### **8.2. Monitoring and measurement**

##### *8.2.1. Feedback*

The manufacturer had implemented a post-market feedback system that required customer feedback from distributors, end users, literature and/or other users. The post market system was the responsibility of the UK site.

##### *8.2.2. Complaint handling*

Procedures for managing customer complaints were in place and reflected the requirements of the regulations and the standard. The effectiveness of the established processes could not be fully determined as very few complaints had been recorded. This will be further monitored with the increase in the volume of manufacture during the subsequent audits.

##### *8.2.4. Internal audits*

The manufacturer performed internal audits in accordance with the annual internal audit program. The relevant standard operating procedure included documented requirements for timely audits by appropriately qualified auditors, independent of the areas being audited. The schedule took into account the status and importance of the areas to be audited.

##### *8.2.6. Monitoring and measurement of product*

The manufacturer had established quality control processes to monitor and measure the characteristics of the product to verify that product requirements had been met. This was carried out for incoming goods, during product realization and before lot release. Evidence of conformity to the acceptance criteria was maintained and the identity of the person authorizing release recorded. Deficiencies initially identified during the inspection were satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

### 8.3. Control of nonconforming product

#### 8.3.1. General

The manufacturer implemented procedures for managing nonconformities and corrective actions that generally satisfied the requirements of the standard. Systems and resources were available to investigate nonconformities, conduct root cause analyses, document investigations and assess the effectiveness of corrective actions taken and their potential impact on product quality. Deficiencies initially identified during the inspection were satisfactorily addressed and brought to compliance as part of the manufacturer's corrective/preventative action plan.

#### 8.3.3. Actions in response to nonconforming product detected after delivery

The procedure for vigilance described the processes for adverse event reporting and product recall management. The WHO requirements were added to the vigilance procedure since the 2017 audit. Of note, there had been no recalls or adverse events reported since the start of manufacturing.

### 8.4. Analysis of data

The manufacturer had a documented process for the analysis of quality data that met the requirements of the standard.

## 9. WHO pre-qualification-specific requirements

The products manufactured at the site had already been pre-qualified. As such, the assessment of compliance to WHO pre-qualification requirements was limited to site-specific requirements, which were met.

### Conclusion – Inspection outcome

Based on the areas inspected, the people met, and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report the company, **Diagnostics for the Real World Ltd.**, located at **San Jose, California** was considered to be operating at an acceptable level of compliance with ISO 13485:2016 and WHO Information for Manufacturers on Pre-qualification Inspection Procedures for the Sites of Manufacture of Diagnostics (PQDx\_014).

All the non-compliances observed during the inspection that were listed in the full report were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided the outcome of any WHO pre-qualification inspection or other audit from regulatory authorities that WHO relies on conducted during this period provides evidence of current compliance with the audit criteria.

### List of WHO Guidelines referenced in the inspection report

1. WHO Information for Manufacturers on Prequalification Inspection Procedures for the Sites of Manufacture of Diagnostics (PQDx\_014).  
([https://www.who.int/diagnostics\\_laboratory/evaluations/en/](https://www.who.int/diagnostics_laboratory/evaluations/en/))
2. ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes
3. ISO 9001:2015 Quality management systems - Requirements
4. WHO Post-market surveillance of in vitro diagnostics 2015 (ISBN 978 92 4 150921 3)
5. Medical devices - Application of risk management to medical devices - ISO14971:2007
6. GHTF/SG3/N19:2012 “Quality management system – Medical devices - Nonconformity Grading System for Regulatory Purposes and Information Exchange”
7. GHTF/SG4/(99)28 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 1: General Requirements
8. GHTF/SG4/N30R20:2006 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 2: Regulatory Auditing Strategy
9. GHTF/SG4(pd1)/N33R16:2007 'Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers - Part 3: Regulatory Audit Reports ISO 13485:2016, Commitments to WHO PQ.