

Field Safety Notice *(FSN 03.2017)*

BÜHLMANN CALEX® Cap

Date: 2017-02-21

Positive bias of calprotectin results obtained with the CALEX® Cap extraction device and corrective action with CALEX® Cap “N”

Dear Customer, dear Distributor,

Our records indicate that your facility received the following products:

| Product | Catalog order code | Lot Number |
|---------------------|---|----------------------|
| BÜHLMANN CALEX® Cap | B-CALEX-C50, B-CALEX-C200, B-CALEX-C500 | All lots without “N” |

Table 1. Affected CALEX® Cap products

With the Marketing Information MI 002.2017 we informed you about the launch of the improved CALEX® Cap extraction device, offering better overall precision, tightness, centrifugation capability up to 3'000g and IATA 650 / UN 3373 classification.

This field safety notice provides additional technical information about the expected calprotectin result agreement between stool specimens extracted with the reference manual weighing and extraction method – 1:50 dilution and stool specimens extracted with the original CALEX® Cap device (lot number without “N”) as well as the recently launched CALEX® Cap device.

We would like to draw your attention to the mean positive bias of 15.6 % of the original CALEX® Cap compared to the manual weighing and extraction method – 1:50 dilution. This bias could be corrected by removing two grooves of the CALEX® Cap sampling pin (CALEX® Cap: 8-groove device, CALEX® Cap “N”: 6-grooves device).

Description of the issue: A mean positive bias of 15.6 % has been confirmed for results obtained with stool extraction using the original CALEX® Cap device in comparison to results obtained with the reference manual weighing and extraction method – 1:50 dilution. Please refer to table 2.

| | Mean Bias (95 % CI) | Bias at 50µg/g (95 % CI) | Bias at 200µg/g (95 % CI) |
|----------------|---------------------------|-----------------------------|------------------------------|
| CALEX® Cap | 15.6 % (11.4 – 19.7 %) | 15.2 % (8.4 – 20.4 %) | 17.4 % (9.6 – 23.9 %) |
| CALEX® Cap “N” | 4.0 % (-1.5 – 9.6 %) | 8.0% (-3.7 – 13.8 %) | 1.6 % (-8.3 – 14.4 %) |

Table 2. Comparison of BÜHLMANN fCAL® ELISA results obtained with the CALEX® Cap as well as the CALEX® Cap “N” with the reference manual weighing and extraction procedure – 1:50 dilution. Method comparison studies were performed according to the CLSI approved guideline EP09-A2. At least 75 stool specimens with calprotectin values in the range of 10 – 600 µg/g were analyzed using multiple (at least 3) CALEX® device lots. Mean bias was determined using Bland-Altman analysis. Bias at clinically relevant decision points was determined using Passing-Bablok regression analysis.

The positive bias of the CALEX[®] Cap device – now corrected with the CALEX[®] Cap “N” - has been also recently reported by Maxime M.W. De Sloovere et al., “*Analytical and diagnostic performance of two automated fCAL immunoassays for detection of IBD*”, Clin Chem Lab Med 2017.

Risk to Health: Given the overall analytical and clinical performance of fecal calprotectin assays and the general imprecision level of stool extraction methods, the above mean bias of 15.6 % is considered to have limited impact on result interpretation.

The positive bias may, in few cases, lead or have led to the interpretation of calprotectin levels as elevated (> 200 µg/g) and requiring further investigative and curative procedures. With stool specimen preparation using the reference manual extraction procedure, they would be determined as having a low inflammatory response thus repeating the measurement and performing further investigations would be recommended.

In few cases patients may be or may have been assigned as having a low inflammatory response (> 50 µg/g), although, with stool specimen preparation using the reference manual extraction procedure, they would be determined as having normal calprotectin values.

Advise on action to be taken by the user

Distributors:

- Distributors have to identify and notify customers who have received the aforementioned product. You may include a copy of this letter in your notification to your customers.
- Distributors have to complete the attached Faxback Form indicating that you have received this notification and acknowledge that you have accomplished the step indicated above.

Users:

- When reviewing current calprotectin results obtained for stool specimens extracted with the original CALEX[®] Cap device (CALEX[®] lots without “N”) please consider the positive bias described above.
- A fast transition to the CALEX[®] Cap “N” device with high method agreement with the manual weighing and extraction – 1:50 dilution method is recommended.

In addition to the advice related to the CALEX[®] Cap and CALEX[®] Cap “N”, we encourage customers and distributors to also take note and follow recommendations related to the stool sampling by patients as described e.g. in Lillian Du et.al, “*Within-stool and within-day sample variability of fCAL in patients with IBD*”, J Clin Gastroenterol 2016; or Anders Lasso et. al., “*The intra-individual variability of fCAL: A prospective study in patients with active UC*”, ECCO 2014. These publications provide additional insight in minimizing intrinsic variability in fecal calprotectin stool analytics.

Transmission of this Field Safety Notice:

This notice needs to be passed on to all those who need to be aware within your organisation or to any organisation where the potentially affected devices have been transferred.

Please transfer this notice to other organisations which may be impacted by this action. Please maintain awareness of this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action.

Should you feel it necessary to return the above mentioned products that is discrepant as outlined in this letter, please direct all return request to our Product Support.

We sincerely apologize for any inconvenience caused as a result of this Field Safety Notice. BÜHLMANN is committed to offering quality products and superior customer service. If you have any questions or comments arising from this Field Safety Notice, please contact

support@buhlmannlabs.ch

Ms Marie-Christine Müller, Ms Camilla Messerli
Telephone: + 41 61 487 12 00

The undersigned confirms that this notice has been notified the appropriate Regulatory Agency

Best regards,



Fabio Perretta
Head Quality Manager



Dr. Alija Ritz
Head Regulatory Affairs

Field Safety Notice FAXBACK FORM

Date: 2017-02-21

Please complete and promptly return (by e-mail or Fax) to:

Dr. Alicja Ritz, Head Regulatory Affairs, BÜHLMANN

Email: alr@buhlmannlabs.ch or Fax: + 41 61 487 12 34

| Product | Catalog order code | Lot Number |
|---------------------|---|------------------------------------|
| BÜHLMANN CALEX® Cap | B-CALEX-C50, B-CALEX-C200, B-CALEX-C500 | All CALEX® Cap Lots without "N" |

Type of Action: Inform customer

Further to the enclosed Field Safety Notice, you are requested to complete the following:

- I have received and reviewed the enclosed Field Safety Notice Yes / No
- I have informed all customers that have already received the above mentioned products Yes / No

| | |
|---------------------|----------------|
| Company Name: _____ | Country: _____ |
| Printed Name: _____ | Signed: _____ |
| Title: _____ | Date: _____ |
| Fax: _____ | Phone: _____ |
| Comments: | |
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