

Memorandum

From: [REDACTED]
Date: 21/06/2019
Subject: Field action – FA-2019-02 – Health Risk assessment

Introduction

Here after will be detailed the health risk assessment for the issues in scope of FA-2019-02:

1. False positive qualitative results due to background signals for all pathogens detected by FTD 1.1 ACE: Human adenovirus (HAdV), human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV).
2. Premature degradation of the quantitative standards (QS) leading to a 4- to 8-fold over-quantification of viremia.

Preliminary remarks

1. The estimation of severity of harm as well as the estimation of probability of occurrence of harm was performed by Dr. Kalen Olson (SHS DX LD QT MBDQ MA).
2. Only false positive or elevated erroneous results for HAdV will be considered as it represents the worst-case scenario in terms of severity of occurrence of harm (see here after).

Part 1 : False positive qualitative signal for HAdV

Risk estimation

A) Severity of harm

The evaluation of severity of harm due to an unnecessary treatment for HAdV has been estimated as S3 – Moderate: Adenovirus antiviral therapy (e.g., cidofovir) adverse effects include nephrotoxicity.

B) Probability of occurrence of harm

Causal chain and associated probabilities:

- Sample is truly negative for HAdV viremia: 50%
- False positive result for HAdV: 6.38%
- Results of PCR is used in isolation to begin treatment (cidofovir): 50%
- Positive HAdV PCR result leads to patient treatment with cidofovir: 22.5%
- Patient experience *significant* nephrotoxicity despite creatinine monitoring and before re-check of viremia when false positive would be detected: 0.25%

Injury event frequency: 9.0×10^{-6} : P2 – Unlikely.

Risk evaluation

Overall risk to health: “Moderate” severity of harm + “Unlikely” probability of occurrence of harm = **Low health risk (LHR)**.

Part 2: Elevated erroneous result for HAdV due to QS premature degradation

A) Severity of harm

The evaluation of severity of harm due to an unnecessary treatment for HAdV has been estimated as S3 – Moderate: Adenovirus antiviral therapy (e.g., cidofovir) adverse effects include nephrotoxicity.

B) Probability of occurrence of harm

Causal chain and associated probabilities:

- Sample is truly positive for HAdV viremia: 50%
- Kit is used after 1 month of age: 96%
- Results of PCR is used in isolation to begin treatment (cidofovir): 50%
- Result goes from below customer cut-off to above cut-off: 2.5%
- Positive HAdV PCR result leads to patient treatment with cidofovir: 60%
- Patient experience *significant* nephrotoxicity despite creatinine monitoring: 1%

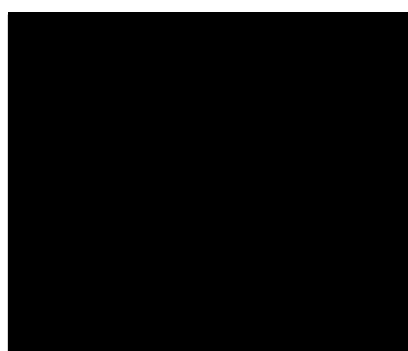
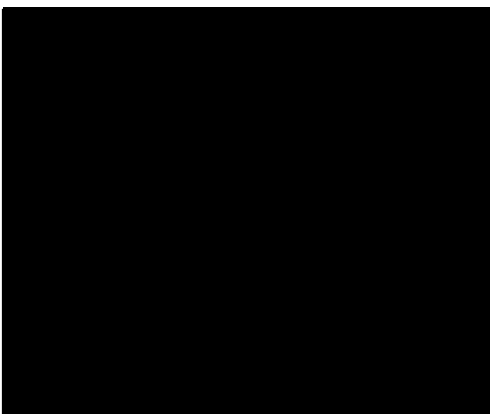
Injury event frequency: 3.6×10^{-5} : P3 – Likely.

Risk evaluation

Overall risk to health: “Moderate” severity of harm + “Likely” probability of occurrence of harm = **Moderate health risk (MHR)**.

Overall risk to health for FA-2019-02

Moderate health risk (MHR).



FTD 1.1 ACE

Potential false positive and over-quantification while using FTD-1.1 ACE kit

Dear customers,

We kindly ask you to urgently review the following communication:

Details on affected product:

Our records indicate that your facility may have received the following product:

Table 1 Affected products

Kit name	Catalog Number	Siemens Material Number (SMN)	Lot Number	Manufacturing /1 st Distribution Date (DD/MM/YYYY)
FTD ACE	FTD-1.1-32, FTD-1.1-64	10921700 10921701	All lots	25/05/2016

Reason for the Field Safety Notification:

The purpose of this communication is to inform you of an issue affecting the product indicated above and to provide instructions on actions that your laboratory must take.

After internal investigation, Fast Track Diagnostics (FTD) has observed that nonspecific low positive signals may be generated for negative samples randomly while using the kit FTD-1.1 ACE. Based on initial analysis of the available data, negative samples may be incorrectly reported as low positive. For an estimation of the rate of nonspecific signals that may be observed, please refer to table 2. Please note that this rate of false positive signals may vary from one laboratory to another.

Table 2 Potential rate of nonspecific signals per pathogen

Pathogen	Potential rate of nonspecific signals
Epstein-barr virus	8,2%
human cytomegalovirus	2,3%
human adenovirus	6,4%

Moreover, potential positive shift of the quantitative standards (QS) for all pathogens has been reported, which may not be detected during validation of the run if the shift occurs simultaneously for all QS. Internal investigation is currently ongoing to determine the magnitude and probability of this issue.

Both nonspecific signals and QS shift may impact patient testing and laboratory Quality Control runs.

FTD 1.1 ACE

Potential false positive and over-quantification while using FTD-1.1 ACE kit

Risk to Health:

Nonspecific low positive signals or degradation of the QS can lead to false positive detection or over-quantification of viral load, respectively, of human cytomegalovirus (HCMV), Epstein-barr virus (EBV) and human adenovirus (HAdV), which may impact treatment considerations. Depending on the pathogen, clinical context and treatment, results would be used in conjunction with clinical presentation, results of other testing, and monitoring protocols.

Actions to be taken by the user:

1. Cease the use of FTD-1.1 for quantitative use during the time of the internal investigation. We will give you an update within 4 weeks.
2. Fast Track Diagnostics recommends a review of previously generated results for patients currently under treatment for HAdV, HCMV, and EBV as follows:

For any suspicious case that produces a low positive result, Fast Track Diagnostics recommends confirmatory testing using another detection technique.

Low positive signals are defined as positive amplification with cycle threshold (Ct) values indicated in Table 3, for users using these products in combination with the easyMag® and Applied Biosystems® 7500 (Thermo Fisher Scientific) instruments:

Table 3: Ct values for nonspecific low positive signals

Pathogen	Ct value*
HAdV	>35
HCMV	>36.5
EBV	>34

* Ct values obtained from the validated cycler Applied Biosystems® 7500

3. For qualitative use, Fast Track Diagnostics recommends the setting up of an internal cut-off threshold as defined in point 2. Here above. For any results coming after this threshold, please confirm the result with a second confirmatory method.
4. If you have received any complaint or report of illness or adverse events associated with FTD-1.1, immediately contact FTD at: support@fast-trackdiagnostics.com.
5. Please complete and return the Field Correction Effectiveness Check Form attached to this letter for the 10th of July 2019.

Customers not running the above-mentioned instruments should review their internal validation files and assess the need for further action.

FTD 1.1 ACE

Potential false positive and over-quantification while using FTD-1.1 ACE kit

This issue remains under investigation at FTD and additional information or updates will be provided as they become available.

Please review this letter with your medical advisor and retain this letter with your laboratory records and forward this letter to those who may have received this product.

If you have any questions, please contact FTD at: support@fast-trackdiagnostics.com.

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FIELD CORRECTION EFFECTIVENESS CHECK

Potential false positive and over-quantification while using FTD-1.1 ACE kit

This response form is to confirm receipt of the enclosed Fast Track Diagnostics Urgent Field Safety Notification FSN-FA-2019-02, dated June 2019 regarding "Potential false positive and over-quantification while using FTD-1.1 ACE kit". Please read each statement and indicate the appropriate answer.

Email this completed form to the email address provided at the bottom of this page, by the **10th of July 2019**.

1. I have read and understood the Field Safety Notice instructions provided in this letter. Yes No

2. I am a distributor of the affected products AND my customers received FTD-1.1 Yes No

If the answer to statement 2 above is yes, please confirm that you forward the relevant information to your impacted customers. Yes No

Name of person completing questionnaire:

Title:

Institution:

Street:

City:

State:

Phone:

Country:

Signature
and date

Please send a scanned copy of the completed form via email to vigilance@fast-trackdiagnostics.com. If you have any questions, contact a Fast Track Diagnostics support representative.