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	18-MAR-2024	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. This report will be the final periodic summary report to the MHRA. The Device Exceptional Use Authorisation DEU/012/2020/003 for the product expired 30th June 2023, and the product expiry date was 31st January 2024. The UKHSA on behalf of DHSC has continued to monitor adverse incidents related to the devices on the market under the authority of the authorisation during the period 1st July 2023 – 8th March 2024, as per the DEU closure letter issued by MHRA 3rd August 2023. UKHSA will continue to provide a product complaints service in order to monitor the use of expired products on behalf of DHSC.

The PSR report outlines, analyses and reports on the activities that were undertaken by UKHSA on behalf of 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 report is looking at the following timeline: 1st July 2023 – 31st January 2024 while the product is within its expiry. And it also documents any complaints received 1st February - 8th March 2024 when the product has expired.

This was performed through 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 3 for conclusions.

3. Reference documents

Doc ID	Doc name	Revision
QM-01	Quality manual	2
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
QOP-08.F02	LFD Hazard Traceability Matrix	3

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

- There were no distributed kits for the DHSC LFD product during this reporting period due to the ending of the EUA for the product.

Between 1st FEB 2024 and 29th FEB 2024, a total of 5 complaints were received post product expiry. none were harm related complaints. UKHSA will monitor for any expired kit complaints as best practice on behalf of DHSC.

- Two complaints were defined as non-reportable as per MEDDEV 2.12-1 Rev 8 through the Qualtrics platform. 0 complaints were reportable during this period.

- A total of **163** 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	29	Not reportable	No batch specific trend observed.	No further action.
Damaged Item	11	Not reportable	No action required; no trend observed	No further action.
Faulty test results	06	Not reportable	There was no trend observed for any batch.	No further action.
Faulty items	22	Not reportable	There was no trend observed for any batch.	No further action.
Empty extraction buffer	10	Not reportable	No batch specific trend observed.	No further action.
Insufficient buffer solution	77	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.
Patient injury/allergic reaction	05	Not reportable	Repeat user submitted harm feedback, no comments provided, and no response received from follow up survey, no further action necessary. Other harm related complaint dealt with via QOP-20 and report signed with no follow up action due to lack of contact details.	UKHSA will monitor for any patient injury/allergic reaction complaints for the expired product, keeping in line with best practices.
Barcode/QR code issues	14	Not reportable	There was no batch specific trend observed for similar type of complaint.	No further action.
Usability	2	Not reportable	Not enough provided by the reporters to confirm the type of usability issue	No further action.
User error	3	Not reportable	There was no trend observed for same type of user error	No further action.
Reporting issue	17	Not reportable	Forwarded to NHS digital for further action	No further action.
Contaminated item	3	Not reportable	There was no trend observed for any batch.	No further action.
Expired kit	3	Not reportable	Limited information available to confirm if the kit was expired at delivery or expired at use	No further action.

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 to the reduced volume of overall complaints, the alert levels for each category are re-calculated each quarter to provide an accurate reflection of performance of the device. The figures below show the re-calculated alert levels for this period.

This methodology is following QMS procedure "QOP-20 Complaints Procedure (Rev 06)" 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). One week reached the alert level on 09 Oct 22 and was reported internally to the patient safety panel with no further actions as trend was not continued. A complaint form (LFD-CTAS-023) was raised and signed off with the requirement that an incident be raised only if the trend continued, which did not occur.

2) **Faulty Test Results:** No sub-categories exist within this category of complaints. Number of complaints for this category reached the alert threshold for 1 week period which is represented by the dark blue line (Refer to Figure 2). This represents the same week as the alert level for material complaints and so, was handled within the same report that was signed and presented to the patient safety panel on the 26th of Oct 2023.

3) **Harm & Allergy:** this includes complaints from Patient Injury and Allergic reactions as sub-categories. (Refer to Figure 3). Multiple harm allergies were reported via the same individual who left no supporting comments. A follow up survey was sent but no reply was given, and no further action was undertaken. Complaint report signed off as per QOP-20 procedure. As for the other complaint shown in the graph, a complaint form was filled out, and the user reported no ongoing symptoms, and they were non-reportable.

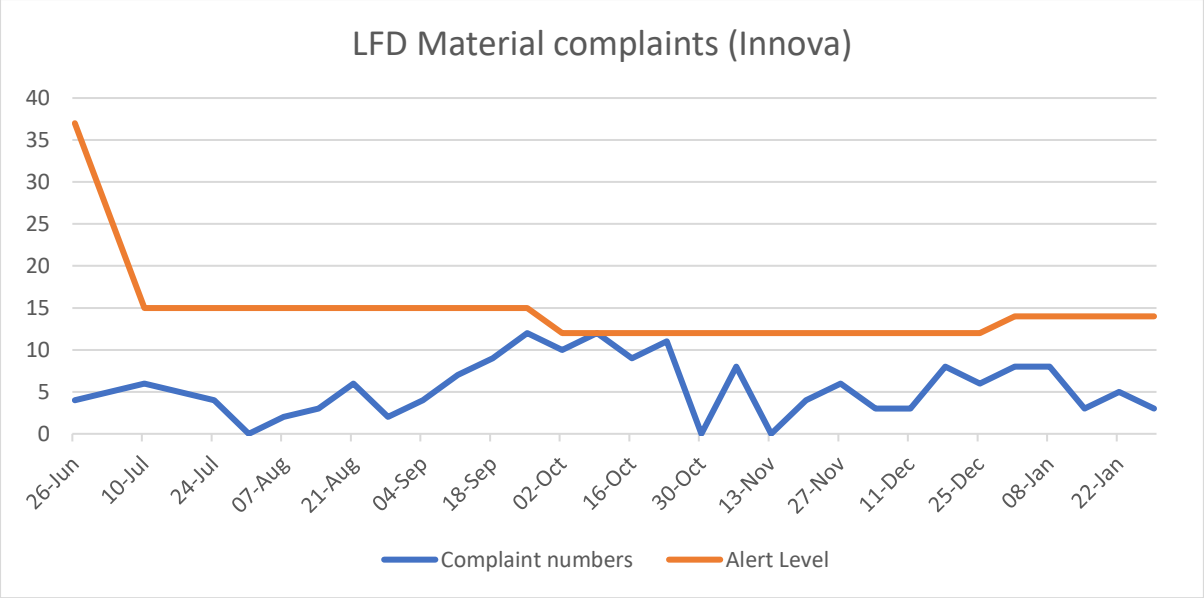

Figure 1: Material complaints weekly trending

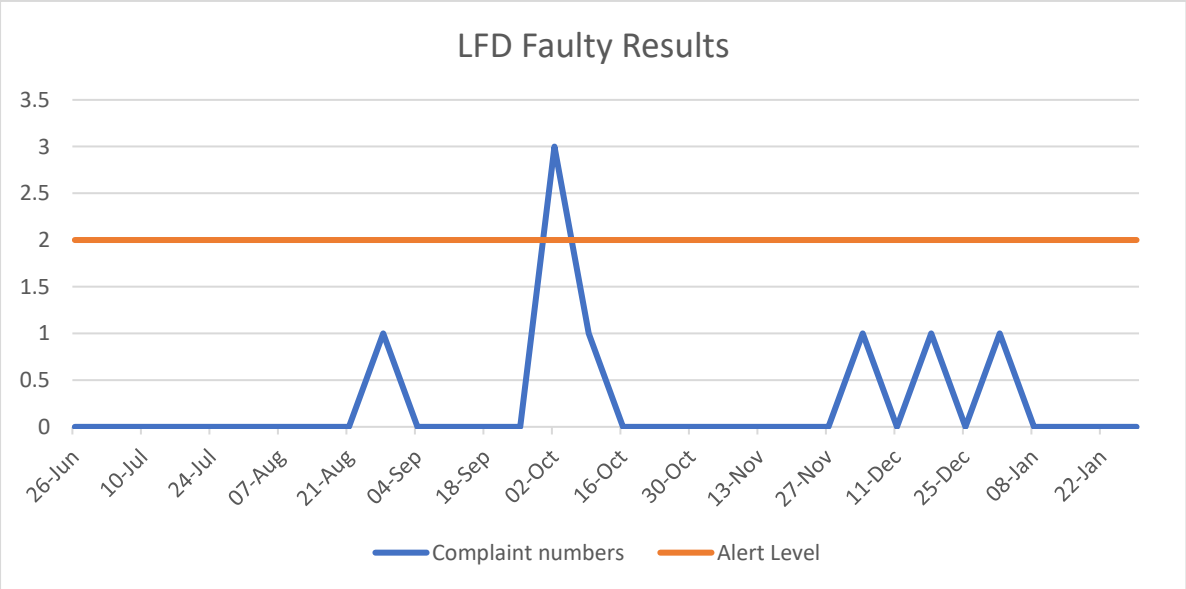

Figure 2: Faulty results complaint weekly trending

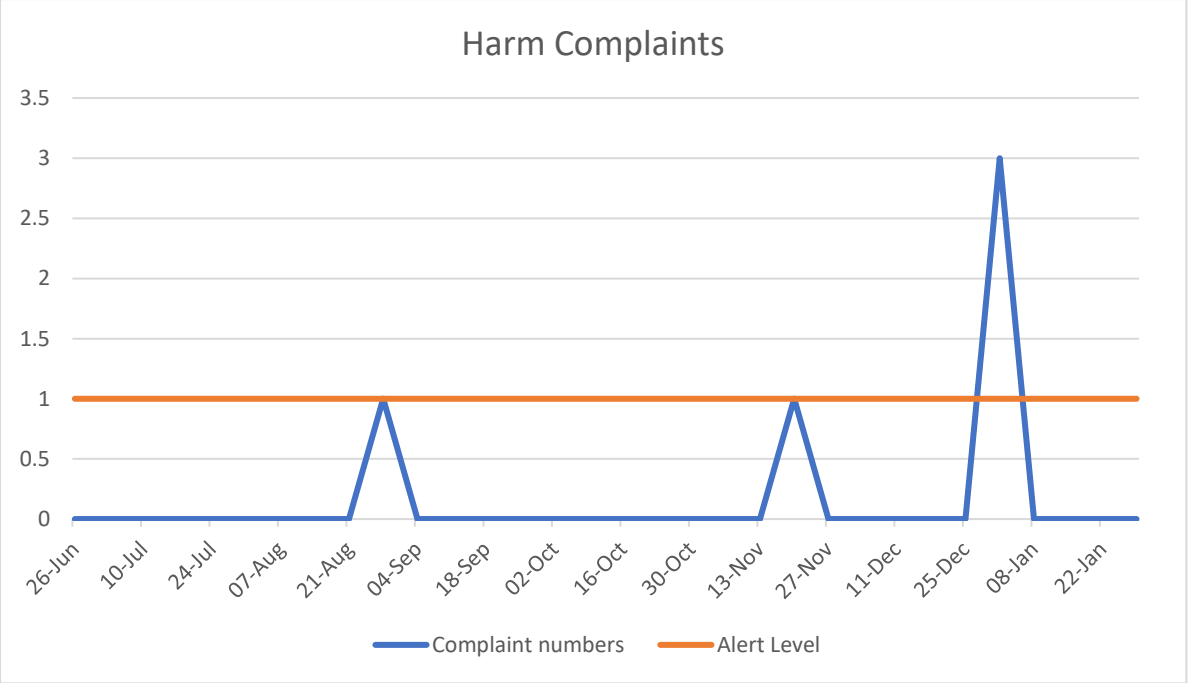

Figure 3: Harm-Allergy complaints weekly trending

(Refer to Attachment 02.2)

6.5 Qualtrics Survey (User Experience)

A total of 635 user responses were received during this reporting window of 01 July 2023 – 29th FEB 2024 for all LFD products for which the DHSC is either the legal manufacturer or importer/distributor (for Acon Flowflex, Orient Gene, Surescreen and GeteinLFDs).

26.5% of these responses were related to the DHSC LFD Products (**highlighted in green in Attachment 02.3**). 329 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, a breakdown of the results can be seen below:

Difficulty of the Process (All)	Preparing the test area and checking the test kit contents	Setting up the test	Taking the swab sample	Taking the swab sample from a child	Processing the swab sample	Reading the Result	Interpreting the Result	Safely disposing of the used kit	Reporting the Result
Did not do this	26	28	36	241	53	78	84	37	106
Extremely difficult	10	9	11	5	89	29	26	4	27
Somewhat difficult	5	8	18	3	22	11	13	1	14
Neither easy nor difficult	45	48	56	6	24	41	37	43	40
Somewhat easy	63	63	70	17	39	42	42	58	47
Extremely easy	162	155	120	39	84	110	109	168	77
Total Rates	285	283	275	70	258	233	227	274	205
Satisfaction	78.95%	77.03%	69.09%	80.00%	47.67%	65.24%	66.52%	82.48%	60.49%

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). All feedback is based on the same version of LFD. There is currently no opportunity to improve feedback by introducing improvements. 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.

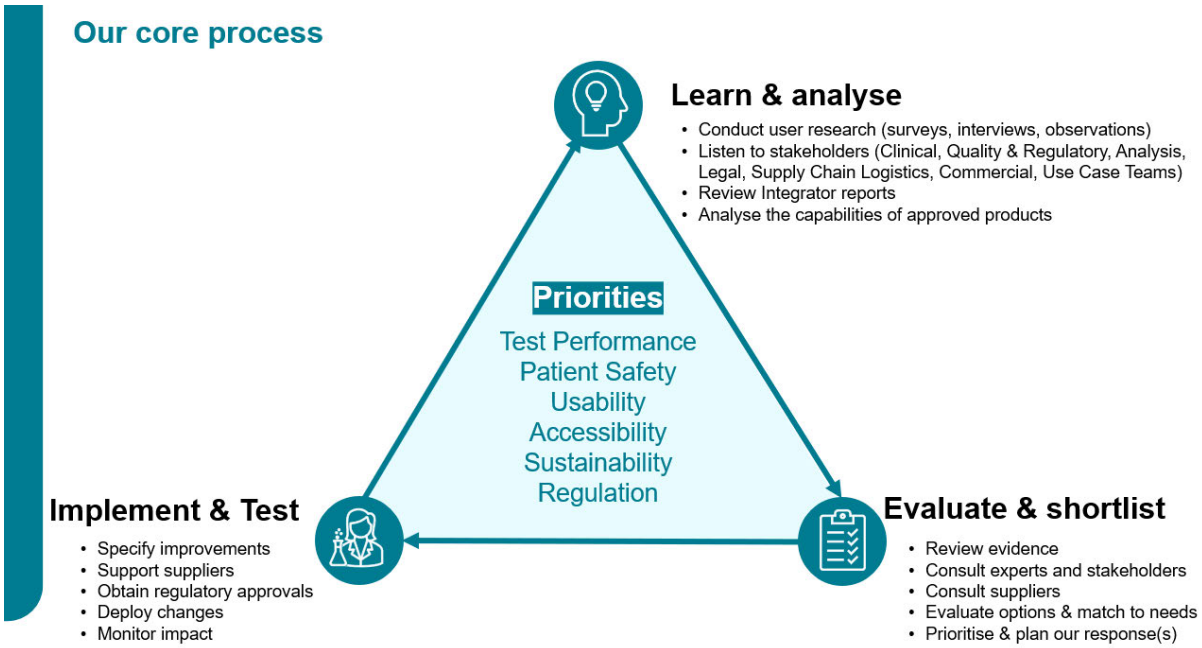

Figure 4: LFD Product Management Teams Core Process

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.

6.7 Post Market Performance Follow Up

DHSC implemented a series of ongoing evaluations. The objective of these evaluations was to determine whether lateral flow device (LFD) performance seen in pre-deployment evaluations were achieved when deployed by the testing service.
Biotime's Ongoing evaluation and DHSC 3&7 self-test post-market clinical performance follow-up report 4 was completed on 12th December 2022 and submitted to the MHRA.

The reporting period for report 4 is 30th Aug 2022 – 12th DEC 2022 and is the final report to be made and submitted.

6.8 Variants of Concern (VOC)

The Pathogen Diagnostic Assurance Group (PDAG) was launched on 1st July 2023 and have replaced the Variants of Concern (VOC) Assurance Group. PDAG are responsible for continuous monitoring of SARS-COV-2 variants within the UKHSA. A cross-functional meeting is held fortnightly with representation from the MHRA and the Regulatory & Quality team in attendance. This fortnightly assurance group meeting provides updates on the status of variants and shares an overview of on-going activities. Fortnightly meetings continue to take place with key stakeholders for continuous monitoring.

Objectives of the PDAG

- 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 (PLOD data, Quality incident reports from the UKHSA and NHS)

c) Conducting regular *in silico* analysis of molecular assays (for selected and available primer and probe sequences)Working with the MHRA to review the bi-monthly VOC Assurance reports submitted by manufacturers of both molecular and antigen assays as part of their PMSP requirements

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 processes 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.

6.9 CAPA

- No CAPA raised in this reporting period

6.10 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.

6.11 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.

6.12 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 three Scientific Papers that were identified for the August 2023 report (27th June to 25th July), zero passed both the first and second appraisal and therefore zero papers have passed into the data extraction stage of this Literature Review.

From the two Scientific Papers that were identified for the September 2023 report (24th July to 29th August), one passed both the first and second appraisal to pass into the data extraction stage of this Literature Review.

From the three Scientific Papers that were identified for the October 2023 report (28th August to 27th September), zero passed both the first and second appraisal and therefore zero papers have passed into the data extraction stage of this Literature Review.

From the two Scientific Papers that were identified for the November 2023 report (25th September to 31st October), zero passed both the first and second appraisal and therefore zero papers have passed into the data extraction stage of this Literature Review.

For December 2023 report (30th October to 30th November), 0 papers were identified that met the inclusive search criteria.

From the two Scientific Papers that were identified for the January report (29th November to 31st December), zero passed both the first and second appraisal and therefore zero papers have passed into the data extraction stage of this Literature Review.

For February 2023 report (31st December to 31st January), 0 papers were identified that met the inclusive search criteria.

Summary of inclusions for this reporting period:

202309.1 Hogg C, Boots S, Howorth D, Williams C, Heginbothom M, Salmon J, et al.
Test performance of lateral flow rapid antigen tests for COVID-19 in Welsh adult care home staff using routine surveillance data
In this study/review, test results from surveillance data were matched by individual where both LFT (Innova) and PCR were taken on the same day. Sensitivity, specificity, positive and negative predictive values, and agreement using Matthew's correlation coefficient were calculated.
Lateral flow testing activity data for Wales (Adult Social Care setting) was sourced from the UK Government Lateral Flow Testing Portal, collated by NHS Digital, and supplied to Public Health Wales (PHW) via a data feed and a set of SQL views from Digital Health and Care Wales (DHCW). PCR testing data was sourced from NHS and lighthouse laboratories across Wales and supplied to PHW through a data feed from DHCW. Individuals included in the study population were residents of Wales, and of working age group age 18 to 67 years old. Other inclusive criteria were that each of the test results (LFT and PCR) must be positive or negative (not void) and conducted between 1st May 2021 and 31st August 2021. The study population is presumed to be primarily asymptomatic.
115,593 paired tests results (surveillance data) of LFT and PCR results were analysed. Of which, 0.43% of PCR results were positive (n = 499) and 99.57% were negative (n = 115,094), whilst 0.20% of LFT results were Positive (n = 229) and 99.80% were negative (n = 115,364). Overall sensitivity of the lateral flow devices was calculated as 25.65% (95%CI 22.02–29.67) and specificity was 99.91% (95%CI 99.89, 99.93). Across the entire study period, Negative Predictive Value (NPV) was estimated to be 99.68% (95%CI 99.64, 99.71), whilst Positive Predictive Value (PPV) was estimated to be 55.90% (95%CI 49.42, 62.17)
The study is believed to be the first study of lateral flow test performance using self-reported results from the UK Government online portal demonstrating real-world test performance estimates. The NPV and Specificity of >99%, indicate that the test is an effective tool for identifying cases of SARS-CoV-2 infection during periods of high prevalence where transmission is likely, due to the presence of high viral loads. PPV and overall Sensitivity were found to be much lower-notably the tests were carried out using samples from asymptomatic individuals and at the time of low prevalence (under 1%). It is also discussed in the paper that due to repeated testing in the study population, it is possible that previous PCR positive samples may continue to test positive post infection, but an LFT is unlikely to capture post infections which may have impacted the sensitivities. Low viral loads are another factor to consider, however limited info is available to analyse this in the paper.
Overall, considering all data and information, results suggest that whilst lateral flow tests are effective for identifying SARS-COV-2 infections with high viral loads, they may not be as effective at identifying cases with a low viral load. When an LFT provides a negative result, false negatives should be considered, and additional diagnostic tests performed.

(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 3 and summarised in this section.

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

All PMPF reports have been submitted to the MHRA as part of the PMS plans for the product and there will be no more PMPF reports submitted.

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.

One new scientific publication was found for this reporting period and was positive in supporting LFDs that remained able to detect emerging SARS-COV-2 variants. A systematic review 202309.1 Hogg C, Boots S, Howorth D, Williams C, Heginbothom M, Salmon J, et al. The study is believed to be the first study of lateral flow test performance using self-reported results from the UK Government online portal demonstrating real-world test performance estimates. The NPV and Specificity of >99%, indicate that the test is an effective tool for identifying cases of SARS-CoV-2 infection during periods of high prevalence where transmission is likely, due to the presence of high viral loads. PPV and overall Sensitivity were found to be much lower-notably the tests were carried out using samples from asymptomatic individuals and at the time of low prevalence (under 1%). It is also discussed in the paper that due to repeated testing in the study population, it is possible that previous PCR positive samples may continue to test positive post infection, but an LFT is unlikely to capture post infections which may have impacted the sensitivities. Low viral loads are another factor to consider, however limited info is available to analyse this in the paper.
Overall, considering all data and information, results suggest that whilst lateral flow tests are effective for identifying SARS-COV-2 infections with high viral loads, they may not be as effective at identifying cases with a low viral load. When an LFT provides a negative result, false negatives should be considered, and additional diagnostic tests performed.
To further mitigate the risk of Variant mutation on device performance, the UKHSA maintains a pathogen diagnostic assurance working group to continuously monitor emerging variants and provide feedback and suggestions on additional studies required, should the need arise.

The UKHSA testing strategy was to detect sufficient cases with transmissible virus to reduce the R number and to help control the pandemic. This required a test to identify people with transmissible virus for quarantine and, thereby, interrupt viral transmission. There are currently no Covid-19 restrictions in the UK. From 8th March 2024, people and settings were no longer able to order free lateral flow tests from the NHS online service, and UKHSA has ceased distributing covid-19 test kits.

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 6.11**
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 6.10**

Table 3: Questions posed by PMS-001 Plan for DHSC LFD Products

No emerging issues or safety signals identified.

8. Recommended Actions

No	Added	Action	Responsible Name	Due Date	Status
1	05 March 2024	Continue to support device feedback while kits may still be reported beyond their expiry	Regulatory & Quality / Complaints team	30th June 2024	OPEN

9. Attachments

Attachment 01: PMS-0001, PMS Plan for the DHSC Covit-19 LFD Devices (3 and 7 kit) Rev2,
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

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