DOCUMENT VERIFICATION

Prior to using this document, the user is responsible for verifying that the revision and effective date are current.

REVISION HISTORY

Rev.	Effective Date	Changes Made to Document
1	20-04-2023	First Issue

1. Content

2. Introduction

The LFD kit is an IVD medical device intended by DHSC to be used *in vitro* for the examination of combined throat and nasal specimens derived from the human body solely for the purpose of providing information concerning Covid-19 infection. The device is classified as a **IVD Device for self-testing.**

The PSR report outlines, analyses and reports on the activities that were undertaken by DHSC to ensure the performance and safety of the DHSC LFD during its life cycle in line with the PMS Procedure and PMS Plan.

This was performed thorough the continuous data generation and assessment of the DHSC LFD performance post market and aims to discuss (through presentation of data) the questions below:

a) Were there any new hazard or hazardous situation(s) identified for the DHSC LFD's or has the risk acceptability changed?
b) Has any misuse of the DHSC LFDs occurred?
c) Do the DHSC LFD's still meet the user's needs after medium/long term clinical use?
d) Do users experience any usability issues?
e) Are there any recurring quality issues DHSC LFD's and can significant increasing/decreasing trends be identified for DHSC LFD' inadequate performance?

Refer to Table 5 for conclusions.

3. Reference documents

Doc ID	Doc name	Revision
QM-01	Quality manual	1
QOP-25	Post- Market Surveillance (PMS) Procedure	4
PMS0001	PMS Plan for the DHSC COVID-19 LFD device (3 and 7 kit)	2
RMF-0001	LFD Risk Management File	5
QP08-F02	LFD Hazard Traceability Matrix	2

Table 1: Reference to internal documentation

4. Standards and guidelines

- ISO 9001:2015 Quality management systems – Requirements.
- ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes.
- ISO 14971:2019 Medical devices -- Application of risk management to medical devices.

5. Methodology

- Data is gathered as per the PMS Plan referenced in Table 1.
- All inputs are stored in a centralised LFD PSR location on SharePoint
- All inputs are submitted via the relevant departments as per the PMS plan.

6. Findings /Results

6.1 In-House manufacturing inspection at Biotime

No further Innova product has been procured during this reporting window.

6.2 Receiving inspection - Intertek Testing in the UK

No further receiving inspections have been carried out for this reporting period as no further product has been procured and all lots received into the UK have been validated.

6.3 Product complaints & Qualtrics Survey Reports

- The number of kits distributed in this reporting period is **~11.5mil which is an increase of ~6 mil since the last reporting period.**

- Three complaints were received from Qualtrics, MHRA Yellow card and 119 Call in this reporting period and were discussed at the weekly incident review meetings and weekly Patient safety panel meetings.

- One complaint is awaiting more information from the citizen before it can be determined whether this is a reportable as per MEDDEV 2.12-1 Rev 8.

- Two complaints were defined as non-reportable as per MEDDEV 2.12-1 Rev 8.

- A total of 323 user reports were received from the Qualtrics survey in relation to the DHSC LFD during this reporting window.

- No Lot specific trend was identified in this reporting window.

- Further information on the trending categories, number of complaints, reportability/non-reportability, investigations and further actions is documented in Table 2.

(Refer to attachment 02.1)

Qualtrics and Yellow card complaints investigation				
Trending category	Number of complaints	Reportability	Investigation	Further actions
Missing components	74	Not reportable	No batch specific trend observed. SCAR was raised in past with the supplier for this issue and corrective action was taken by supplier. However, as we are not procuring any more kits from the supplier no further action is required.	No further action. Complaints will be monitored for trending purposes. The supplier will be informed in case of a trend or an increased number of complaints.
Damaged Item	11	Not reportable	No action required; no trend observed	Complaints will be monitored for trending purposes
Faulty test results	05	Not reportable	There was no trend observed for any batch.	No further action. Complaints will be monitored for trending purposes.
Faulty items	55	Not reportable	There was no trend observed for any batch.	No further action. Complaints will be monitored for trending purposes.
Empty extraction buffer	20	Not reportable	No batch specific trend observed. A SCAR was raised in past with the supplier for this issue and corrective action was taken by supplier. However, as we are not procuring any more kits from the supplier no further action is required.	No further action. Complaints will be monitored for trending purposes. The supplier will be informed in case of a trend or an increased number of complaints
Insufficient buffer solution	96	Not reportable	No batch specific trend observed. A SCAR was raised in past with the supplier for this issue and corrective action was taken by supplier. However, as we are not procuring any more kits from the supplier no further action is required.	No further action. Complaints will be monitored for trending purposes. The supplier will be informed in case of a trend or an increased number of complaints
Allergic reaction	01	Not reportable	There was no trend observed for any batch.	No further action as no link with the device identified. Complaint was more related to user experiencing covid symptoms. Complaints will be monitored for trending purposes.
Patient injury	02	Not reportable	There was no trend observed for any batch.	No further action. Complaints will be monitored for trending purposes.
Barcode/QR code issues	09	Not reportable	There was no batch specific trend observed for similar type of complaint.	No further action. Complaints will be monitored for trending purposes
Usability	02	Not reportable	Not enough provided by the reporters to confirm the type of usability issue	Updating Qualtrics survey to get more specific information about what was the exact usability issue faced by the reporter.
User error	06	Not reportable	There was no trend observed for same type of user error	No further action. Complaints will be monitored for trending purposes
Reporting issue	42	Not reportable	Forwarded to NHS digital for further action	No further action required

Contaminated item	00	Not reportable	There was no trend observed for any batch.	No further action. Complaints will be monitored for trending purposes.
Expired kit	00	Not reportable	Limited information available to confirm if the kit was expired at delivery or expired at use	Updating Qualtrics survey to get more specific information if the kit was expired at delivery or expired at use

Table 2: Summary of reportability/non-reportability for all complaints

*Not reportable: these complaints did not meet the reportability criteria set out in MEDDEV 2.12-1 rev 8 vigilance standard and hence were decided to be non-reportable.

MED DEV 2.12-1 rev 8 vigilance Guidance to support discussions at Incident Review Meetings & Patient Safety Panel:

- *Question A "Has an event occurred etc."*
- *Question B "Is DHSC device cause of incident"*
- *Question C "Has the event led to death or serious deterioration in health"*

6.4 Complaints Trending

Due the reduced volume of overall complaints, the alert levels set for each category has been re-calculated for October 2022 to provide an accurate reflection of performance of the device. Figures below are the re-calculated alert levels on separate lines as described in the legend of the graphs below.

This methodology is following QMS procedure "QOP-20 Complaints Procedure (Rev 04)" and is defined as "Mean and standard deviation should be recalculated every quarter to ensure that they are still appropriate considering the changes in the number of complaints and distribution volume."

Current trending categories analysed through the Qualtrics data are grouped into three main categories:

1) **Material:** this includes trending categories: Missing item, Damaged Item, Faulty item, Contaminated Item, QR code issues, Empty Buffer Solution Sachet, Insufficient Buffer Solution. The number of complaints received in this category are below the updated alert threshold which is represented by the dark blue line (Refer to Figure 1).

2) **Faulty Test Results:** No sub-categories exist within this category of complaints. Number of complaints for this category is below the new alert threshold which is represented by the dark blue line (Refer to Figure 2).

3) **Harm & Allergy:** this includes complaints from Patient Injury and Allergic reactions as sub-categories. Harm-allergy complaints for this reporting period is below the new alert threshold which is represented by the dark blue line (Refer to Figure 3).

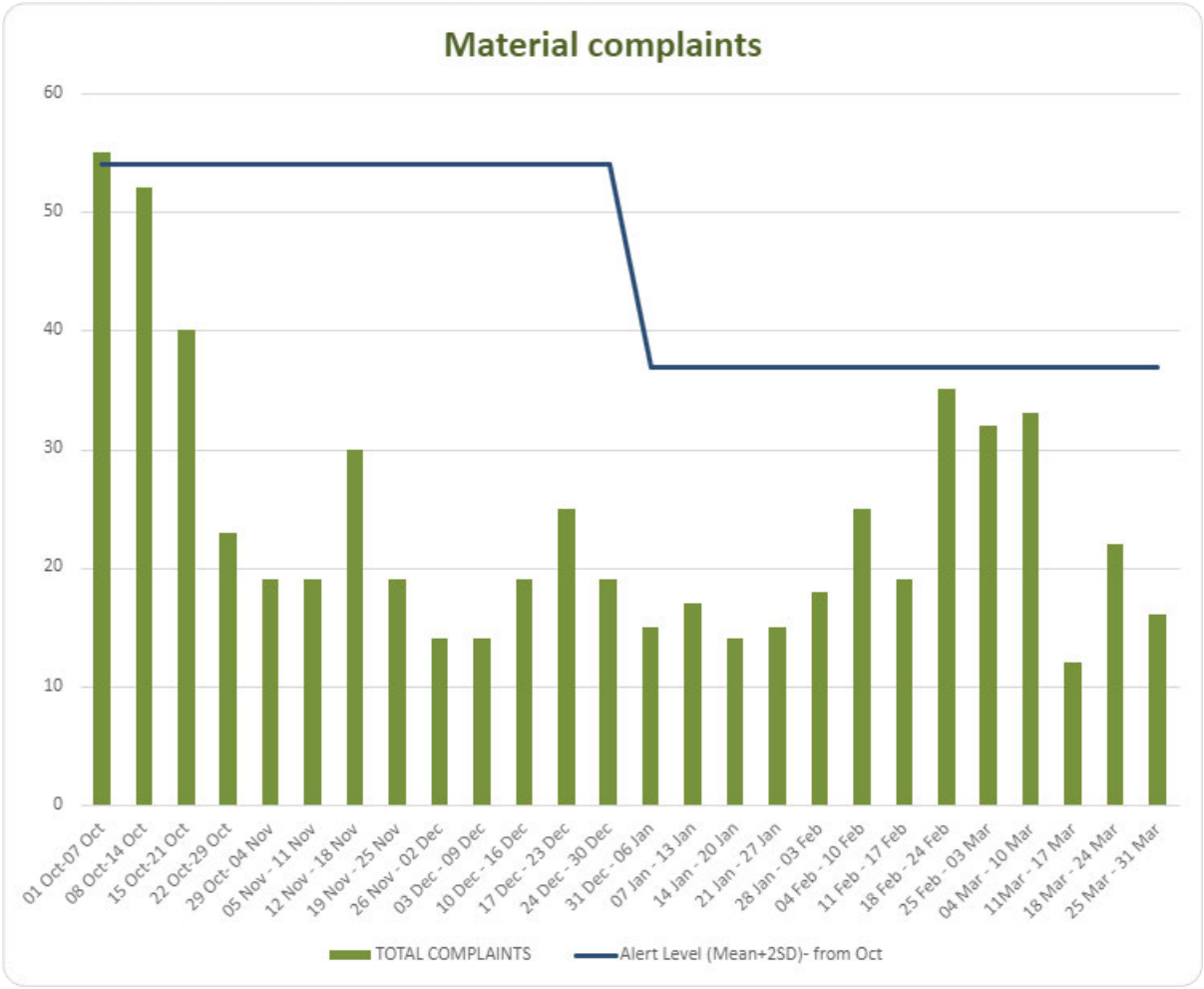

Figure 1: Material complaints weekly trending

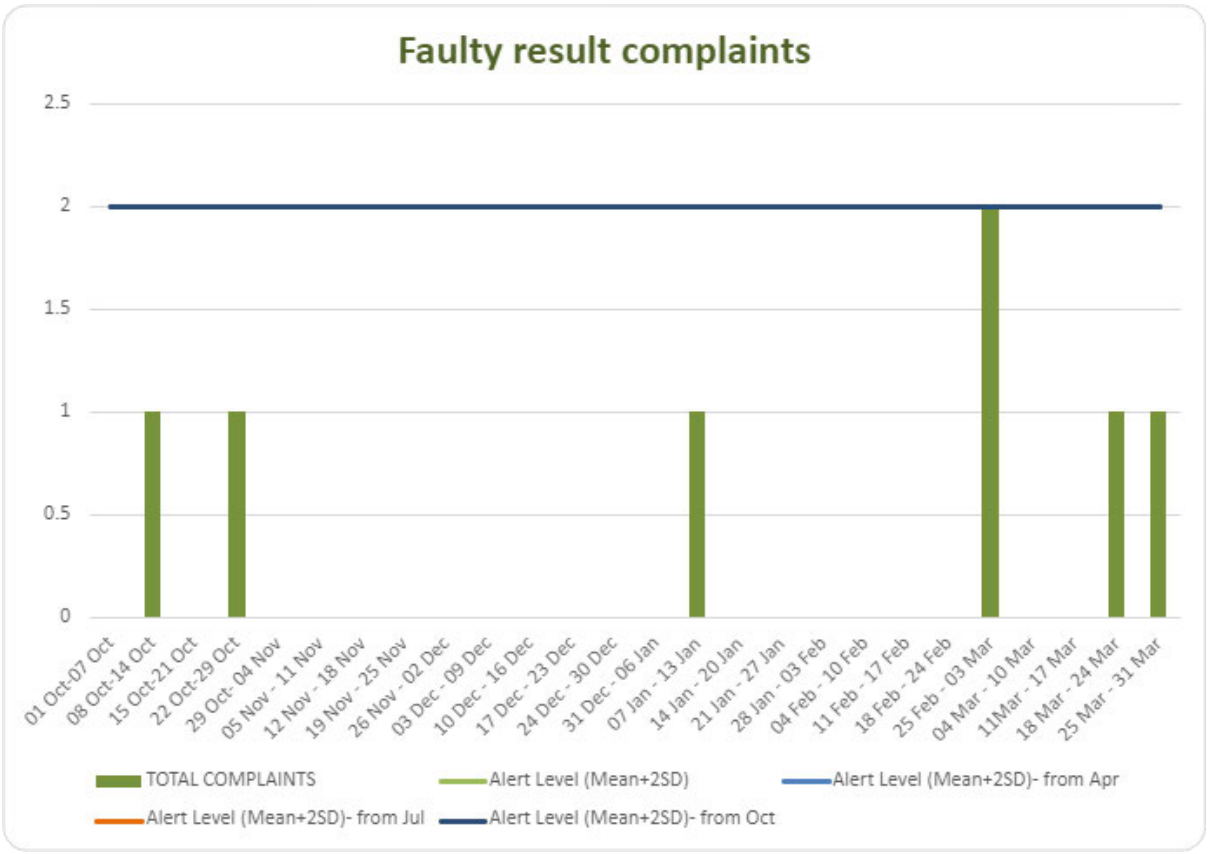

Figure 2: Faulty results complaint weekly trending

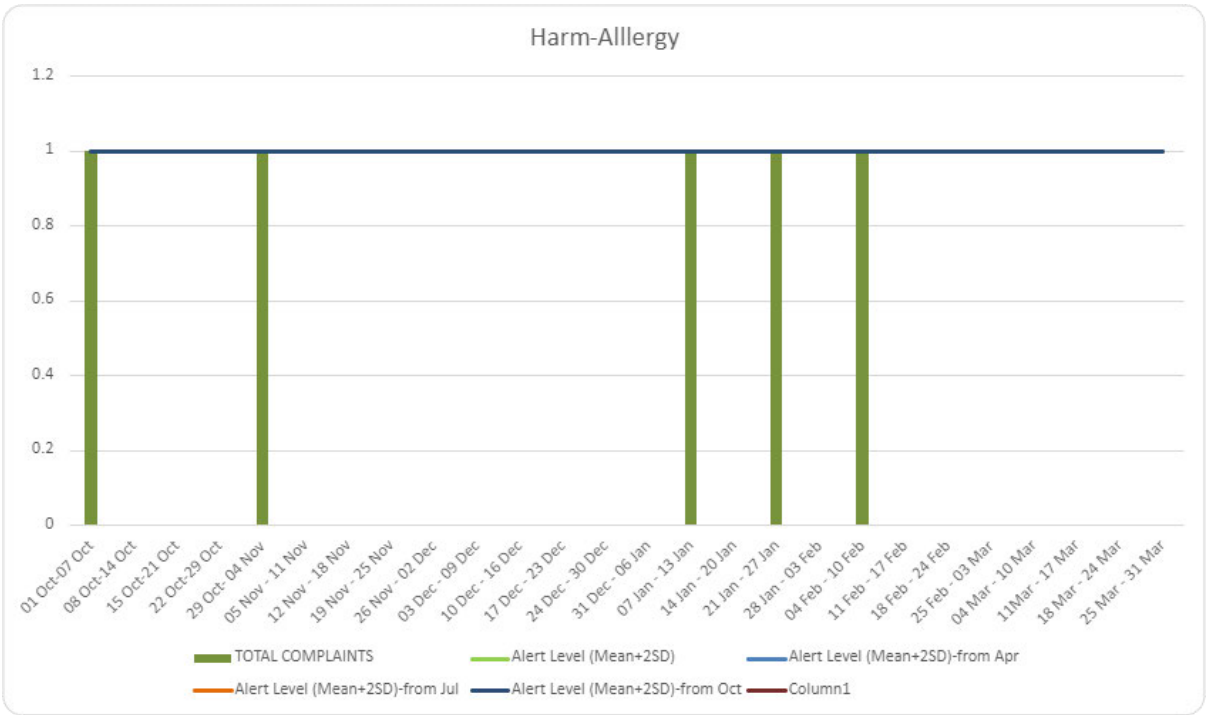

Figure 3: Harm-Allergy complaints weekly trending

(Refer to Attachment 02.2)

6.5 Qualtrics Survey (User Experience)

A total of 611 user responses were received during this reporting window of 01 January to 31st March 2023 for all LFD products for which the DHSC is either the legal manufacturer or importer/distributor (for Acon Flowflex, Orient Gene and Surescreen LFDs).

36.99% of these responses were related to the DHSC LFD Products (**highlighted in green in Attachment 02.3**). 333 users completed 100% of the survey in an average time of 8.8 minutes.

A series of questions relating to the user's overall experience can be seen in **Attachment 02.3**. Satisfaction rates were predominantly above 70% for most queries relating to the usability of the LFD products, except for:

1) ***Reporting of results (Understanding of IFU):*** 66.06% satisfaction rate which is a reduction on improvement since the last reporting period of 3.2%%.
2) ***Processing the swab (Difficulty of process):*** 55.33% satisfaction rate which is reduction on improvement of 1.04% since the last reporting period.
3) ***Reporting of results (Difficulty of process):*** 62.98% satisfaction rate which is an improvement of 5.19% since the last reporting period.

On-going product improvements are supported at the procurement stage by the LFD Product Management team and information on user experience from the Qualtrics survey is to be shared with the team for continual improvement. As discussed in previous reporting periods, actions have already been instigated at the next round of invitation to tender (ITT). Further information has been retained in this PSR from the previous reporting period and referenced in **Section 6.6.**

(Refer to Attachment 02.3)

6.6 Product Management (Usability Studies)

The LFD Product Team are involved in a Three-Stage process aimed at continuously improving the usability of LFD products sourced by DHSC and supplied to the end users (see Figure 4).

The team have carried out usability research activities with 2000 users through a mixture of surveys and one to one interview. The purpose of this research is to understand (from the user's perspective) what improvements can be made to the LFD product supplied.

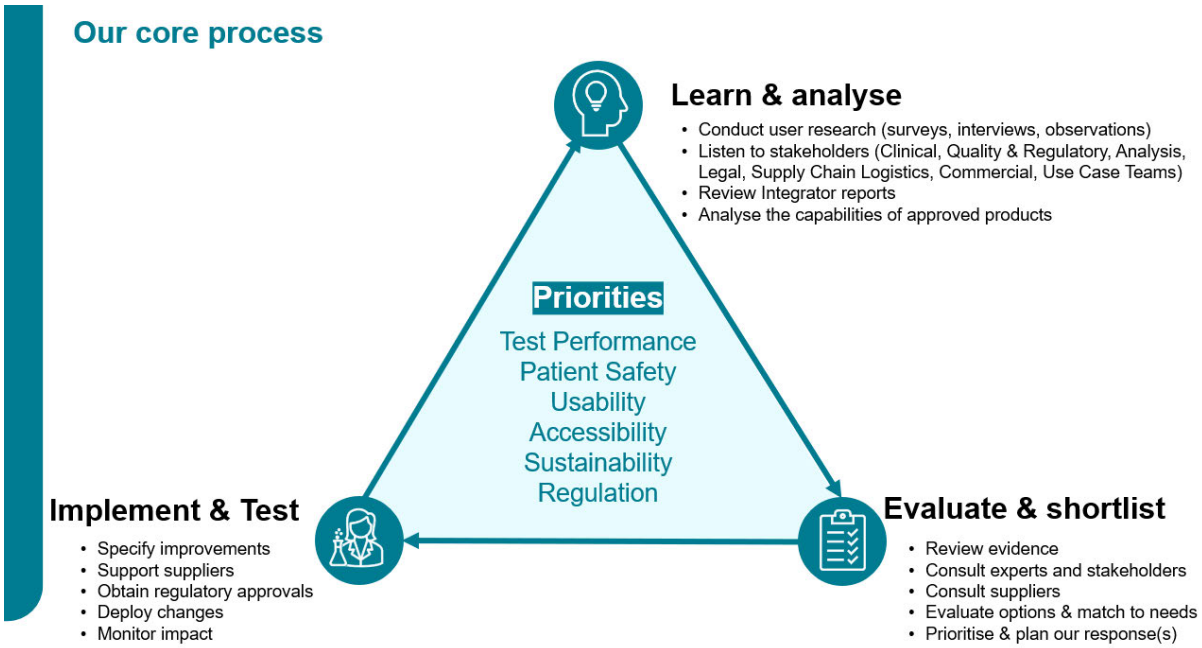

Figure 4: LFD Product Management Teams Core Process

Findings from these usability studies feed into improvements in the procurement exercises (Invitation to Tender ITT).

Further information on some of the findings and actions were shared in the previous report and have therefore been omitted from this submission.

No further updates or planned studies are planned from the LFD Product Management team as sufficient data has been collected for the current range of LFD's. Any future studies planned will be discussed in the PSR report.

6.7 Real World Performance Monitoring

The Real-World Performance Monitoring Team carry out routine performance of device and service performance using real-world data generated within NHS Test & Trace covering all services and devices.

For this reporting period, UKHSA has announced the conclusion of the Real-World Performance Monitoring service. A risk assessment was drafted to assess and reduce the residual risk of conclusion of this service as per QOP-45 Risk Assessment Procedure ISO 13485 Rev 2. The risk assessment procedure is a four-step process as follows:

1) **Step 1:** Assessing the inherent risk determined by severity (s) and probability (p) against criteria defined in the QOP.
2) **Step 2:** Assessing the strength of the controls (c) as per criteria defined in the QOP.
3) **Step 3:** calculating the Risk Value where Risk = [S x P x C] and correlating to a High, Medium or Low Risk rating as defined in QOP-45.
4) **Step 4:** Taking further action to mitigate and reduce the residual risk as far as possible depending on the outcome of the risk rating above. i.e. a High Risk/Medium Risk Rating may require additional actions to reduce the residual risk as far as possible.

Following the above risk assessment procedure, the conclusion of the RWPM service was assigned a risk value of 10 which is an overall “Low Risk”. This was due to having the following controls in place:

1) Continued oversight of Post Market Surveillance activities including vigilance reporting and clinical assessment of complaints.

2) Continued literature reviews as part of Post Market Surveillance activities to ensure any publications highlighting issues with similar devices are reviewed and assessed by DHSC (UKHSA) and any triggers actioned.

3) Continued Variant Of Concerns monitoring activities to be carried out by the VOC team to ensure that new strains of SARS-CoV-2 are assessed against the performance of the device.

4) On-going service evaluations to be carried out if a "trigger" is identified from any of the activities listed above.

(Refer to attachment 03.0)

6.8 Post Market Performance Follow Up

DHSC has implemented a series of ongoing evaluations. The objective of these evaluations is to determine whether lateral flow device (LFD) performance seen in pre-deployment evaluations are achieved when deployed by the testing service and to ensure that these continue to be suitable for use in services offered by NHS Test and Trace.

Biotime Ongoing evaluation and DHSC 3&7 self-test post-market clinical performance follow-up report 3 was submitted to the MHRA on Tuesday 20th September 2022.

The reporting period for report three is 22nd Sep 2021 – 21st Mar 2022. The overall objective of the report is as follows:

a. To confirm the safety and performance of Biotime LFD throughout its expected lifetime
b. To identify previously unknown risks or limitations to performance and contra-indications to changing epidemiological factors e.g., variant, vaccination status, prevalence
c. To identify and analyse emergent risks based on factual evidence
d. To ensure the continued acceptability of the clinical evidence and of the benefit-risk ratio
e. To identify possible systematic misuse.

A summary of the report is as follows:

- Sensitivity was higher in post-deployment than at baseline in self-test settings and not different to baseline in assisted test settings
- Sensitivity in all analysis sets was non-inferior to baseline
- Specificity was higher in post-deployment than at baseline in all analysis sets
- Symptomatic disease independently increased the sensitivity of LFDs
- The sensitivity of LFDs did not appear to be significantly affected by variant, vaccination status, time period, or the time delay between symptom onset and taking the LFD test.
- All other outcomes showed similar or improved results in post-deployment than at baseline

The evidence generated as part of this evaluation demonstrates that the LFD kits utilised as part of the National Testing Programme continue to provide sufficient diagnostic performance relative to baseline for use as part of a public health intervention within NHS Test & Trace to curb the spread of the SARS-CoV-2 pandemic

6.9 Variants of Concern (VOC)

The Variant of Concern Assurance Group (VOC) within the UKHSA are responsible for continuous monitoring of SARS-COV-2 variants. A cross-functional VOC meeting has now been setup and the MHRA and the Regulatory & Quality team are in attendance to provide weekly updates on the status of variants and share an overview of on-going activities. Weekly meetings continue to take place with key stakeholders for continuous monitoring.

Objectives of the VOC Assurance Group

- A robust system of assay performance monitoring and appropriate mitigations
- Appropriate governance structure
- Effective communication and escalation of issues and decisions to relevant partners

How is this achieved

a) Horizon scanning of variants and mutations

b) Evaluating real time test performance data (Real World Data, PLOD data, Quality incident reports)

c) Conducting regular *in silico* analysis of assay (molecular) and development of new requirements for MHRA IVD process

d) Putting in place an early warning system for laboratories to report and refer concerns in assay performance that may be related to new or unidentified variants. (Antigen/LFDs & Molecular Testing)

e) Establishing process for the ongoing assurance of assays through in vitro “wet-testing” of assays using virus materials for variants of concern.

f) Risk assessments of tests predicted to be impacted by novel variants or mutations

Impact of current circulating VOCs on the DHSC 3T/7T Covid-19 Self-Test LFD

There are currently no concerns about the mutations contained within any of the circulating VOCs having a negative impact on the DHSC 3T/7T COVID-19 Self-Test LFD.

6.10 CAPA

- Refer to Table 3 for a CAPA Status Overview
- Table 4 for List of open CAPA's and current progress and due dates.

CAPA Status	No
Open	00

Table 3: CAPA Status Overview

No	CAPA No	Start Date	Source	Problem statement	Status/ progress
28	CAPA-22-07-0049	01-Jul- 22	PMS Activities	CAPA raised to address the issue of incorrect brand of LFD sent to Welsh Home channel without welsh IFU.	Closed

Table 4: List of open CAPA's, Status & Due date

6.11 SCAR – Supplier Corrective Action Report

No new SCARs were raised by DHSC to Innova for this reporting period. It is important to note that no new EUA stock will be ordered from Innova. Any actions from existing SCARs will not be realised as all stock is already received by UKHSA. SCARs are being raised to support the supplier to continuously improve processes.

6.12 Risk Management

LFD Risk management File (RMF) was updated to RMF-0001 Revision 5 and HTM Hazard traceability Matrix Rev5. The RMF updated to new template for compliance with ISO 14971:2019.

No new Hazards were identified during this reporting period as part of the continual monitoring through post-market surveillance activities.

6.13 Literature Review & State of the Art (SOTA)

In collaboration with an external consultancy, DHSC has developed a Literature Search Protocol. The intention of the literature search is to review the continued clinical safety and effectiveness of the Lateral Flow Device kit when used for the intended purpose. Furthermore, the MedBoard platform is utilized to obtain current data on incidents, Field Safety Corrective Actions (FSCAa), etc. reported to or by regulatory agencies internationally.

The literature search & SOTA search is carried out monthly in line with the PSR reporting schedule and utilizes multiple electronic search databases (e.g., PubMed, Embase & Medboard) as highlighted in the protocol. It is worth highlighting that due to the frequency and timing of the LFD PSR reports, it is not practical nor feasible to provide a detailed analysis and conclusions of findings from the literature search report. However, the literature searches will be continuously reviewed with the support of PHCO for on-going performance evaluation and separately, a high-level summary is provided in the monthly PSR report.

In August 2022, the contract with the external consultancy carrying out the Literature Review as a service to UKHSA ended. The UKHSA has subsequently worked cross-functionally to implement an internal literature review process utilizing the Knowledge & Libraries team services and appraisal through a UKHSA Scientific Advisor.

UKHSA Internal Literature Review Update:

From the eight Scientific Papers that were identified for the January 2023 report, **two** passed both the first and second appraisal to pass into the data extraction stage of this Literature Review.

From the four Scientific Papers that were identified for the February 2023 report, **three** passed both the first and second appraisal to pass into the data extraction stage of this Literature Review.

From the four Scientific Papers that were identified for the March 2023 report, **one** passed both the first and second appraisal to pass into the data extraction stage of this Literature Review.

From the one Scientific Paper identified for the April 2023 report, **zero** passed both the first and second appraisal and therefore zero papers have passed into the data extraction stage of this Literature Review.

Summary of inclusions for this reporting period:

202301.1 *H. Houston, A. Gupta-Wright, E. Toke-Bjolgerud, J. Biggin-Lamming, L. John*

Diagnostic accuracy and utility of SARS-CoV-2 antigen lateral flow assays in medical admissions with possible COVID-19

Between 17th November 2020 and 31st December 2020, 728 individuals presented at the Emergency Department at Northwick Park Hospital with COVID-19 symptoms. The mean age of these individuals was 67.5 years (53-82 years) with 55.1% being male.

Two hundred and sixty-four patients tested positive on Innova LFA. Patients with positive LFA results were younger (median age 65 vs 71 years; P<0.038), more unwell (National Early Warning Score 5 vs 3; P<0.001) and more often febrile on arrival (temperature >38^{o}C in 41.9% vs 15.8%; P<0.001) compared with patients with negative LFA results. Overall, admission SARS-CoV-2 RT-PCR was positive in 38.5% (280/728) of patients. Compared with SARS-CoV-2 RT-PCR as the reference standard, the Innova LFA had sensitivity of 86.4% [242/280, 95%confidence interval (CI) 81.9 to 90.0] and specificity of 95.1% (426/448, 95% CI 92.6 to 96.7).

Twenty-two of 448 (4.9%) patients with a negative SARS-CoV-2 RT-PCR on admission had a positive LFA result. Eight of these 22 patients reported a positive COVID-19 test result up to 14 days prior to admission, and five patients subsequently had a positive PCR result within 5 days of admission.

Thirteen of 22 patients had chest radiograph features consistent with 'classic/probable COVID-19' as reported by a radiologist. Only five of 22 patients had no PCR or radiological evidence of COVID-19: one reported a confirmed household contact, and two left hospital with a diagnosis other than COVID-19.

This suggests that the lower than-expected specificity of Innova LFA is likely to be the result of an imperfect reference standard, and specificity would be higher if using a clinical and RT-PCR-based composite reference standard.

Thirty-eight patients had negative Innova LFA results but positive PCR results. Twenty of these patients had cycle threshold (Ct) values available, with a median Ct value of 29 [interquartile range (IQR) 27 to 35].

Innova LFA results were available 3.2 h (median) after arrival at the ED (IQR 2.0 to 4.3, N=681) compared with 13.8 h (IQR 9.9 to 18.2, N=679) for RT-PCR. Thirty-five (57.1%) patients had chest radiographs that were reported as typical for COVID-19. Of those with symptom duration recorded, 77.3% (17/22) were symptomatic for at least 7 days prior to attending the Emergency Department.

In summary, the Innova LFA can be used with good diagnostic accuracy for rapid identification of patients with COVID-19 amongst hospital admissions meeting the COVID-19 case definition, and patients that can be allocated to COVID-19 cohort areas. Based on these data, this application of COVID-19 LFAs has been recommended by NHS England.

202301.2 *David Eyre, Matthias Futschik, Sarah Tunkel, Jia Wei, et al*

Performance of antigen lateral flow devices in the United Kingdom during the Alpha, Delta, and Omicron waves of the SARS-CoV-2 pandemic

To understand the changes in LFD sensitivity and detection of infectious individuals during the pandemic with successive variants, vaccination, a prospective study was conducted. The three LFDs tested were Acon Flowflex, Innova and Orient Gene.

Paired LFD and PCR tests were collected from asymptomatic and symptomatic participants, across multiple settings in the UK between 04-November-2020 and 21-March-2022.

Multivariable logistic regression was used to analyse LFD sensitivity and specificity, adjusting for viral load, LFD manufacturer, setting, age, sex, assistance, symptoms, vaccination, and variant.

National contact tracing data were used to estimate the proportion of transmitting index cases (with ≥1 PCR/LFD-positive contact) potentially detectable by LFDs over time, accounting for viral load, variant, and symptom status.

There were 4131/75,382 (5.5%) participants that tested PCR-positive. Sensitivity vs. PCR was 63.2% (95%CI 61.7-64.6%) and specificity 99.71% (99.66-99.74%). Increased viral load was independently associated with being LFD-positive.

There was no evidence LFD sensitivity differed between Delta vs. Alpha/pre-Alpha infections, but Omicron infections were more likely to be LFD positive.

Sensitivity was higher in symptomatic participants, 68.7% (66.9-70.4%) than in asymptomatic participants, 52.8% (50.1-55.4%). 79.4% (68.6-81.3%) of index cases resulting in probable onward transmission with were estimated to have been detectable using LFDs, this proportion was relatively stable over time/variants, but lower in asymptomatic vs. symptomatic cases.

The authors concluded that the LFDs have remained able to detect most SARS-CoV-2 infections throughout the roll-out of vaccination and with several different viral variants. Although on-going monitoring of performance with new variants is required while tests are used, it is reassuring that LFDs are probably likely to remain able to detect future variants. LFDs potentially detect most infections that have the potential to transmit to others, however performance is lower in asymptomatic compared to symptomatic individuals and this needs to be considered when designing testing programs.

202302.1 *Maniya Arshadi, Fatemeh Fardsanei, Behnaz Deihim, et al*

Diagnostic Accuracy of Rapid Antigen Tests for COVID-19 Detection: A Systematic Review With Meta-analysis

This paper is a current systematic review and meta-analysis were conducted to evaluate the diagnostic accuracy of Rapid Antigen Tests (RA)T against RT-PCR methods as the reference standard.

The authors searched the MEDLINE/Pubmed and Embase databases for the relevant records. The QUADAS-2 tool was used to assess the quality of the studies. Diagnostic accuracy measures [i.e., sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratios (PLR), negative likelihood ratios (NLR), and the area under the curve (AUC)] were pooled with a random-effects model. All statistical analyses were performed with Meta-DiSc (Version 1.4, Cochrane Colloquium, Barcelona, Spain).

Sixty studies that met the inclusion criteria, of which one study looked at the Innova Rapid Antigen Test. The overall pooled sensitivity and specificity of the rapid antigen tests against the reference test (the real-time PCR) were 69% (95% CI: 68–70) and 99% (95% CI: 99–99). The result for the study looking at Innova demonstrated a sensitivity and specificity of 0.86 (0.82 - 0.90) and 0.95 (0.96 - 0.97) respectively.

The PLR, NLR, DOR and the AUC estimates were found to be 72 (95% CI: 44–119), 0.30 (95% CI: 0.26–0.36), 316 (95% CI: 167–590) and 97%, respectively.

The authors concluded that the present study indicated that using RAT kits is primarily recommended for the early detection of patients suspected of having COVID-19, particularly in countries with limited resources and laboratory equipment. However, the negative RAT samples may need to be confirmed using molecular tests, mainly when the symptoms of COVID-19 are present.

202302.2 *David M. Hughes, Sheila M. Bird, Christopher P Cheyne, et al*

Rapid antigen testing in COVID-19 management for school-aged children: an observational study in Cheshire and Merseyside, UK

This study was designed to evaluate the use of self-administered Lateral Flow Tests (LFTs) for school aged children within the Cheshire and Merseyside area, either supervised at a test centre or at home.

The study looked at the number of positive LFT results and the confirmatory positive results from RT-PCR

A total of 1,248,468 LFTs were taken by 211,255 children aged 12–18 years old, and 163,914 by children aged 52,116 5–11 years old between 6 November 2020 and 31 July 2021. Five thousand three hundred and fourteen (n=5,314 or 2.5%) 12–18 years old and 1,996 (3.8%) 5–11 years had a positive LFT result.

Of these, 3,829 (72.1%) and 1,535 (76.9%) had confirmatory PCR test. A total of 3,357 (87.7%) and 1,383 (90.1%) confirmatory PCR results were positive, respectively.

The authors took into consideration the prevalence of COVID-19 throughout the study and saw that monthly proportions of LFT positive with PCR negative varied between 4.7% and 35.3% in 12–18 years old (corresponding proportion of all tests positive: 9.7% and 0.3%). Deprivation and non-White ethnicity were associated with reduced uptake of confirmatory PCR.

The authors noted that substantial inequalities in confirmatory testing need more attention to avoid further disadvantage through education loss. When prevalence is low additional measures, including confirmatory testing, are needed. Local Directors of Public Health taking more control over schools testing may be needed.

202302.3 *Tim Peto, On behalf of the UK COVID-19 Lateral Flow Oversight Team*

COVID-19: Rapid antigen detection for SARS-CoV-2 by lateral flow assay: A national systematic evaluation of sensitivity and specificity for mass-testing

Between 1st August and 15th December 2020, this study looked at 64 different Lateral flow device (LFD) viral antigen immunoassays that had been developed around the world as diagnostic tests for SARS-CoV-2 infection.

The study was broken down in a 4 different phases, which included standardised laboratory evaluations, and for those that met the published criteria, field testing in the Falcon-C19 research study and UK pilots were performed (UK COVID-19 testing centres, hospital, schools, armed forces).

Four of the LFDs demonstrated desirable performance characteristics (orient Gene, Deepblue, Abbott and Innova SARS-CoV-2 Antigen Rapid Qualitative Test). All these LFDs have a viral antigen detection of >90% at 100,000 RNA copies/ml.

Eight thousand, nine hundred and fifty one (n=8951) Innova LFD tests were performed with a kit failure rate of 5.6% (502/8951, 95% CI: 5.1–6.1), false positive rate of 0.32% (22/6954, 95% CI: 0.20–0.48). Viral antigen detection/sensitivity across the sampling cohort when performed by laboratory scientists was 78.8% (156/198, 95% CI 72.4–84.3).

The authors state that the results suggest that LFDs have promising performance characteristics for mass population testing and can be used to identify infectious positive individuals. The Innova LFD shows good viral antigen detection/sensitivity with excellent specificity, although kit failure rates and the impact of training are potential issues. These results support the expanded evaluation of LFDs, and assessment of greater access to testing on COVID-19 transmission.

202303.1 *Zahra Eslami Mohammadie, Saeed Akhlaghi, Saeed Samaeinasab, et al*

Clinical performance of rapid antigen tests in comparison to RT-PCR for SARS-COV-2 diagnosis in Omicron variant: A systematic review and meta-analysis

This systematic review and meta-analysis investigated whether Omicron had a significant influence on rapid antigen test(RAT) performance in comparison to PCR. This systematic review and meta-analysis are registered in PROSPERO with the registration number CRD42022355510.

PubMed, Scopus, Embase, and Web of Science databases were systematically searched to 1 August 2022.

After article screening, the quality of the included studies were assessed based on the JBI checklist.

Following data extraction, a meta-analysis was performed using R software. Eighteen articles presented sufficient data about RATs performance in comparison to RT-PCR in Omicron infections.

The overall result for this systematic review was a pooled specificity and sensitivity of RATs were 1.000 (0.997–1.000) and 0.671 (0.595–0.721), respectively. The FDA-approved kits showed a better performance than WHO-approved ones with a sensitivity of 0.728 (0.620–0.815). The use of RATs with nasal swabs showed a higher sensitivity compared with nasopharyngeal swabs. The sensitivity for samples with a CT-value >25 was 0.108 (0.048–0.227).

There were four articles that used the ACON Flowflex LFD included within this systematic review, with three out of the four (J-L Bayart et al, M Bekliz et al and K Leuzinger et al) that have been discussed in our Sept 2022 Literature Review.

One article, G. Marais et al, has not been included in previous Literature Reviews and the data for this article demonstrated that nasopharyngeal samples were used on a population in South Africa. A total of 29 individuals tested positive for the Omicron variant resulting in a specificity 0.997 (0.982-0.999) and a sensitivity of 0.68.

The overall conclusion from this systematic review is that rapid antigen tests show impaired performance for COVID-19 diagnosis when the Omicron variant is circulating, particularly in samples with low viral loads.

(Refer to Attachment 04)

7. Conclusion & Risk-Benefit Determination

The DHSC LFD test is intended to detect the presence of coronavirus (Covid-19) antigen in humans to enable the spread of the virus to be reduced in the community. The overall purpose of post-market surveillance activities is to ensure that the device continues to meet its intended purpose.

Questions posed in the Post Market Surveillance plan (PMS-001) and at the beginning of this report have been addressed in Table 5 and summarised in this section.

The Real-World Performance Monitoring Service (RWPM) has concluded however a risk assessment has been drafted and the residual risk remains low.

PMPF Report 3 was submitted to the MHRA 20th September 2022, titled "Biotime Ongoing evaluation and DHSC 3&7 self-test post-market clinical performance follow-up report 3" and published on 25th August 2022 and covering the period 22nd Sep 2022– 21 Mar 2022. Findings from this report confirmed that the DHSC LFD performance is equivalent to or better than those in the baseline performance and following the ASC Staff Root Cause Analysis and Risk Assessment Report, the Biotime LFD remains appropriate for use as a public health intervention to reduce the impact of the SARS-CoV-2 pandemic in all archetypes assessed. On-going evaluations will take place on ad-hoc basis should an indication of declining performance is signaled from the Post Market Surveillance activities.

No new Hazards were identified during this reporting period as part of the continual monitoring through post-market surveillance activities.

UKHSA has not instigated a re-call nor issued any Field Safety Corrective Action Notices during this reporting period.

Six new scientific publications were found for this reporting period and were predominantly positive in supporting LFDs remained able to detect emerging SARS-COV-2 variants. A systematic review by Zahra Eslami Mohammadie, Saeed Akhlaghi, Saeed Samaeinasab, et al indicated reduced performance of LFD's in the presence of the Omicron variant. While the UKHSA acknowledges the potential impact of emerging variants on the performance of the device, the UKHSA has maintained a series of on-going evaluations to ensure that the performance of the devices deployed as part of the national testing programme performed at similar levels to pre-deployment. In the latest report published in March 2022, the sensitivity of LFDs did not appear to be significantly affected by variant, vaccination status, time, or the time delay between symptom onset and taking the LFD test. To further mitigate the risk of Variant mutation on device performance, the UKHSA maintains a Variant Of Concern working group to continuously monitor emerging variants and provide feedback and suggestions on additional studies required, should the need arise.

Based on the information discussed in this periodic summary report, the DHSC maintain the position that the benefits of use of Lateral Flow Devices continue to outweigh the risks identified in the risk management report, the formers include:

a) Early indication of possible infection with Covid-19 while still asymptomatic
b) Prevention of spread of Covid-19 virus
c) Prevention of the need for unnecessary self-isolation/travel restriction therefore improving patient/user quality of life.
d) Widespread PCR testing is operationally unfeasible

Question	Answer	Comments	Evidence
a) Were there any new hazard or hazardous situation(s) identified for the DHSC LFD's or has the risk acceptability changed?	No	No new hazards identified in this reporting period.	**Section 6.12**
b) Has any misuse of the DHSC LFDs occurred?	No	No formal complaints or reports in Qualtrics received to indicate the DHSC LFD was misused.	**Section 6.3**
c) Do the DHSC LFD's still meet the user's needs after medium/long term clinical use?	Yes	Findings from PMPFR report 3 confirmed that the DHSC LFD performance is equivalent to or better than those in the baseline performance and following the ASC Staff Root Cause Analysis and Risk Assessment Report, the Biotime LFD remains appropriate for use as a public health intervention to reduce the impact of the SARS-CoV-2 pandemic in all archetypes assessed.	**Section 7**
d) Do users experience any usability issues?	No	Satisfaction rates are above 70% with regards to usability of the devices. Any minor issues identified are feeding into continuous improvement activities at the procurement stage.	**Section 6.5** **Section 6.6**
e) Are there any recurring quality issues DHSC LFD's and can significant increasing/decreasing trends be identified for DHSC LFD' inadequate performance?	No	Issues relating to missing items were observed. A SCAR has already been raised against Innova/Biotime. Immediate containment action not deemed necessary as the risk on patient safety is minimal. Any improvements by Innova will not be realised as all products are received by UKHSA.	**Section 6.4** **Section 6.11**

Table 5: Questions posed by PMS-001 Plan for DHSC LFD Products

No emerging issues or safety signals identified. As result of the PMS activities analysed/discussed in this report the PMS Team advice is to continue distributing the current EUA cleared product.

8. Recommended Actions

No	Added	Action	Responsible Name	Due Date	Status
1	20th January 2023	Flag study (Roderick P. Venekamp, Ewoud Schuit, Lotty Hooft, et al) found during the UKHSA literature search to PHCO [redacted]	[redacted]	Immediate	Closed
2	17th April 2023	There is conflicting information on the impact of the omicron variant on LFDs across the papers within the literature review for this and the previous reporting period. This was discussed with key UKHSA experts, including PHCO. A recent publication using paired LFD and RT-PCR test results that were prospectively collected from asymptomatic and symptomatic participants in the UK between Nov 4, 2020, and March 21, 2022, to support the National Health Service (NHS) England's Test and Trace programme (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00129-9/fulltext) confirmed that the LFDs for which the DHSC is either the legal manufacturer or importer/distributor are not negatively impacted by the omicron variant. In addition to this and to continue to monitor and mitigate this risk, UKHSA carries out its own LFD Service Evaluations and discusses the potential impact of the Variant of Concern (VOC) on the LFDs on a weekly basis.	[redacted]	Immediate	Ongoing (weekly VOC meetings)

9. Attachments

Attachment 01: PMS-0001.Rev2 DHSC LFD Plan - PMS Plan for the DHSC Covit-19 LFD Devices (3 and 7 kit) Rev2, 29-July-2021
Attachment 02: DHSC PSR – Complaints & Qualtrics data (Attachments 02.1 – 02.3)
Attachment 03: RA-22-15 - Conclusion of Real-World Performance Monitoring Service
Attachment 04: Literature Review on the safety and performance of the DHSC Innova Lateral Flow Device_v3.0

10. Author

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