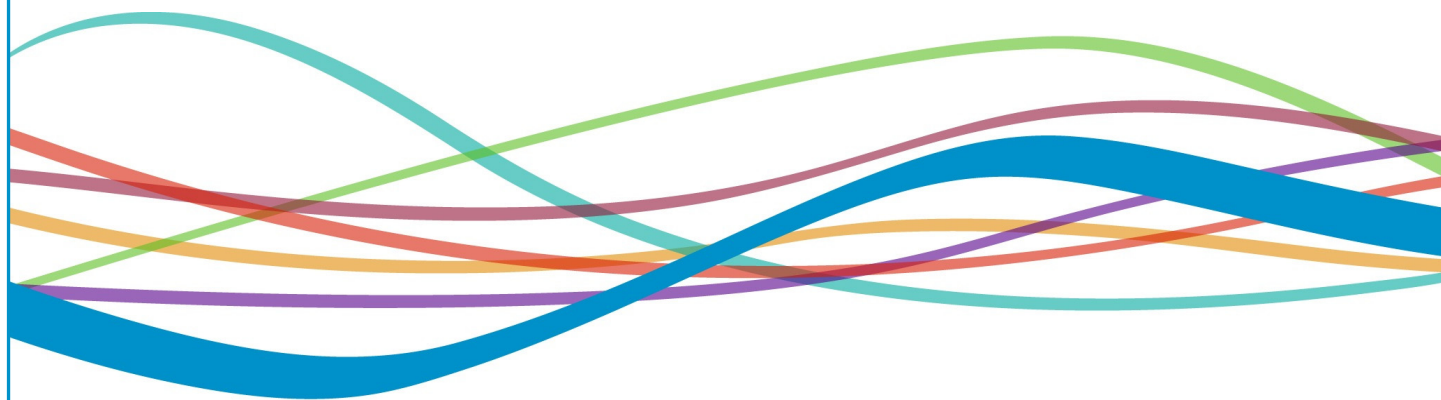


Evaluation report

Immunochemical faecal occult blood tests

CEP09042

November 2009



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The product

Immunological faecal occult blood tests (iFOBT) use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces. The presence of blood in a faecal sample can be used as a marker to detect significant neoplasia in otherwise asymptomatic people.

Field of use

iFOBT have the potential to be used in bowel cancer screening programmes. They are more sensitive and specific than the current guaiac-based faecal occult blood test and can be automated.

National guidance

There is no national guidance in England on the use of iFOBT for bowel cancer screening.

Methods

Instruments were installed in the GMEC laboratory where the GMEC team received standard training from the suppliers. The evaluation was performed over a period of four months from April to August 2009. Samples examined included faecal samples prepared from a faecal pool and spiked with varying measured amounts of Hb, and also Hb solutions prepared in the manufacturers' system buffers. User surveys were conducted to obtain information on the reliability and ease of use of the analytical systems and the collection devices.

Technical performance

In this report we present data for imprecision, linearity, the effect of antigen excess (hook effect-false negative results at high Hb concentrations), carryover and haemoglobin variants, for three automated analytical iFOB methods: HemSp / MagStream HT, OC-Sensor / DIANA and FOB Gold / SENTiFOB. Stability and imprecision data for four associated sample collection devices (New HEMTUBE, OC-Auto sampling bottle 3, FOB Gold tube and DEVEL-A-TAB card) are also presented.

Sample collection devices

Our data show that, even when the faecal collection devices were used by experienced evaluation staff processing hundreds of samples, none of the sampling devices gave reproducible results, thus contributing to the overall imprecision of the methods.

Manufacturers' claims for stability of the Hb in faecal samples added to the collection devices and stored at room temperature (23 to 26°C) prior to analysis were confirmed for the OC-Sensor / DIANA method. However, these claims were not confirmed for the HemSp / MagStream HT, FOB Gold / SENTiFOB or the DEVEL-A-TAB methods.

Analytical methods

Our data on the performance of each method were obtained using solutions of human Hb prepared in buffers supplied by the relevant manufacturers. This ensured that the measured performance of the assay was not affected by the performance of the sample collection devices. None of the systems demonstrated a carryover effect between sampling and all systems gave similar results in our Hb variant experiment.

The qualitative HemSp / MagStream HT method:

- had poor imprecision and results were not consistent with the manufacturer's claims at low Hb concentrations
- was not linear since the method is not designed to be linear across a broad measuring range.

The OC-Sensor / DIANA method :

- had good imprecision and results were consistent with the manufacturer's claims
- was linear in the range 50 – 500 ng Hb/mL buffer
- identified a problem with samples with very high Hb concentration and did not produce a result.

The FOB Gold / SENTiFOB method:

- had poor imprecision and results were not consistent with the manufacturer's claims at low Hb concentrations
- was linear in the range 50 – 500 ng Hb/mL buffer
- identified a problem with samples with very high Hb concentration and did not produce a result.

Operational considerations

All three analytical platforms are easy to operate and maintain once appropriate training has been received.

The throughput and therefore the number of analysers required to deal with the daily workload in each bowel cancer screening hub will vary. We found that the HemSp / MagStream HT can process 800 samples per hour, the OC-Sensor / DIANA 245 samples per hour and the FOB Gold / SENTiFOB 65 samples per hour. The FOB Gold method has the potential to be run on high throughput automated clinical chemistry analysers, an option we have not investigated.

The NEW HEMTUBE picks up approximately 0.3 mg of faeces which is added to 1 mL of buffer. The device is provided in two parts and has a long handled sample probe to keep the user's hands clear of the faecal sample. The tube is very narrow and therefore has limited space for participant identification information.

The OC-Auto sampling bottle 3 picks up approximately 10 mg of faeces which is added to 2 mL buffer and will only fit on the manufacturer's analysers. It has an internal filter system that removes debris from the buffer solution before analysis. A foil cover protects the analyser sampling area of the tube and makes it obvious if it has been accidentally opened. The sample buffer only enters the sampling area when pressure is applied by the analyser. There is potential for fluid loss from the device when removing the sample probe prior to sampling. The tube has a flat surface which makes the addition of a user identification label easy.

The FOB Gold tube picks up approximately 10 mg of faeces which is added to 1.7 mL buffer. The tube has been designed to fit into primary sample tubes racks on most automated clinical chemistry analysers. The sample probe is held in the sample tube with a screw thread so that users can easily identify that the probe has been securely returned to the tube. There is potential for fluid to be lost from the device because there is a cap at the other end of the tube where the buffer is contained.

The DEVEL-A-TAB sample collection card requires two samples from separate bowel motions. The Hb from the collection tab is eluted in 1.7 mL of buffer.

Once returned to the screening hub both the New HEMTUBE and OC-Auto sampling bottle 3 are very similar to use. The FOB Gold tube involves the additional step of removing the cap at the buffer end of the tube before analysis. The DEVEL-A-TAB sample collection card involves a sample elution step before analysis and is therefore more labour intensive than other systems.

Economic considerations

iFOBT sampling devices, reagents and analysers are more expensive than the current guaiac-based faecal occult blood test. However, automated testing technology could reduce the number of staff required in a screening hub, reducing staff costs. Cut-off Hb concentrations can be adjusted in the light of subsequent colonoscopy results in order to optimise resource usage.

CEP verdict

All manufacturers state that liquid samples stored at room temperature for more than three days are not suitable for analysis, due to deterioration of any Hb present. If samples are to be sent via the UK postal system, a significant number will not be returned within this time.

The HemSp / MagStream HT has a non-adjustable cut-off, making it unsuitable for the English bowel cancer screening programme, which requires the cut-off to be adjustable in order to optimise the referral rate. The method is not CE marked for quantitative measurement of human Hb. The system gave negative results for samples that were positive by the other methods.

The DEVEL-A-TAB card demonstrated better sample stability than the other systems tested. However the potential for introduction of errors during the processing of the tabs from the cards and the lack of an automated system to elute the Hb from the card means that this is not a practicable option for a large screening programme.

The FOB Gold / SENTiFOB analyser has a very low sample throughput so the method would need to be run on a high throughput automated clinical chemistry analyser to make it suitable for the English screening programme.

The OC-Sensor / DIANA analyser is well designed but has limited reagent, wash and waste capacity so would require regular attention when used in a busy screening laboratory. Though not ideal, this is the most suitable system for the English bowel cancer screening programme.

Bowel cancer is the third most common cancer in men, and the second most common cancer in women in the UK. Each year, there are over 18,700 new cases of bowel cancer in men and 16,800 cases in women. Bowel cancer screening aims to detect bowel cancer at an early stage in people with no symptoms, when treatment is more likely to be effective.

The current English bowel cancer screening programme uses a guaiac-based faecal occult blood test which must be read visually. Following an announcement by the Prime Minister in 2007, the programme is extending the screening age range from 60-69 to 60-74 in 2010. This will significantly increase test numbers.

Immunochemical faecal occult blood (iFOB) methods have the potential to further enhance the efficiency and clinical effectiveness of the English screening programme. These methods use antibodies raised against human haemoglobin (Hb) to detect blood present within faeces. Although they are more expensive than guaiac-based tests, they can be automated and demonstrate increased specificity since only human Hb is detected. They therefore provide an opportunity to improve the detection of colorectal cancers, whilst maximising efficiency of resource usage.

Scope

The iFOB systems selected for evaluation for the bowel cancer screening programme had to meet the following criteria:

- available in the UK
- easily automated on instrumentation that has acceptable processing speed and is easy to use and maintain
- utilise antibodies specific for human Hb
- allow the user to select cut-off concentrations
- have sample collection systems that have acceptable sample stability at room temperature
- have sample collection systems that are suitable for automated packaging systems and meet UK postal regulations.

National guidance

There is no national guidance in England on the use of iFOBT for bowel cancer screening.

Product overview

Three analytical platforms and four collection systems have been identified as potentially suitable for the English screening programme:

HemSp / MagStream HT, *Fujirebio Inc. Japan*

OC-Sensor / DIANA, *Eiken Chemical Co., Tokyo, Japan*

FOB Gold / SENTiFOB, *Sentinel Diagnostics SpA, Milan, Italy*

DEVEL-A-TAB / SENTiFOB, *Sentinel Diagnostics SpA, Milan, Italy*

Table 1. Overview of the available systems

	HemSp / MagStream HT	OC-Sensor / DIANA	SENTiFOB
Method	magnetic particle agglutination	latex agglutination	latex agglutination (open method)
Analyser name	MagStream HT	OC-Sensor / DIANA	SENTiFOB
Instrumentation	dedicated bench top analyser	dedicated bench top analyser	bench top analyser
Footprint (instrument + peripherals) cm	150 x 88	110 x 74	130 x 74
Instrument weight	165 kg	60 kg	45 kg
Sample collection system	New HEMTUBE	OC-Auto sampling bottle 3	FOB Gold tube DEVEL-A-TAB card
Measuring range	greater than 20 ng/mL	50 – 1050 ng/mL	14 – 1000 ng/mL
Measuring cell	microtitre plate	washed cuvettes	single use cuvette ring
Analyser sample volume	25 µL	35 µL	10 µL
Throughput	claimed	960 / hour	280 / hour
	measured by GMEC	800 / hour	245 / hour
Memory capacity	9,999 JOB files 50,000 tests per JOB file	100,000 test results	Dependent of the size of the hard disk

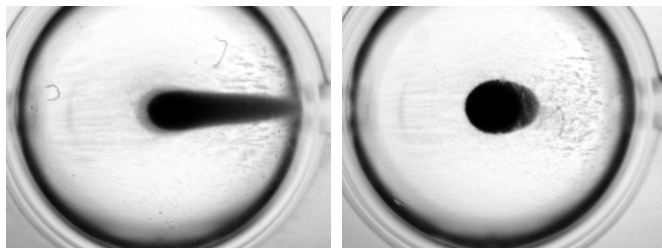
HemSp / MagStream HT

Figure 1. MagStream HT



The HemSp/MagStream HT (figure 1) is a dedicated analyser for the detection of human Hb in faecal samples. This method is qualitative and uses magnetic particle agglutination. It has a non adjustable cut-off at a Hb concentration equal to or greater than 20 ng/mL. The magnetic particles are coated with rabbit anti-human Hb antibodies. The analyser automatically dispenses sample and reagent into a microtitre plate. The plate is agitated before being placed over a magnet which attracts the magnetic particles, resulting in a particle reaction pattern being formed. The magnetic particle pattern (figure 2) is measured by a digital camera and the presence of Hb is assessed according to the pattern length (negative - particle tail extends towards the edge of well, positive - no particle tail).

Figure 2. Magnetic particle pattern



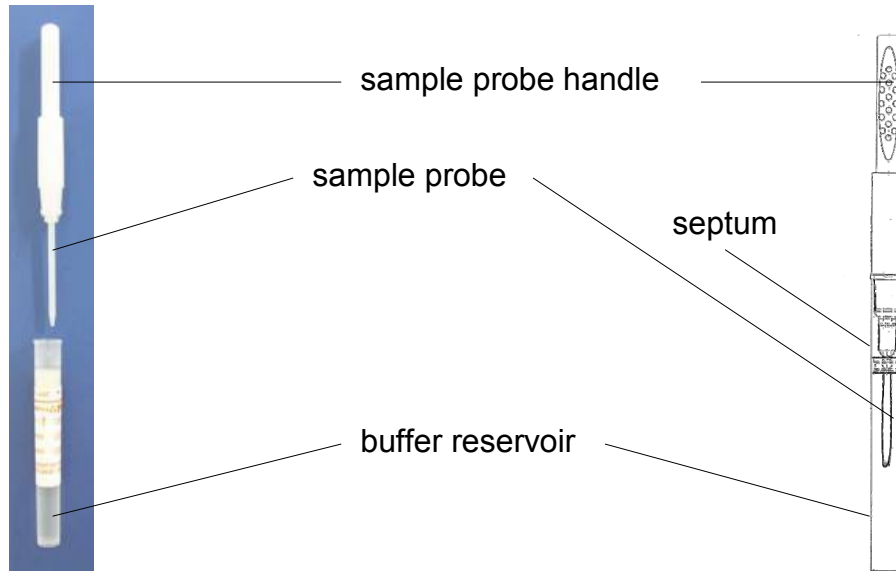
Negative

Positive

The HemSp/MagStream HT is only CE marked for qualitative measurement.

Sample collection system

Figure 3. NEW HEMTUBE



The faecal sample is collected into the NEW HEMTUBE™ (figure 3) using the separate collection probe provided. The fine pointed end of the sample collection probe is inserted five or six times into the faecal sample and then scraped over the surface of the sample several times. Once loaded with faeces the probe is inserted into the open end of the tube. On insertion, the collection probe passes through a septum which removes excess material, and clicks into place to seal the unit. At this stage the faecal material on the probe is introduced into the buffer already present within the tube. The device is now ready to return to the laboratory. Fujirebio states that this system delivers approximately 0.3 mg of faeces into 1 mL of buffer. The tubes are loaded into HemSp / MagSteam HT racks with the probe end down and placed onto the analyser for analysis.

The manufacturer states that analysis should be performed as soon as possible after sample collection. If there is any delay, either in return to the laboratory or within the laboratory, the sample collection bottles should be stored at 2 - 10 °C. Fujirebio state that freezing causes deterioration of Hb in their sample tubes and must therefore be avoided.

OC-Sensor / Diana

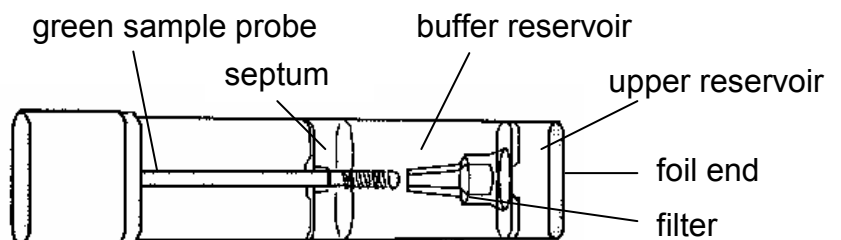
Figure 4. OC-Sensor / Diana



The OC-Sensor / DIANA (figure 4), supplied in the UK by Mast Diagnostic Division, measures human Hb concentration in faecal samples by quantitative latex antigen-antibody agglutination with polyclonal rabbit anti-human HbA₀ antibodies. The instrument dispenses and mixes sample and reagents into multiple-use pre-washed reaction cells. A light beam passes through the reaction liquid to measure changes in absorbance at 660 nm. When installed the system is set with a cut-off value of 100 ng/mL which can be adjusted by the user to the concentration determined by the screening programme.

Sample collection system

Figure 5. OC-Auto sampling bottle 3



The faecal sample is collected into the OC-Auto sampling bottle 3 (figure 5) using the green sample probe which is removed by twisting and pulling from the sampling device. The threaded end of the green sample probe is scraped over the surface of the faecal sample until the grooves are filled. Once loaded with faeces the sample probe is placed back into the tube. On insertion into the tube, the probe passes through a septum which removes excess faecal material and delivers the faecal material to the buffer contained within the tube. The device is now ready to return to the laboratory. The manufacturer states that the probe delivers approximately 10 mg

of faeces into 2 mL of buffer. The sampling tubes are loaded into the analyser racks with the green probe end downwards. The analyser pierces the foil seal and squeezes the tube to force the liquid through the filter into the upper reservoir, ready for sampling.

The manufacturer states that analysis should be performed as soon as possible after sample collection. If there is any delay either in returning to the laboratory or within the laboratory then the sample tubes should be stored at 2 - 10 °C.

SENTiFOB / FOB Gold / DEVEL-A-TAB

Figure 6. SENTiFOB

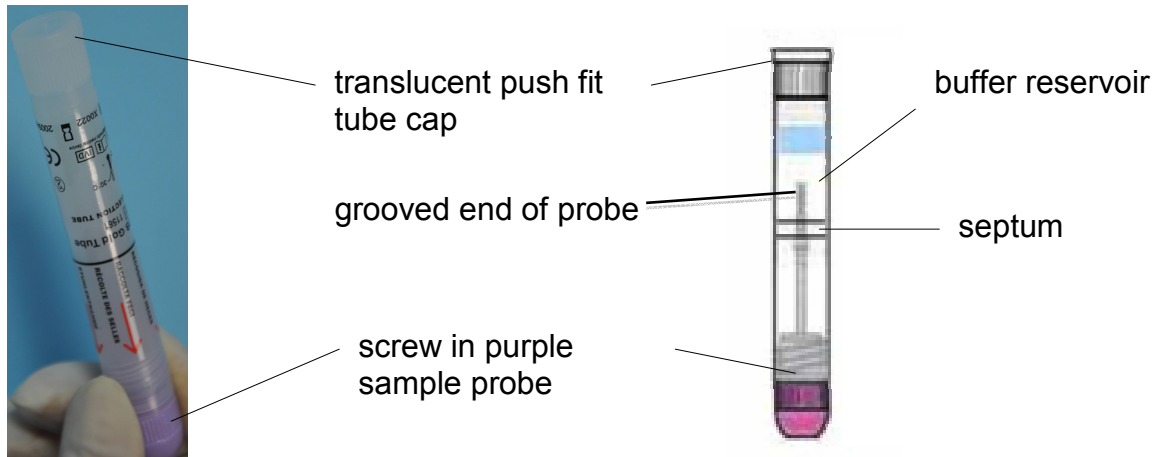


The SENTiFOB (figure 6), supplied in the UK by Alpha Laboratories Ltd, is a dedicated analyser for the detection of faecal occult blood using the FOB Gold method. FOB Gold is a quantitative latex antigen-antibody agglutination assay that uses polyclonal anti-human Hb antibodies that can also be run on high throughput automated clinical chemistry analysers. The SENTiFOB dispenses sample, buffer and latex reagent into a single use reaction cell. Agglutination is measured as an increase in absorbance at 570 nm and is proportional to the concentration of human Hb in the sample. The cut-off is set by the user.

Sample collection systems

FOB Gold tube

Figure 7. FOB Gold tube

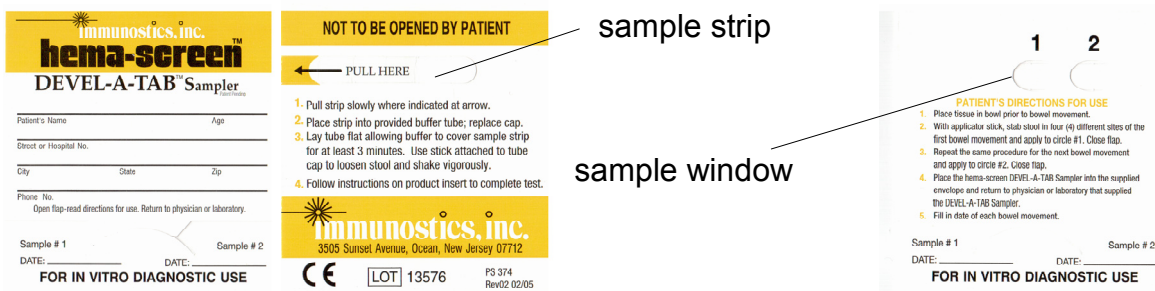


The faecal sample is collected into the FOB Gold tube (figure 7) using the purple sample probe which unscrews from the sampling device. The grooved end of the purple probe is inserted five or six times into the faecal sample to fill the grooves. The sample probe is then screwed back into the tube, passing through a septum, which removes excess faecal material and delivers the sample into the buffer in the tube. The device is now ready to return to the laboratory. The manufacturer states that the probe delivers approximately 10 mg of faeces into 1.7 mL of buffer. The tubes are loaded onto the analyser purple probe side downwards. The translucent cap at the top end of the tube must be removed prior to analysis to allow access for sampling.

The manufacturer states that analysis should be performed as soon as possible after sample collection. If there is any delay either in return to the laboratory or within the laboratory, the sample tubes should be stored at 2 - 8 °C.

DEVEL-A-TAB card

Figure 8. DEVEL-A-TAB card



The DEVEL-A-TAB card (figure 8) has a flap on the front which is opened to reveal two small sample windows. Using the applicator sticks provided with the card, the faeces is sampled in four different areas before being applied to window one. This process is repeated on a separate motion for window two. The flap on the card is then closed. The card is placed inside the envelope provided and returned to the laboratory for analysis. Before analysis, the Hb in the faecal material collected on the card must be eluted into system buffer (see *Methods* for elution protocol).

The DEVEL-A-TAB card is not yet CE marked for use in combination with the SENTiFOB analyser.

Evaluation methods

Preparation of faecal pool

A faecal pool with a total mass of 800 - 900 g was prepared from faecal samples collected from healthy volunteers who were not receiving any medication. Prior to addition to the pool, each sample was tested on all the evaluation systems to ensure negativity for occult blood. The pooled sample was well mixed and divided into multiple portions which were weighed prior to being frozen.

Preparation of human haemoglobin

A human Hb solution was prepared from a whole blood sample obtained from a healthy volunteer. The total volume of the sample was recorded prior to centrifugation and plasma removal. The resulting cells were washed three times with physiological saline before being re-constituted to the original sample volume with deionised water. The solution was frozen overnight and the Hb concentration of the resulting lysate was measured on an Advia[®]120 haematology system using a 1 in 2 dilution in physiological saline.

DEVEL-A-TAB elution protocol

Before analysis on the SentiFOB analyser the human Hb needed to be eluted from the DEVEL-A-TAB card into Sentinel sample buffer. The perforated sample strip behind the loading windows was removed from the card and placed into a tube containing 1.7 mL of Sentinel sample buffer. The samples were mixed for 30 minutes on a roller mixer and a filter was then inserted into the tube to remove any particulate matter and push the sampling strip to the bottom of the tube. The combined tube and filter was then loaded onto the SentiFOB for analysis.

Imprecision

Within-run and total imprecision were assessed following the Clinical and Laboratory Standards Institute (CLSI) protocol EP-15-A [1]. This protocol has been designed to demonstrate whether imprecision and accuracy are consistent with manufacturers' claims, and assumes that the method's performance has previously been evaluated by the manufacturer using CLSI EP5-A [2] or a similar protocol designed to validate and verify performance.

CLSI protocol EP15-A states that the user's standard deviation (SD) can be larger than the manufacturer's claimed SD but not significantly different from it. A verified manufacturer's SD was calculated using the prescribed formula to allow for this difference. We have compared our SD results with the verified manufacturers' SDs in this evaluation.

To assess analytical performance, solutions of human Hb were prepared at four different concentrations for each of the systems under evaluation, using the buffers supplied by their respective manufacturers. The prepared Hb solutions were divided into aliquots and frozen. On each of five days, a fresh aliquot at each of the four concentrations was thawed and measured four times on each system.

To assess the performance of the collection systems, four faecal samples spiked with different concentrations of human Hb were prepared from the faecal pool. The initial Hb concentration of the faecal material was then measured on the samples using the appropriate sampling device for each of the four methods under evaluation. The faecal samples were then divided into aliquots and frozen. On each of five days a faecal aliquot at each of the four concentrations was thawed, mixed and loaded onto each of the four sampling devices. The sampling devices were left to stand for 30 minutes, and mixed for 30 minutes on a roller mixer prior to analysis.

Collection device sample stability

Five faecal samples at each of four different concentrations of human Hb, ranging from the detection limit to a strong positive for each method under evaluation, were analysed on each day of the sample stability assessment. Samples were analysed daily for the first 10 days and then on alternate days to cover a total period of 25 days. All sample tubes/cards were loaded on day 0 and then stored in thermostatically monitored conditions at a selection of temperature ranges (29 to 34°C, 23 to 26°C, 4 to 8°C and -24 to -18°C) until analysis. Prior to analysis all samples were allowed to equilibrate to room temperature (23 to 26°C) then mixed for 10 minutes.

Carryover test

Sample carryover was assessed according to the procedure outlined by Broughton *et al* [3]. Solutions of human Hb were prepared for each system using the buffer supplied by the manufacturer. Three samples with high Hb concentrations (a_1, a_2, a_3) followed by three samples with low Hb concentrations (b_1, b_2, b_3) were measured. This set of six measurements was then repeated ten times. The carryover factor, k , was calculated as follows.

$$k = \frac{b_1 - b_3}{a_3 - b_3}$$

Hook effect

A series of human Hb solutions in manufacturers' buffer was prepared at very high Hb concentrations: 62,500, 125,000, 250,000 and 500,000 ng/mL. All samples were measured in duplicate using each of the systems, to test for the presence of a hook effect.

Haemoglobin variants

Lysates were prepared from whole blood samples obtained from patients with the following haemoglobinopathies, where the % variant is shown in brackets. HbS (32.0, 32.6, 80.7, and 91.8%), HbC (38.3 and 40.3%), HbD (43.9 and 37%), HbE (27.2%). Lysates were also prepared from a whole blood sample obtained from a newborn infant with 71.1% HbF and an adult patient with 14.0% HbA_{1c}. The Hb concentration of each lysate was determined on an Advia[®]120 haematology system using a 1 in 2 dilution in physiological saline. For each method, each lysate was diluted using the appropriate manufacturer's buffer to obtain a series of three Hb concentrations within the manufacturer's quoted measuring range. All lysates were then analysed using the relevant method.

User surveys

Sample collection

A sample of each faecal collection device was given to 48 individuals along with instructions on how to collect faecal samples. The users were asked to collect samples of their faeces using each device and complete a short questionnaire, giving their opinions on the devices.

Sample handling

Collection devices were sent to the Bowel Cancer Screening Hubs where the staff were asked to identify the likely impact of their use in a screening environment, from sample collection through to analysis and send their findings to GMEC.

System use

Questionnaires on the use of each system were distributed internationally to laboratories where the systems are already in use. The questions covered the whole screening system from identification and distribution of the samples through analysis to result handling.

Logistics

Meetings were held with two companies involved in the logistics of distributing sampling devices and invitation letters to screening participants. They were asked to assess the impact of a change to immunochemical testing systems.

Units of measurement

In this evaluation the units of measurement for the concentration of Hb in the system buffer are expressed in ng/mL. The formula below was used to convert the concentration of Hb present in a faecal sample (mg Hb/g faeces) to that in the system buffer (ng/mL)

$$\text{ng/mL} = \frac{\text{mg Hb/g faeces} \times \text{mass of faecal sample added (mg)} \times 1000}{\text{volume of buffer in the sample tube (mL)}}$$

The mass of faecal material added is that quoted by the manufacturer as being delivered using their sample probe.

In this evaluation concentrations produced by the OC-Sensor DIANA and the SENTiFOB have all been recorded in ng/mL. The HemSp / MagStream HT does not report concentrations since it is designed to indicate either a positive or negative outcome. GMEC exported the raw optical measurements described as 'pixel data' from the HemSp / MagStream HT system; this option is not routinely available to users. We found that 208 pixels is approximately equivalent to a Hb concentration of 20 ng/mL which is the quoted HemSp / MagStream HT cut-off between positive and negative values, and 150 pixels is approximately equivalent to 30 ng/mL (note that it is an inverse relationship).

There are some discrepancies between the results when the same faecal samples are analysed on the three systems. Notably the HemSp / MagStream HT gave negative results for samples found positive on the other two systems. An explanation for this discrepancy has not been found.

When applying the calculation above to a faecal sample with a Hb concentration of 0.034 mg Hb/g faeces and using the appropriate sample mass and buffer volume, the Hb concentration in the buffer for each of the systems is:

- HemSp / MagStream HT 10 ng/mL
- OC-Sensor DIANA 168 ng/mL
- SENTiFOB / FOB Gold 198 ng/mL

These concentrations equate to a 'negative' result on HemSp / MagStream HT with its designated 20 ng/mL cut-off, to a 'positive' result on OC-Sensor DIANA with its default 100 ng/mL cut-off and to a 'positive' result on SENTiFOB / FOB Gold if the same 100 ng/mL cut-off is applied.

Experiments performed during the evaluation showed that by adhering to the manufacturers prescribed sample collection protocols, the Hb concentrations measured in the buffer were consistent with the equation given above. The practical consequences of this are that samples with a concentration of 0.067 mg Hb/g faeces will be negative using the HemSp / MagStream HT with its 20 ng/mL cut-off but positive with the OC-Sensor DIANA and SENTiFOB / FOB Gold using the 100ng/mL cut-off.

Sample collection systems

The data presented in this section of the report, both from the manufacturers and GMEC, have been obtained using faeces sampled using the appropriate sample collection devices. All GMEC data were obtained using faecal material from a single pool spiked with human Hb. It is not always clear what type of samples the manufacturers used in preparing their data.

When loading the sampling devices with faeces it is inevitable that there will be some variation due to the technique used and the consistency of the faecal material. In our evaluation we have used a single pool sample to minimise variation in sample consistency.

Sample collection system stability

When used in the bowel cancer screening programme the collection devices could be subjected to a variety of different temperatures between the loading of the sample device by the participant and its arrival for testing in the laboratory. In order to mimic these conditions we have looked at the stability of the results obtained for a range of storage temperatures that could be routinely experienced. Table 2 shows the manufacturers' stability claims alongside our stability findings. We have been unable to obtain information on exactly how manufacturer stability claims have been calculated and have no information on what is considered an acceptable fall in Hb concentration for these devices. Our results are reported as 'agree' or 'do not agree' with the manufacturers' claims. Where results did not always agree they are marked as 'inconsistent'. Graphs of the data obtained can be found in appendix 2.

Table 2. Stability of sample collection systems

Storage temperature		NEW HEMTUBE	OC-Auto sampling bottle 3	FOB Gold tubes	DEVEL-A-TAB card
-18 to -24°C	claimed measured	Not suitable for freezing	10-14 days agree	20 days agree	Not quoted
4 to 8°C	claimed measured	15 days agree	7 days agree	7 days inconsistent	Not quoted
23 to 26°C	claimed measured	7 days do not agree	3 days agree	3 days do not agree	30 days do not agree
29 to 34°C	claimed measured	4 day do not agree	Not quoted less than 3 days	Not quoted less than 3 days	Not quoted

Sample collection system imprecision

To assess the performance of the collection devices we have assessed the imprecision of the results obtained from four samples loaded and tested daily for 5 days. Table 3 show our imprecision data for samples with negative, weak positive and strong positive Hb concentrations. These results show that even when loaded by experienced users all these sampling devices had poor imprecision.

None of the manufacturers quoted any data for the performance of their assays in conjunction with their faecal sample collection devices.

Table 3. Sample collection device imprecision

NEW HEMTUBE			OC-Auto sampling bottle 3			FOB Gold tubes			DEVEL-A-TAB card		
pixels	%		Hb ng/mL	%		Hb ng/mL	%		Hb ng/mL	%	
Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
Within-assay imprecision											
298.6	2.94	1.0	92.4	18.7	20.2	100.6	19.1	18.9	23.7	6.4	27.0
282.6	14.2	5.0	95.2	47.1	49.5	166.2	49.2	29.6	44.2	7.6	17.1
202.3	48.1	23.8	237.0	41.6	17.6	286.6	82.2	28.7	58.1	19.9	34.3
154.4	34.4	22.3	224.5	32.6	14.5	562.3	121.0	21.5	130.2	31.7	24.3
Total imprecision											
298.6	3.8	1.3	92.4	20.1	21.8	100.6	24.0	23.9	23.7	8.5	35.9
282.6	24.1	8.5	95.2	45.4	47.7	166.2	49.1	29.6	44.2	17.6	39.8
202.3	67.1	33.2	237.0	39.9	16.8	286.6	147.5	51.5	58.1	28.8	49.6
154.4	50.3	32.5	224.5	31.4	13.9	562.3	119.7	21.3	130.2	68.6	52.7

Analytical methods

The data presented in this section of the report from both the manufacturers and GMEC has been obtained using solutions of Hb prepared in manufacturers' buffers.

Analytical method imprecision

Tables 4 - 6 compare the imprecision of the evaluated methods against available manufacturers' claims. Our within-assay imprecision data for the OC-Sensor DIANA indicates very good performance, consistent with the manufacturer's claims. The HemSp / MagStream HT and FOB Gold / SENTiFOB assays do not demonstrate such good performance and at low Hb concentrations the performance is not consistent with the manufacturers' claims.

Table 4. Analytical imprecision - HemSp / MagStream HT

Fujirebio quoted data			GMEC pool results			Manufacturer's verified data *		GMEC findings Consistency with manufacturer's claims
pixels		%	pixels		%	pixels	%	
Mean	SD	CV	Mean	SD	CV	SD	CV	
Within-assay imprecision								
350.6	3.1	0.9	320.4	4.4	1.4	4.2	1.2	Not consistent
271.7	6.5	2.4	267.6	10.3	3.8	8.8	3.2	Not consistent
219.9	5.7	2.7	197.0	5.8	2.9	7.7	3.5	Consistent
175.3	5.5	3.2						
136.6	4.9	3.6	138.8	3.2	2.3	6.6	4.8	Consistent
Total imprecision								
			320.4	17.8	5.6			
			267.6	31.6	11.8			
No data available			197.0	31.4	15.9			
			138.8	4.4	3.2			

* [see methods imprecision](#)

Table 5. Analytical imprecision - OC-Sensor / DIANA

OC-Sensor / DIANA			GMEC pool results			Manufacturer's verified data*		GMEC findings Consistency with manufacturer's claims
Hb ng/mL Mean	SD	% CV	Hb ng/mL Mean	SD	% CV	Hb ng/mL SD	% CV	
Within-assay imprecision								
45.3	2.5	5.41	62.6	1.4	2.2	3.3	7.3	Consistent
156.9	4.8	3.09	127.0	1.2	0.9	6.6	4.2	Consistent
			192.8	1.1	0.6			
327.1	6.5	1.98	375.0	3.0	0.8	8.8	2.7	Consistent
619.3	11.4	1.84				15.5	2.5	
Total imprecision								
			62.6	1.6	2.6			
No data available			127.0	1.3	1.0			
			192.8	2.6	1.3			
			375.0	4.2	1.1			

* [see methods imprecision](#)

Table 6. Analytical imprecision - FOB Gold / SENTiFOB

FOB Gold / SENTiFOB			GMEC pool results			Manufacturer's verified data*		GMEC findings Consistency with manufacturer's claims
Hb ng/mL Mean	SD	% CV	Hb ng/mL Mean	SD	% CV	Hb ng/mL SD	% CV	
Within-assay imprecision								
			50.1	3.5	7.0			
100.7	1.0	0.9	105.9	4.2	4.0	1.4	1.3	Not consistent
			152.3	4.9	3.2			
384.9	3.2	0.9	303.5	5.6	1.8	4.4	1.1	Not consistent
Total imprecision								
			50.1	4.3	8.6			
100.7	4.1	4.1	105.9	7.0	6.6	6.5	6.4	Not consistent
			152.3	7.9	5.2			
384.9	13.1	3.4	303.5	14.8	4.9	20.9	5.4	Consistent

* [see methods imprecision](#)

Hook effect

Immunoassay methods can be affected by what is known as a 'hook effect' where a sample with a very high analyte concentration gives a false negative result. We examined all the iFOB methods for this phenomenon (table 7). Although the HemSp / MagStream HT gave negative results for the two samples with the highest concentration of Hb, these concentrations exceed the maximum concentration possible when correctly using the NEW HEMTUBE collection device. The OC-Sensor / DIANA and FOB Gold / SENTiFOB methods both identified a problem with all the samples and did not give results. However, the messages on the SENTiFOB analyser for the two lower Hb concentration samples only indicated that the result was 'out of the normal range' rather than outside of the measuring range.

Table 7. Hook effect results

Hb concentration ng/mL	HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
62,500	Positive	Prozone check	Concentration out of normal range
125,000	Positive	Prozone check	Concentration out of normal range
250,000	*	Prozone check	Out of curve high
500,000	*	Prozone check	Out of curve high

* This Hb concentration exceeds that which is possible using the MagStream NEW HEMTUBE

Carryover

All of the evaluated analysers use a sample probe that is washed between the additions of samples to the measuring cells. To check the adequacy of probe washing a carryover test was performed. A *k* value of less than 5 indicates acceptable performance [3]. None of the systems demonstrated a carryover effect.

Table 8. Carryover data

HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
K= -0.2	K= 0.5	K= 3.2

Haemoglobin variants

Whole blood samples were used to assess the ability of the three methods to cross-react with human Hb variants. Both of the quantitative methods were able to recover all the tested Hb variants except fetal haemoglobin (HbF) (table 9). Similarly the qualitative HemSp / MagStream HT system was able to successfully determine positive results for all examined Hb variants at the tested concentrations, with the exception of HbF. To determine the effect of a high proportion of HbF on the qualitative HemSp / MagStream HT system, the sample containing a high proportion of HbF was diluted to produce a Hb concentration of 46.3 ng/mL. This concentration is well above the HemSp / MagStream HT cut-off of 20 ng/mL, but the sample gave a negative result.

Table 9. Recovery of haemoglobin variants

Hb variant	% variant %	OC-Sensor / DIANA		FOB Gold / SENTiFOB	
		Mean recovery %	SD	Mean recovery %	SD
Hb A _{1c}	14.0	99.4	1.2	103.9	0.1
HbS	32.0	104.8	3.0	105.5	4.4
	32.6	91.5	0.5	96.1	0.2
	91.8	89.8	2.7	92.4	1.3
	80.7	95.2	1.9	101.5	2.1
HbC	38.3	95.6	1.6	107.0	1.7
	40.3	100.7	3.1	97.5	4.1
HbD	43.9	94.3	0.6	100.5	1.0
	37.0	97.3	1.8	99.3	2.9
HbE	27.2	102.0	1.9	106.7	0.6
HbF	71.1	50.8	2.0	42.4	5.6

Linearity

The OC-Sensor / DIANA and the SENTiFOB methods (figures 9 and 10) both exhibited a positive bias, but showed good linearity in the range 50 – 500 ng/mL. However, this demonstrated linearity did not extend to the upper end of the quoted measuring range for either of these methods. The HemSp / MagStream HT (figure 11) is a qualitative method with a cut-off at 20 ng/mL for a positive result. This method is not designed to have a linear response across a broad measuring range.

Figure 9. OC-Sensor / DIANA

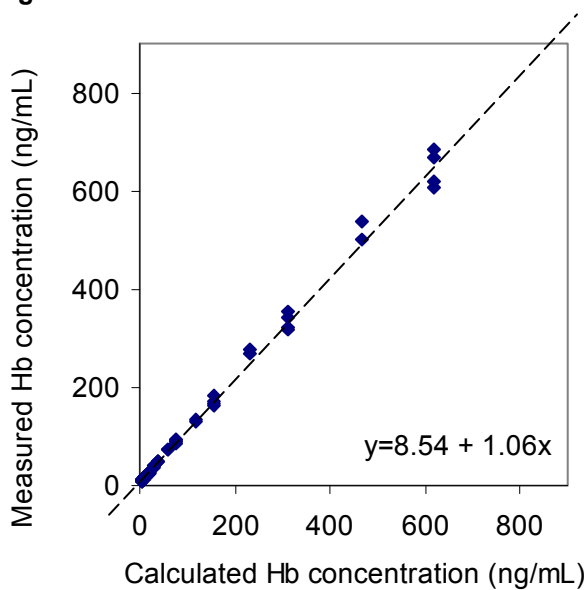


Figure 10. FOB Gold / SENTiFOB

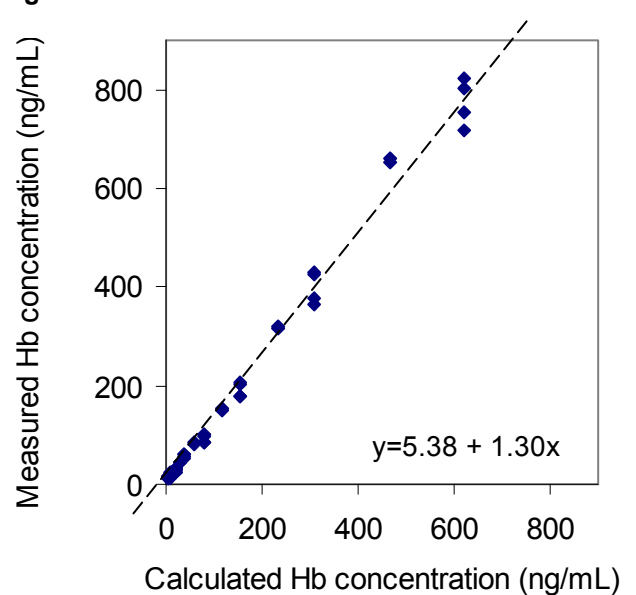
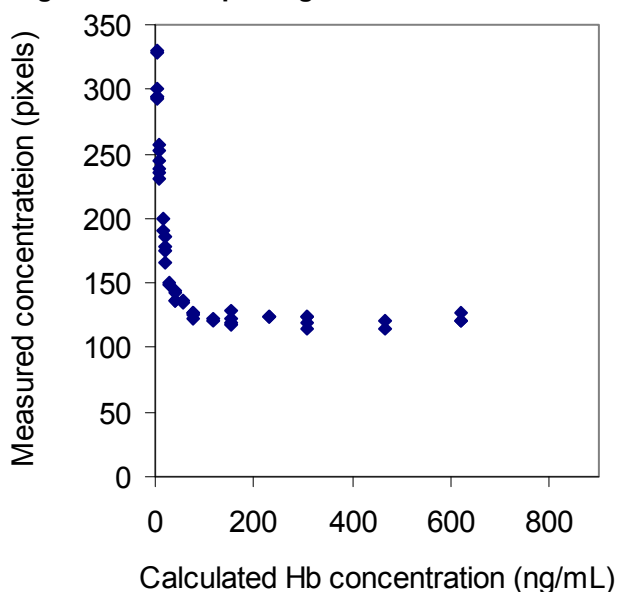


Figure 11. HemSp / MagStream HT



iFOB technology

The potential advantages of iFOB methods include:

- automated analysis
- specificity for *human* Hb, reducing the number of false positive results
- increased sensitivity to human Hb
- ability to adjust the cut-off Hb concentration.

The disadvantages of iFOB methods include:

- sample instability in liquid collection devices
- additional requirements for packaging of the liquid sample collection devices to meet UK postal regulations
- cost of the test.

Guaiac-based technologies

The English bowel cancer programme currently uses a guaiac-based faecal occult blood test.

Advantages of the guaiac-based test, when used in the English bowel cancer programme, are:

- the collection card and reagent are cheap (less than 40p per test)
- the card based collection system is easy to pack using automated machinery and easy to send by post
- it is easy to print patient details on the card
- the samples are considered to be stable on the cards for up to 21 days
- the system has been validated in numerous randomised controlled trials, has been implemented in a number of bowel cancer screening programmes and has been demonstrated to work successfully.

Disadvantages of the guaiac-based test, when used in the English bowel cancer programme, are:

- testing is not automated, is labour intensive and involves subjective visual reading
- the participant is required to provide samples from three separate bowel motions
- it is not specific for human Hb
- it is not as sensitive as iFOBT to human Hb
- it is not possible to adjust the cut-off Hb concentration of the test

User evaluation

Sampling devices

The DEVEL-A-TAB card is similar to the guaiac cards currently used in the screening programme. Sixteen of the 23 returned questionnaires from the sample collection survey indicated that it was easy to use.

Observations made about three liquid based devices showed an equal preference for the Eiken and Sentinel samplers, the MagStream devices being less favoured. Probe removal was easy for both the Eiken and Sentinel tubes; this is not an issue for the MagStream NEW HEMTUBE since the probe is supplied separately.

Table 10. User preferences for the liquid sampling devices

	MagStream NEW HEMTUBE	Eiken OC-Auto sampling bottle 3	Sentinel FOBGold
Collecting the sample onto the probe	Equal 2nd	Best	Equal 2nd
Re-inserting the probe	Equal 2nd	Equal 2nd	Easiest
Closing the device	3rd	Equal 1st	Equal 1st
Overall	3rd	Equal 1st	Equal 1st

The main concern with the NEW HEMTUBE was its small diameter, leading to difficulties with handling, particularly for those with poor eyesight or diminished dexterity. The narrow entrance increased the potential for contamination of the outside of the tube. The Eiken OC Auto sampling bottle 3 was considered to be easier to handle, but to have similar problems with probe insertion. The FOB Gold tube's wider diameter made reinsertion of the probe easier, but the capped buffer compartment, designed for removal by the laboratory could be mistakenly removed resulting in spillage in the home and leakage during transit. All the sample collection devices gave problems with very firm samples.

The sampling device needs to be easy to use to minimise the risk of poor sample collection, leakage and contamination of external surfaces. It should be easy to label with adequate information to positively identify the sample and its collection date, and preferably to carry that information through to the analysis. It should also be suitable for automatic packing and dispatch by normal post. None of the devices evaluated is ideal.

A comparison of the collection devices is shown in table 11.

Table 11. Comparison of the sample collection devices relative to the requirements for use in a screening programme

Feature	MagStream NEW HEMTUBE	Eiken OC-Auto sampling bottle 3	Sentinel FOB Gold tube	DEVEL-A-TAB
Ease of handling during sampling	Less acceptable due to small size	Equal most acceptable	Equal most acceptable	Least acceptable
Facility to collect the correct amount of sample	Yes, but the sample size is very small and inconspicuous. Risk of participants repeating the sampling procedure till the presence of faeces is obvious.	Yes. It is obvious when the grooves are filled. Buffer discoloured by faecal sample	Yes. It is obvious when the grooves are filled. Buffer discoloured by faecal sample	The amount of sample will vary according to the thickness of the smear applied to the card
Susceptibility to leakage	Robust construction, unlikely to leak in transit.	Robust construction, unlikely to leak in transit.	Buffer compartment has a stopper which could be removed by the participant in error, causing leakage of the fluid	Sample dried onto card, no liquid present
Susceptibility to contamination of external surfaces	Risk of contamination due to narrow opening for probe reinsertion	Risk of contamination due to narrow opening for probe reinsertion, although this is within a wider space	Lower risk of contamination since opening is wide	Low risk of contamination
Ease of labelling (user name, sample ID)	Difficult due to small surface area and diameter (highly curved). Could barcode the bag but then the device itself would have no participant ID.	Two flat surfaces offer opportunities for direct printing or adhesive labelling. Need to ensure that any adhesive label used does not interfere with the compression of the tube during analysis	Large surface area but curved, presenting greater challenges for labelling.	Easy to label collection card, but less surface area than current card. Requires transfer of sample to secondary tubes with risk of loss of ID.

Feature	MagStream NEW HEMTUBE	Eiken OC-Auto sampling bottle 3	Sentinel FOB Gold tube	DEVEL-A-TAB
Ease of writing sample collection date	Difficult due to tube size and very curved surface	Easy; sufficient space on flat surface	Plenty of space but curved surface	Easy
Suitability for automated packing machinery. (Any outer packaging should be of even thickness and neither slippery nor flexible.)	Supplied in plastic zip seal bag which is too slippery, flexible and uneven for easy automated packing. Difficult to pack two separate pieces automatically. Packing is likely to be a slow process.	Would need a feeder system but could be kept in the right plane for barcode to be read and automatically matched with participant letter.	Could be packed automatically but there are potential difficulties matching the tube ID with the participant letter since the tube would roll, so that the barcode might not align with the reader.	Little change from current system
Suitability for posting to and from the participant	Sent by post elsewhere in Europe. Would exceed 5 mm thickness when packed and would therefore be classified as large letter by Royal Mail.	Sent by post elsewhere in Europe. Would exceed 5 mm thickness when packed and would therefore be classified as large letter by Royal Mail.	No evidence that it has been accepted for transport by post. Would exceed 5 mm thickness when packed and would therefore be classified as large letter by Royal Mail.	As current system, exempt from the IATA UN3373 transport regulations for clinical samples[4] and classified as standard letter
Minimal handling by laboratory staff	Collection device placed directly into racks for analysis	Collection device placed directly into racks for analysis.	Requires de-capping before analysis. For large numbers, this would need to be automated.	Sample elution process involves considerable manual handling by laboratory staff.

Royal Mail did not respond to requests for assessment of the possibilities of sending the tube devices by post. Both Real Digital and Neopost felt that the Eiken tube was likely to be the easiest to pack and label automatically but Real digital also stated that a solution could be found for whichever system was selected.

Analytical system

None of the system users who completed the questionnaire was analysing the large numbers of samples that would be generated by the English Bowel Cancer Screening Programme. One reply was received for each of the analysers so the information was limited. The overall opinion of the analysers from all these users was good. There had been few analyser problems and low levels of unsuitable samples.

Connecting for Health

The introduction of iFOBTs will have an impact on the way data are handled by the Bowel Cancer Screening System (BCSS), and Connecting for Health (CfH) will need to modify the software to accommodate these changes.

CfH has produced an options paper outlining the possible approaches and their feasibility. CfH has considered the impact of each option on CfH resources, the mailing system, the hubs and the linkage of sample to subject, and has assessed the associated risks. The software changes will depend on:

- what changes will be required for sending out the kits, including labelling and matching to participant. What would be the minimum requirement for identification of the sample? Could the sampling device be labelled with a BCSS generated ID number or would it be necessary to match pre-barcode devices to each screening participant?
- how the sample collection date will be recorded by the participant and in the laboratory
- how the samples will be received and logged in the laboratory (manually or using a scanner)
- the number of samples required from each participant
- how the results will be received by BCSS, sequentially (all completed tests available) or as batches. The analytical systems all produce results in formats which could be managed by BCSS.

Instructions for use

The quality of information included in the instructions for use (IFU) varies and is not always found in a single document.

Table 12. Quality of information in main IFU

	HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
Length of document	Two pages	Single page	Two pages
Test principles	Good	Good	Good
Reagent details and preparation	Good	Limited	Good
Test procedure	Detailed	Detailed	Detailed
Calibration	Not required	Not included in main IFU	Details in main IFU
Quality control	Mentioned	Mentioned	Mentioned
Sample collection	Details in main IFU	Limited information in main IFU	Details in main IFU
Performance data	Limited information but adequate for a qualitative test	Very limited information	Detailed information
Overall impression	Good	Poor	Good

Service requirements

All analysers require a 13 amp power supply and purified water either to wash the cuvettes (OC-Sensor/ DIANA) or for preparation of wash solutions (OC-Sensor / DIANA, HemSp / MagStream and SentiFOB) and system solution (SentiFOB).

Connectivity

The three analysers all have RS 232-C serial interface ports. Manufacturers have all indicated that they would be able to provide interfaces that would allow their systems to connect to the required information systems.

Consumables

Table 13 shows the specific storage temperature requirements and table 14 shows the dimensions of the consumables required to run each of the systems.

During the evaluation the supply of reagents and consumables was good from both Fujirebio and Alpha Laboratories. Some delays were experienced with deliveries from Mast, who supply the OC-Sensor DIANA consumables in the UK.

Table 13. Temperature storage requirements of consumables

		HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
Collection devices		2 - 30°C until expiry date	1 - 30°C until expiry date	2 - 30°C until expiry date
Latex/ magnetic particles	Unopened	2 - 10°C until expiry date	2 - 10°C until expiry date	2 - 8°C until expiry date
	Opened	7 days at 2 – 10° C	14 days	60 days 2 - 8°C
	On analyser		14 days	28 days 2 - 12°C
Buffer	Unopened		2 - 10°C until expiry date	2 - 8°C until expiry date
	Opened	Not applicable	14 days	60 days 2 - 8°C
	On analyser		14 days	28 days 2 - 12°C
System buffer	Concentrate			15 - 30°C until expiry date
	Diluted	Not applicable	Not applicable	
Wash solution	Concentrate	1 - 30°C until expiry date	Domestic bleach	15 - 30°C until expiry date
	Diluted	30 days 15 - 30°C		
Calibrators	Unopened		2 - 10°C until expiry date	2 - 8°C until expiry date
	Reconstituted	Not applicable	8 hrs 2 – 25°C	8 hrs 2 -8°C
				60 days -20°C
QC	Unopened	2 - 10 °C until expiry date	2 - 10°C until expiry date	2 - 8°C until expiry date
	Reconstituted	2 hours 15 – 30°C	8 hrs 2 – 25°C	8 hrs 2 -8°C
			1 month -20°C	60 days -20°C
Cuvettes/Microtitre plates		Not stated	Room temperature	Not stated
Reagent tips		Not stated	Not applicable	Not applicable

Table 14. Package dimensions (cm) and volumes

	HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
Collection devices	Outer pack Inner pack	38.5 x 33 x 31 (500 sets) 18.5 x 15 x 11.5 (100)	60 x 39.5 x 18 (1000) 19.6 x 12.6 x 11 (100)
Latex/magnetic particles	19 x 6.7 x 7 (4 sets)	5.5 x 12 x 13.6 (5)	11 x 10.7 x 2.4 (1 set)
Buffer	With magnetic particles	6 x 7.5 x 18.5 (1)	With latex
System buffer	Not applicable	Not applicable	1L square bottle
Wash solution	19 x 14 x 9 (2)	Domestic bleach	100 mL bottle
Calibrators	Not applicable	18.5 x 3.5 x 10.6 (10 sets)	10 x 9.6 x 6.4 (2 sets)
QC	18.4 x 6.8 x 6.4 (5 sets)	12 x 4 x 5	10 x 9.6 x 6.4 (2 sets)
Cuvettes/Microtitre plates	37.5 x 19 x 15.1 (50)	12 x 17.5 x 3.3	51.5 x 25.7 x 25 (10)
Reagent tips	10.2 x 12.3 x 4 (100)	Not applicable	Not applicable
Paper rolls	Not applicable	14 x 7 x 5 (5)	Not applicable

Sample collection system characteristics

The NEW HEMTUBE is provided in two parts and has a long handled sample probe to keep the user's hands clear of the faecal sample. The tube is very narrow and therefore has limited space for participant identification information.

The OC-Auto sampling bottle 3 will only fit on the manufacturer's analysers. It has an internal filter system that removes debris from the faeces /buffer solution before analysis. A foil cover protects the analyser sampling area of the tube and makes it obvious if this has been accidentally opened. The sample buffer only enters the sampling area when pressure is applied by the analyser. However, if the sample probe is not removed carefully from the device before sampling, a small volume of fluid can be lost. Removal of the sample probe is easier if the cap is first twisted; removal without this twisting motion requires more force which increases the risk of fluid loss. The tube has a flat surface which makes the addition of a participant identification label easier than for the other devices.

The FOB Gold Tube has been designed to fit into primary sample tubes racks on most automated clinical chemistry analysers. The sample probe is held in the sample tube with a screw thread so that it is easy to know that the probe has been securely returned to the tube. There is potential for fluid to be lost from the device if the translucent push fit cap at the buffer end of the tube is inadvertently removed.

The DEVEL-A-TAB card is very similar in use to the current collection system. However there is potential for sample identification errors during the processing of the tabs, which need to be removed from the cards and placed in a secondary tube for sample elution.

Maintenance and servicing

Table 15. Tasks and time required for routine analyser maintenance

	HemSp / MagStream HT		OC-Sensor / DIANA		SENTiFOB	
	Tasks	Time	Tasks	Time	Tasks	Time
Daily	Empty waste Top up wash solution	Less than 5 minutes	Empty waste Top up wash solution Clean touch screen	Less than 5 minutes	Empty waste Top up system solution	Less than 5 minutes
Weekly	Clean: sample rack loading areas reagent loading area reagent level sensor	Less than 5 minutes	Cuvette wash Clean: sample and reagent probes	Less than 20 minutes	Clean: Probe and self adjust plate	Less than 10 minutes
Monthly	Clean wash container and wash through lines	Less than 30 minutes	Clean water, waste and wash solution containers	Less than 20 minutes	Clean: Reagent lines	Less than 30 minutes

The frequency of waste bottles emptying will depend on the workload. The OC-Sensor / DIANA method generates more liquid waste than the other systems because the measuring cells are washed and reused. It therefore requires more frequent emptying (approximately every 300 samples) of the waste and re-filling of water and wash solution containers.

All analysers require routine preventative maintenance visits, which are provided as part of the service contract. Typically, these visits are annual but this is workload dependent.

Calibration and quality control

Table 16. Calibration and quality control information

		HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
Calibration	Traceability		Haemoglobin cyanide 98/708, WHO standard	Traceable to WHO reference standard
	Frequency	Calibrated by supplier, no recalibration by the user	Weekly /New batch of reagents	Monthly /New batch of reagents
	Preparation time		Less than 20 minutes (includes 15 minute incubation)	Less than 30 minutes (includes 25 minute incubation)
	Analytical time		Less than 25 minutes	Less than 25 minutes
Quality control	Measurement frequency	Daily	Daily	Daily
	Preparation time and frequency	Less than 35 minutes, daily (includes 30 minutes incubation)	Less than 25 minutes, weekly (includes 15 minutes incubation)	Less than 35 minutes, weekly (includes 25 minute incubation)

Daily start up and shutdown

Table 17. Time required for analyser daily start up and shut down

Operation	HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
Daily start up	Less than 5 minutes	Less than 20 minutes	Less than 25 minutes
Daily shutdown	Less than 1 minute	Less than 10 minutes	Less than 3 minutes

Sample storage

Once sample collection devices have been returned to the laboratory they need to be analysed promptly. Any that are not analysed on the day of receipt or require retesting must be stored between 2 and 10°C so refrigerated storage space will be required.

Analyser requirements

The number of analysers required will depend on the laboratory workload. We have calculated the number of each analyser required for a projected laboratory workload of 5,000 samples per day.

Table 18. Number of analysers required for a 5,000 sample per day workload

HemSp / MagStream HT	OC-Sensor / DIANA	FOB Gold / SENTiFOB
1	5	15 SentiFOB 1 chemistry analyser

Staff requirements

Receipt of samples

Unpacking of iFOB liquid sampling devices may take longer than for the current system due to the increased packing material that is required to meet UK postal regulations.

Analysis of samples

The iFOB analysers require more technical knowledge than the current guaiac-based tests. This would not be beyond the capabilities of a suitably trained medical laboratory assistant when supervised by a biomedical scientist. Specialist training is provided by the manufacturers, which includes instruction on routine use and maintenance of the analysers.

Results management

Staff (biomedical scientist band 7 or above) will be required to authorise each batch of results generated from the iFOB analysers and transfer the data to the bowel cancer screening programme database.

The iFOB methods are all more expensive than the current guaiac FOB test. The device, its reagents, refrigerated storage, waste disposal, postage and packaging will all be more expensive. Fraser [5] has estimated iFOBT to be approximately 10 times more expensive than guaiac FOBT.

Grazzini [6] reports that iFOBT methods are more cost-effective than guaiac-based tests for screening. Grazzini *et al* compared their figures for cost per cancer detected 11270€, with those of two guaiac based programmes. Grazzini *et al* have assumed that their screening policy is more sensitive than that of the Nottingham trial [7], which reported a cost of 7778€ per cancer detected. The second comparator trial [8] reported a cost of 13466€ per cancer detected.

iFOBT methods are capable of detecting Hb at much lower concentrations which can result in a substantially higher rate of positive results [9]. However, with appropriate adjustment of the cut-off Hb concentration, iFOB tests can provide higher detection rates for advanced neoplasia (true positives) than guaiac tests [10]. Grazzini [11] noted that colonoscopies account for 50% of the total screening costs so this is an important issue.

The introduction of automated testing technology could reduce the number of staff required to perform analyses. However, the staff with the skills required to use the automated equipment are likely to prove more expensive.

Purchasing procedures

The Trust Operational Purchasing Procedures Manual provides details of the procurement process [12].

European Union procurement rules apply to public bodies, including the NHS, for all contracts worth more than £90,319 (from January 1st 2008) [13]. The purpose of these rules is to open up the public procurement market and ensure the free movement of goods and services within the EU. In the majority of cases, a competition is required and decisions should be based on best value.

NHS Supply Chain (www.supplychain.nhs.uk), a ten year contract operated by DHL on behalf of the NHS Business Services Authority, offers OJEU compliant national contracts or framework agreements for a range of products, goods and services. Use of these agreements is not compulsory and NHS organisations may opt to follow local procedures.

Purchasing options

Table 19. Purchasing options available for the analysers

HemSp / MagStream HT	OC-Sensor / DIANA	SENTiFOB
Capital purchase	Capital purchase	Capital purchase
Lease / purchase	Reagent rental	Lease / operate
	Lease / purchase	
	Lease / operate	

Service contracts

The suppliers have not yet established service contracts in the UK. Details of their proposed service would be provided during the tender process.

Warranty

Regardless of the purchase option selected, the analysers all come with one year's warranty for parts and labour.

Sustainable procurement

The UK Government launched its current strategy for sustainable development, *Securing the Future* [14] in March 2005. The strategy describes four priorities in progressing sustainable development:

- sustainable production and consumption – working towards achieving more with less
- natural resource protection and environmental enhancement – protecting the natural resources and habitats upon which we depend
- sustainable communities – creating places where people want to live and work, now and in the future
- climate change and energy – confronting a significant global threat.

The strategy highlights the key role of public procurement in delivering sustainability.

Clinical waste

As well as liquid waste, the iFOB systems produce sample collection device waste that contains liquid. The cost of disposal the sample collection devices could therefore be more expensive than for the current system. At present the collection cards can be disposed of into clinical waste sacks collected into large clinical waste bins. This system requires minimal manual handling and waste can be processed using hydroclaves, shredding, and compression before incineration. iFOB sample collection tubes will require disposal in rigid bins to contain any liquid. These bins require a different procedure and more manual handling.

We have estimated that the HemSp / MagStream HT (sample collection tubes and microtitre plates) and the OC-Sensor DIANA (sample collection tubes) produce approximately the same volume of clinical waste. The SENTiFOB /FOB gold with its disposable cuvette rotors produces a slightly larger volume of clinical waste.

End-of-life disposal

Consideration should be given to the likely financial and environmental costs of disposal at the end of the product's life. Where appropriate, suppliers of equipment placed on the market after the 13th August 2005 should be able to demonstrate compliance with the UK Waste Electrical and Electronic Equipment (WEEE) regulations (2006) [15]. The WEEE regulations place responsibility for financing the cost of collection and disposal on the producer. Electrical and electronic equipment is exempt from the WEEE regulations where it is deemed to be contaminated at the point at which the equipment is scheduled for disposal by the final user. However, if it is subsequently decontaminated such that it no longer poses an infection risk, it is again covered by the WEEE regulations, and there may be potential to dispose of the unit through the normal WEEE recovery channels.

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Table 20. Suppliers

Product	Manufacturer	Supplier
HemSp/MagStream HT	FUJIREBIO inc 62-5 Nihonbashi-Hamacho 2- chrome, Chuo-ku Tokyo 103-0007 Japan	FUJIREBIO EUROPE B.V Takkebijsters 69c 4817 BL Breda The Netherlands
OC-Sensor/ DIANA	EIKEN Chemical Co.Ltd 4-19-9 Taito Taito-ku Tokyo 110-8408 Japan	Mast Diagnostics Division Mast Group Limited Mast House Derby Road Bootle MERSEYSIDE L20 1EA
FOB Gold/SENTiFOB	SENTINEL Diagnostics Via Robert Koch 2 Milano 20152 Italy	Alpha Laboratories Ltd 40 Parham Drive Eastleigh Hampshire SO50 4NU
hema-screen/DEVEL-A- TAB	immunostics inc. 3505 Sunset Avenue Ocean New Jersey 07712 USA	Alpha Laboratories Ltd 40 Parham Drive Eastleigh Hampshire SO50 4NU

25 day sample collection stability graphs

The data obtained from our stability experiment were examined and, using the principles of Healy trimming [16] and a 2.5 SD limit, outliers were removed. Figures 20-25 show the daily mean of the data on each of the systems evaluated at the temperatures tested.

Table 21. Legend with calculated spiked Hb concentrations for each method

	HemSp / MagStream HT ng/mL	OC-Sensor / DIANA ng/mL	FOB Gold / SENTiFOB ng/mL	DEVEL-A-TAB card ng/mL
		86	101	130
		154	181	262
	14	237	279	375
	19	311	366	493
	65			
	102			

The same spiked pool samples were used for the OC-Sensor / DIANA, FOB Gold SENTiFOB and the two low concentration HemSp / MagStream HT experiments. The DEVEL-A-TAB used a separate set of pool samples but with target concentrations similar to those of the OC-Sensor / DIANA and the FOB Gold SENTiFOB.

Figure 12. HemSp / MagStream HT 4 to 8°C stability data

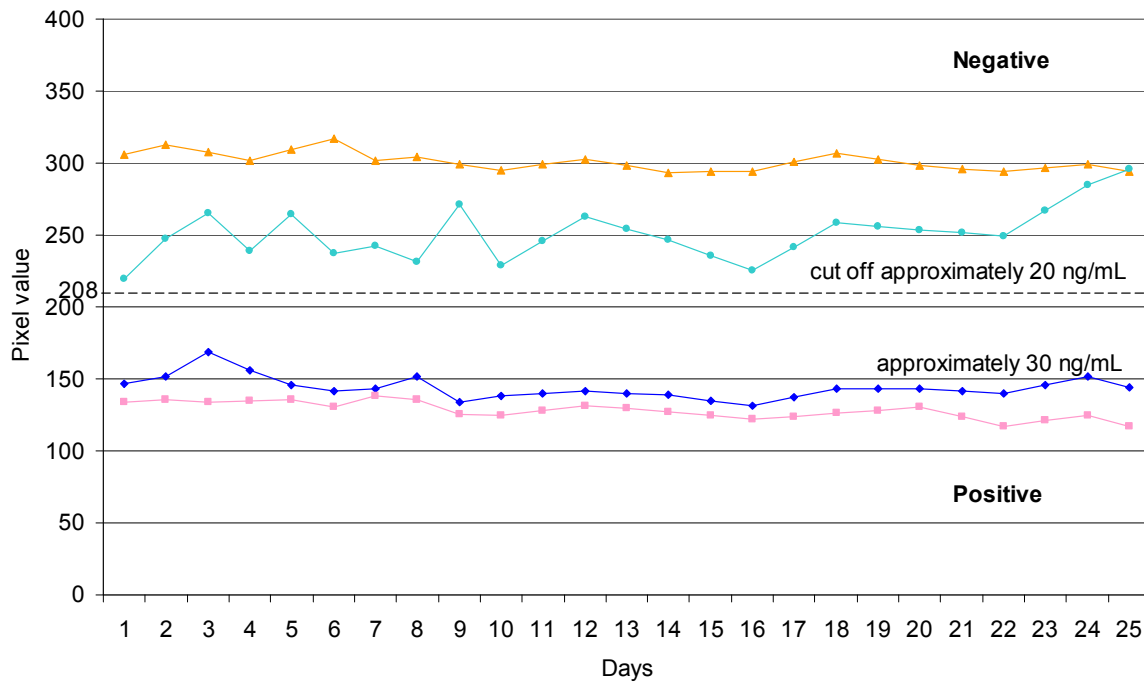


Figure 13. HemSp / MagStream HT 23 to 26°C stability data

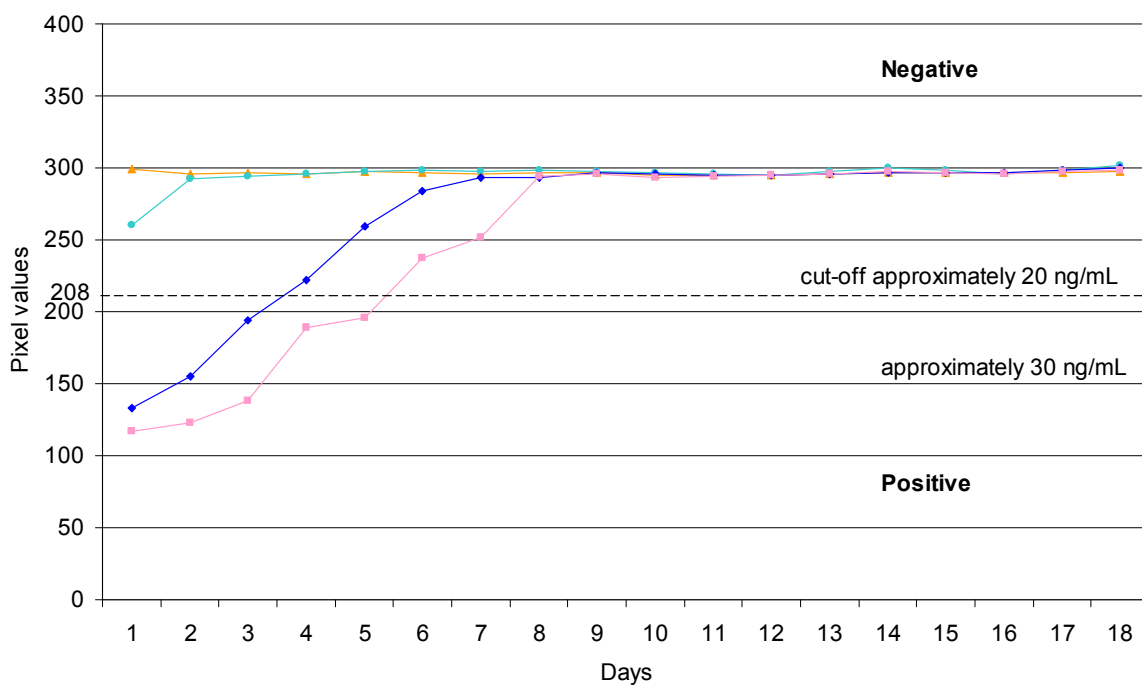


Figure 14. HemSp / MagStream HT 29 to 34°C stability data

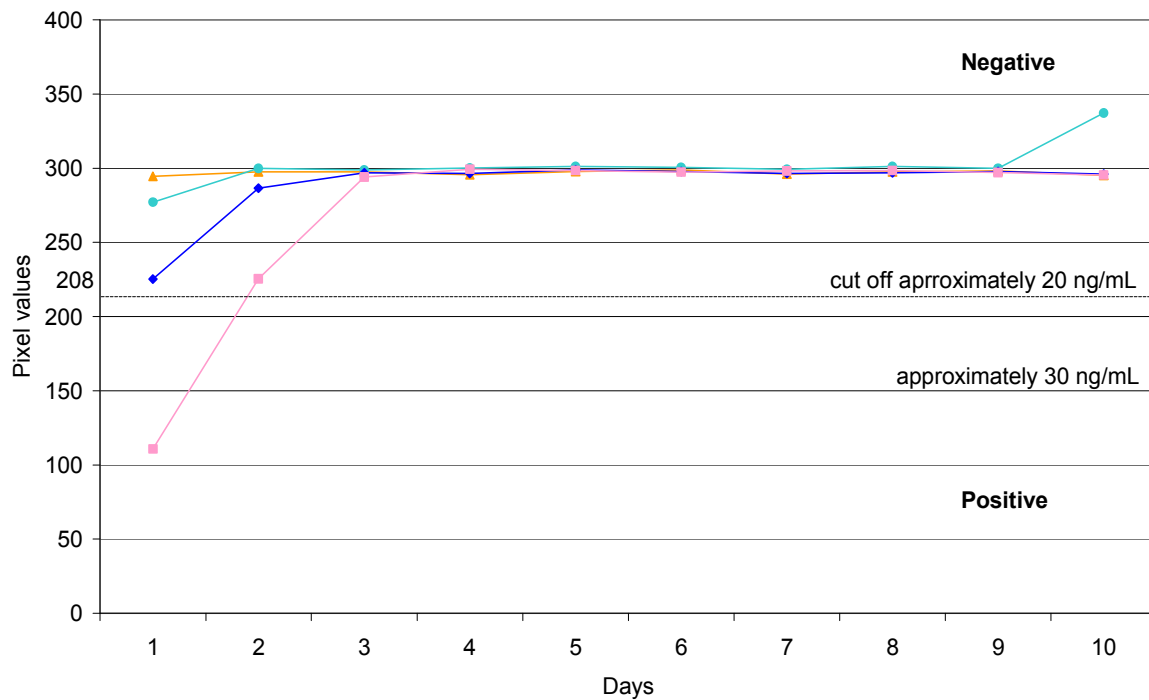


Figure 15. OC-Sensor / DIANA -24 to -18°C stability data

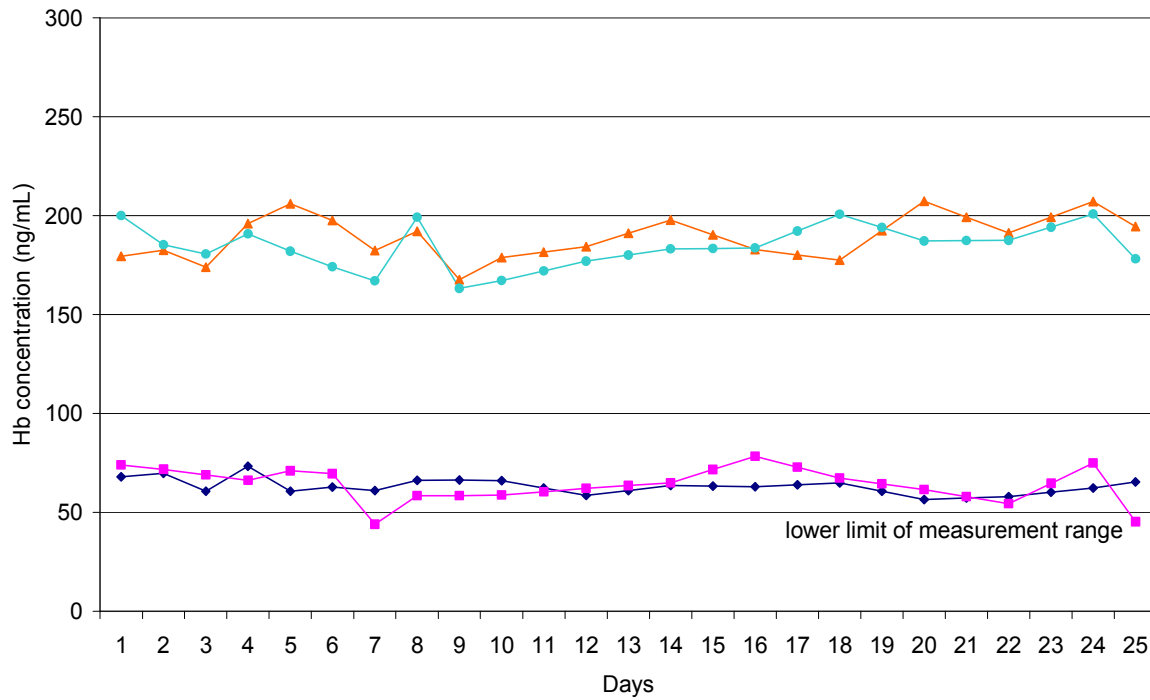


Figure 16. OC-Sensor / DIANA 4 to 8°C stability data

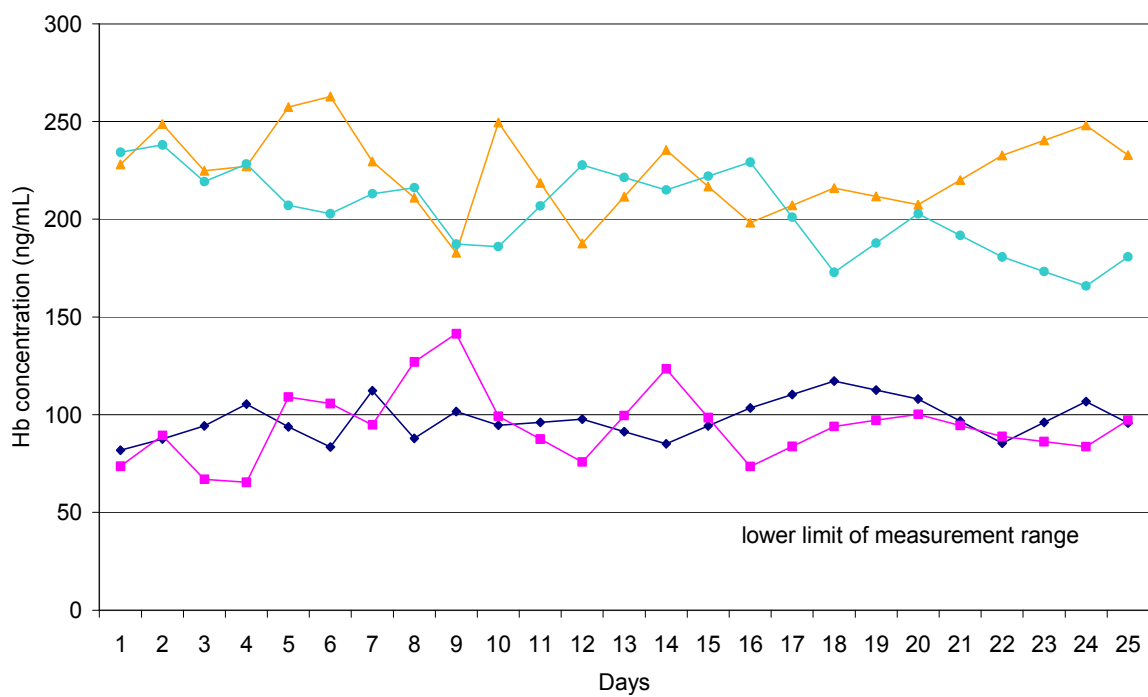


Figure 17. OC-Sensor / DIANA 23 to 26°C stability data

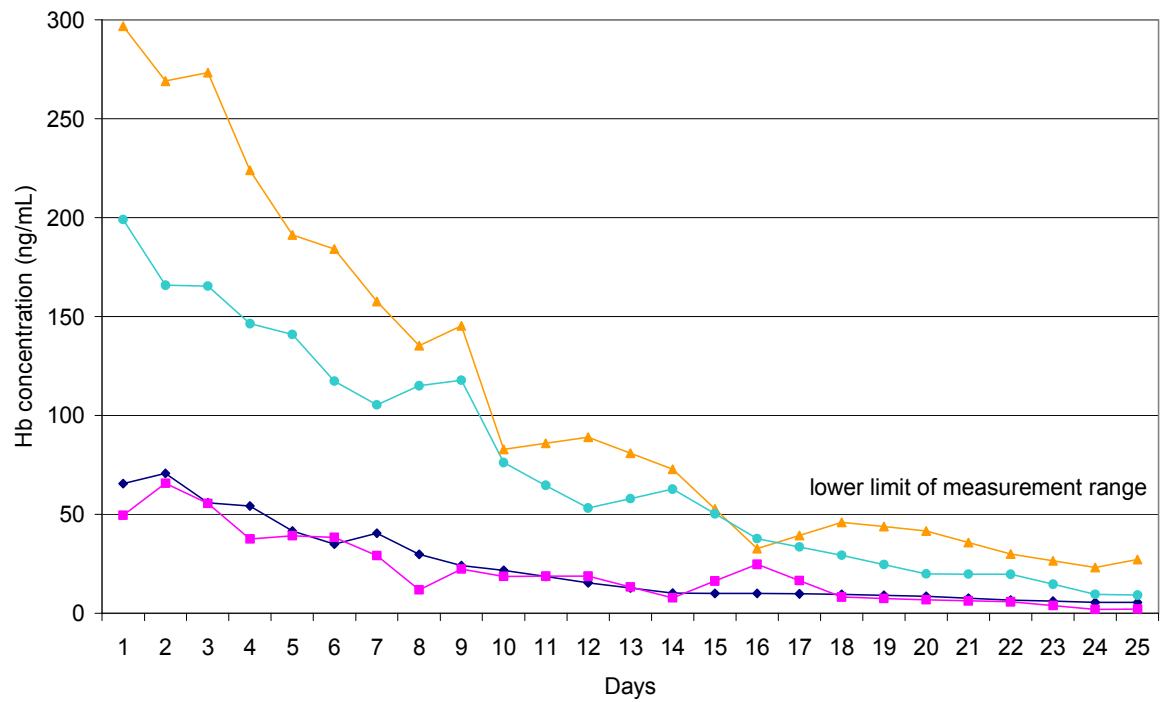


Figure 18. OC-Sensor / DIANA 29 to 34°C stability data

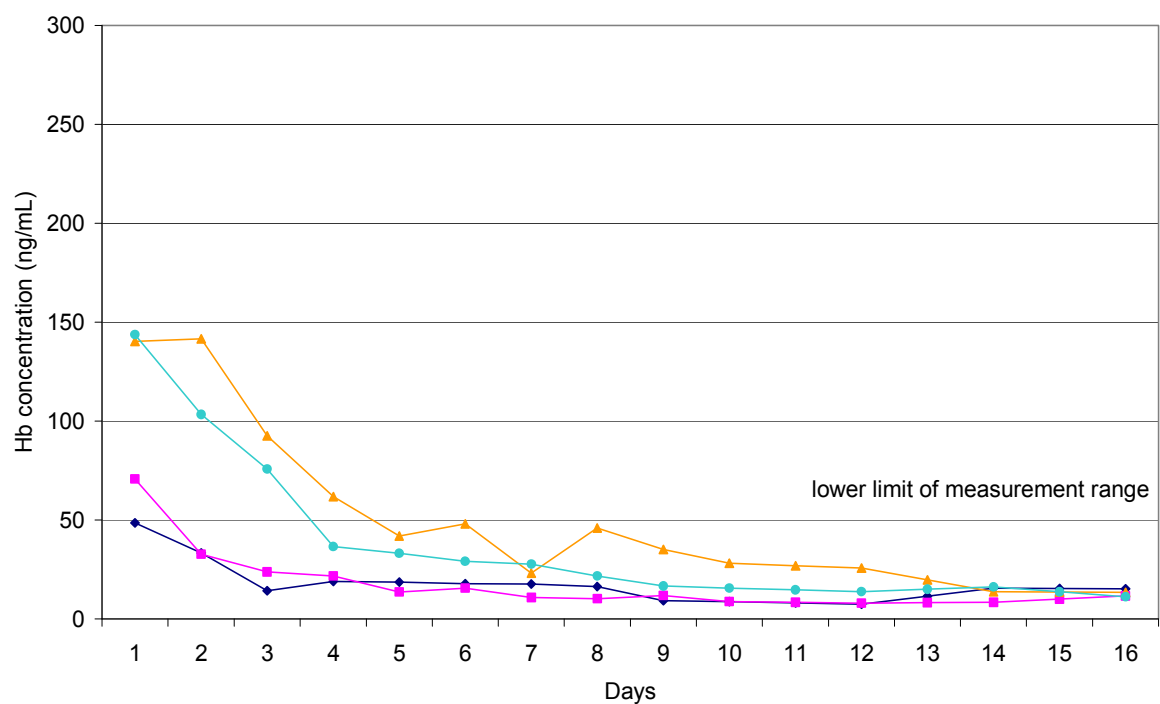


Figure 19. FOB Gold / SENTiFOB -24 to -18°C stability data

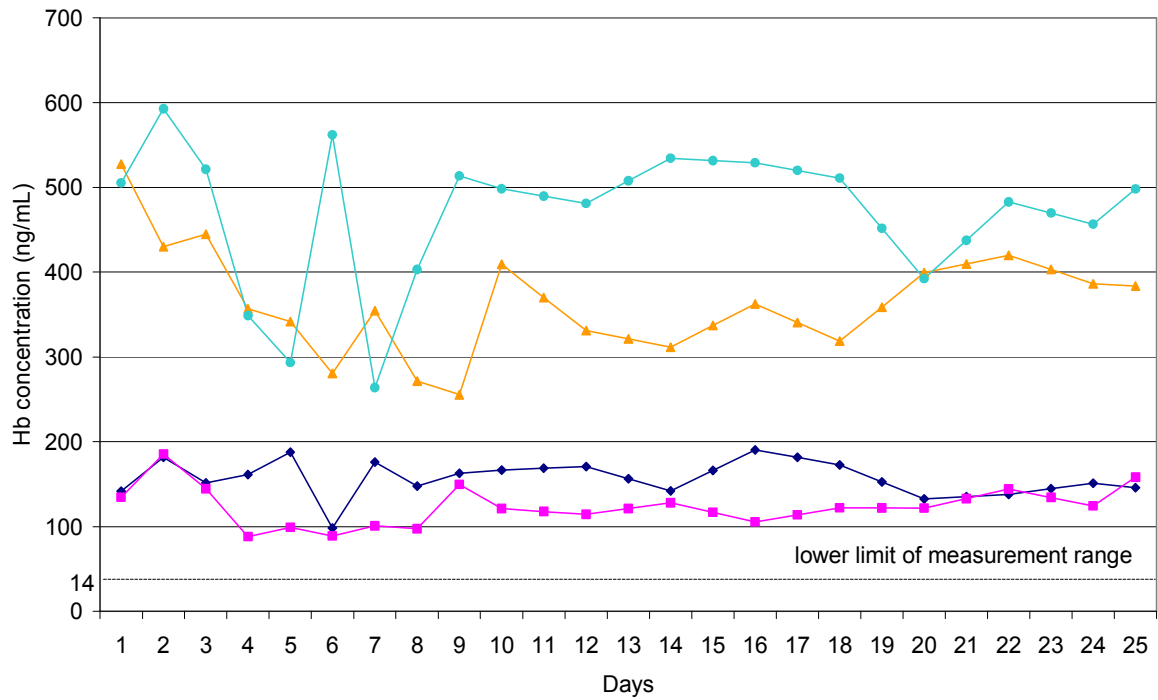


Figure 20. FOB Gold / SENTiFOB 4 to 8°C stability data

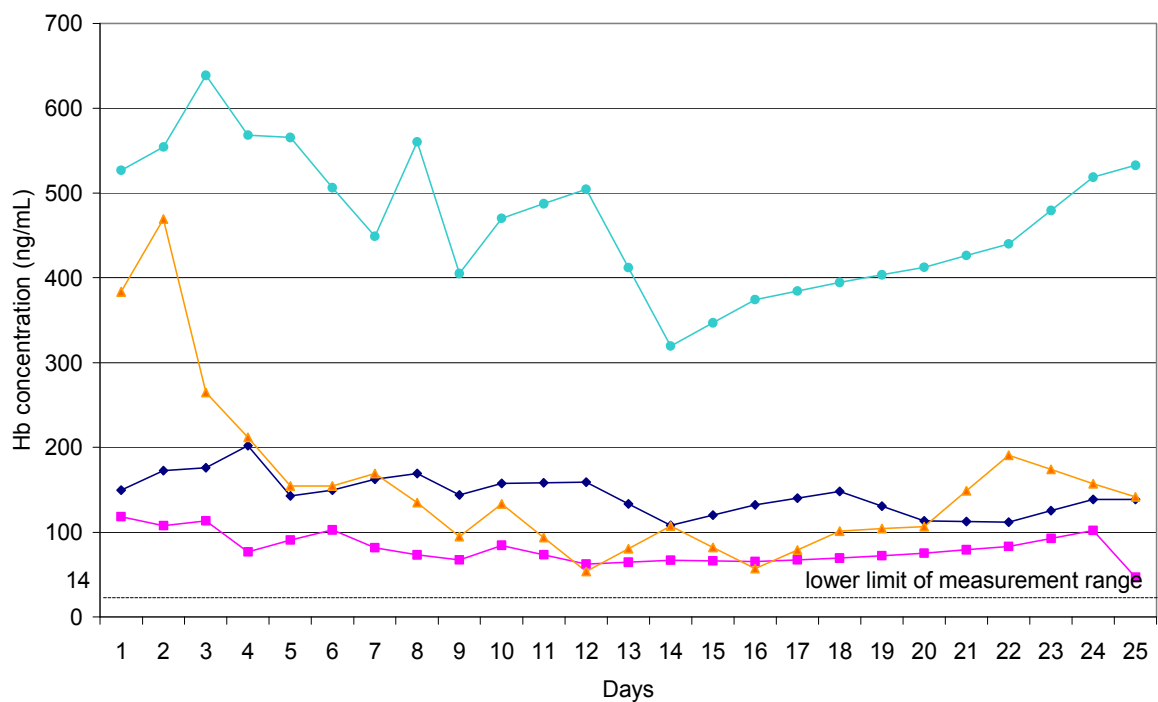


Figure 21. FOB Gold / SENTiFOB 23 to 26°C stability data

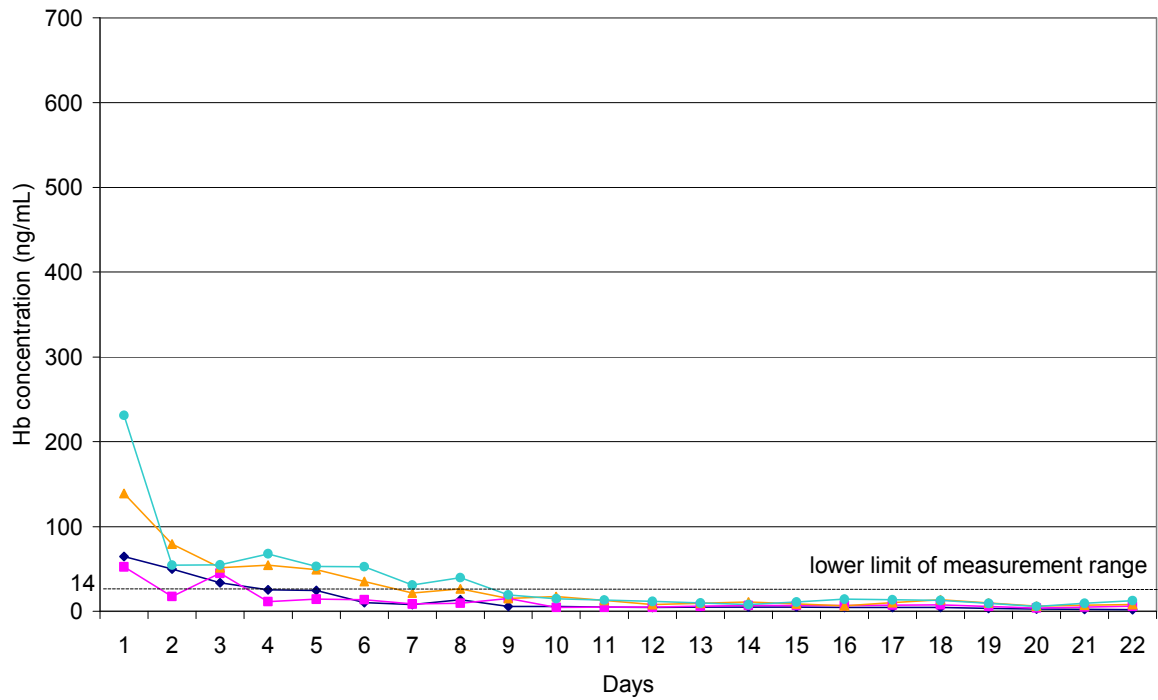


Figure 22. FOB Gold / SENTiFOB 29 to 34°C stability data

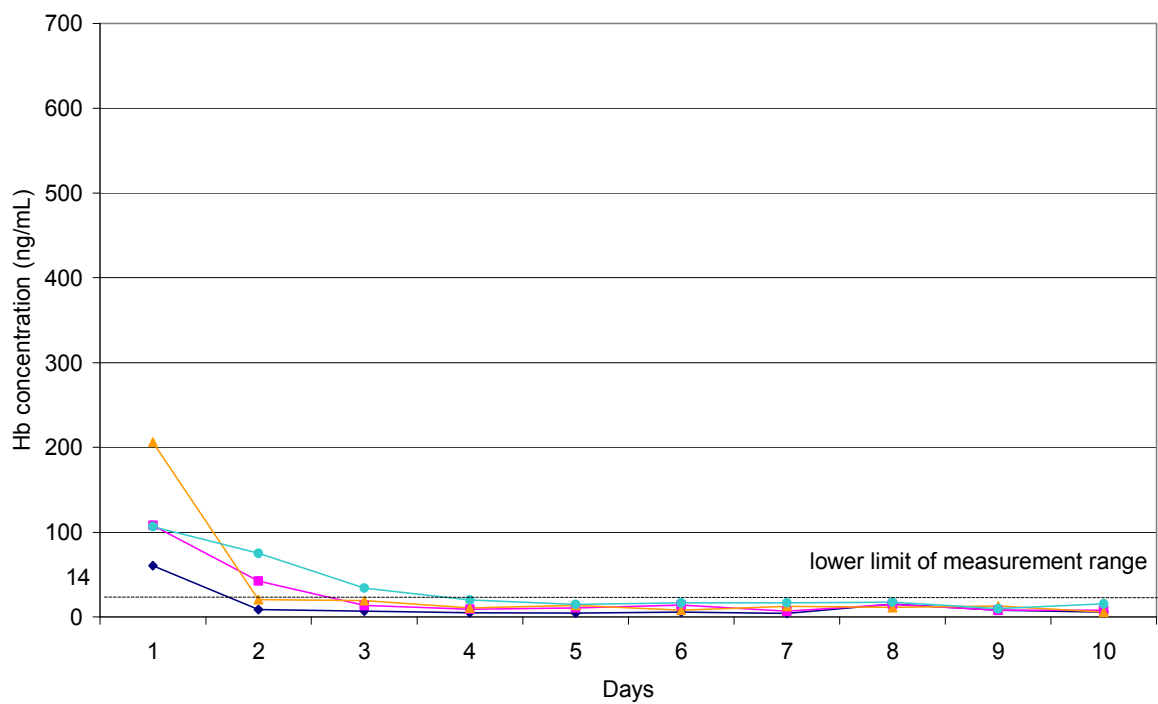


Figure 23. DEVEL-A-TAB card 4 to 8°C stability data

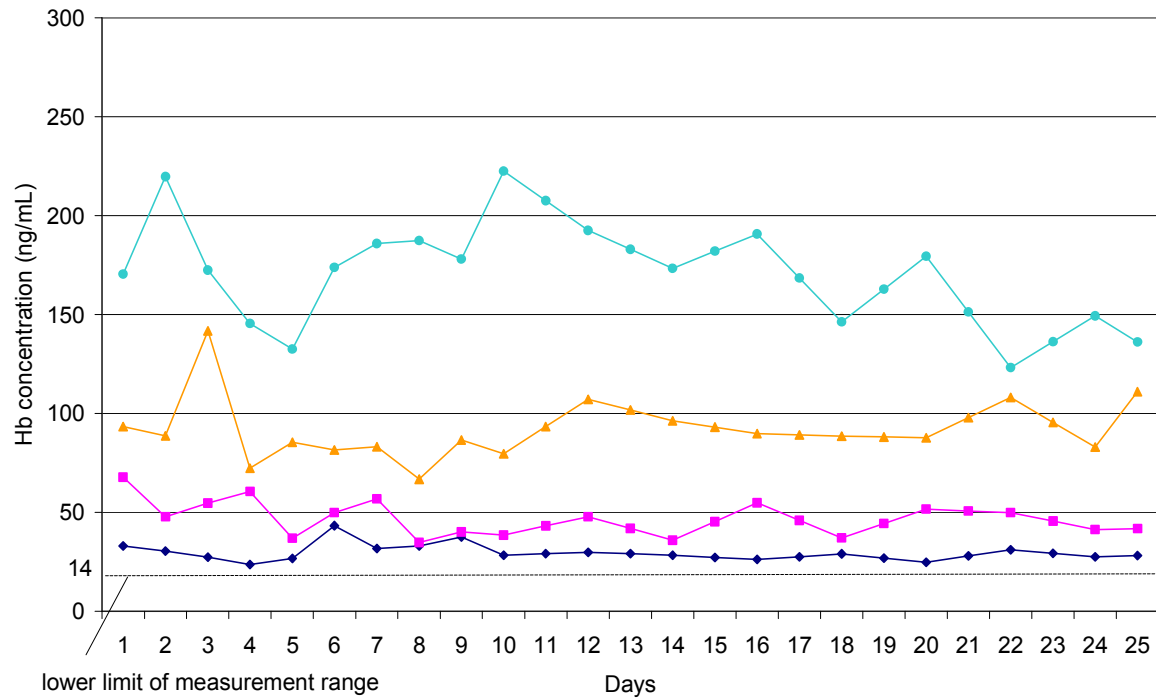


Figure 24. DEVEL-A-TAB card 23 to 26°C stability data

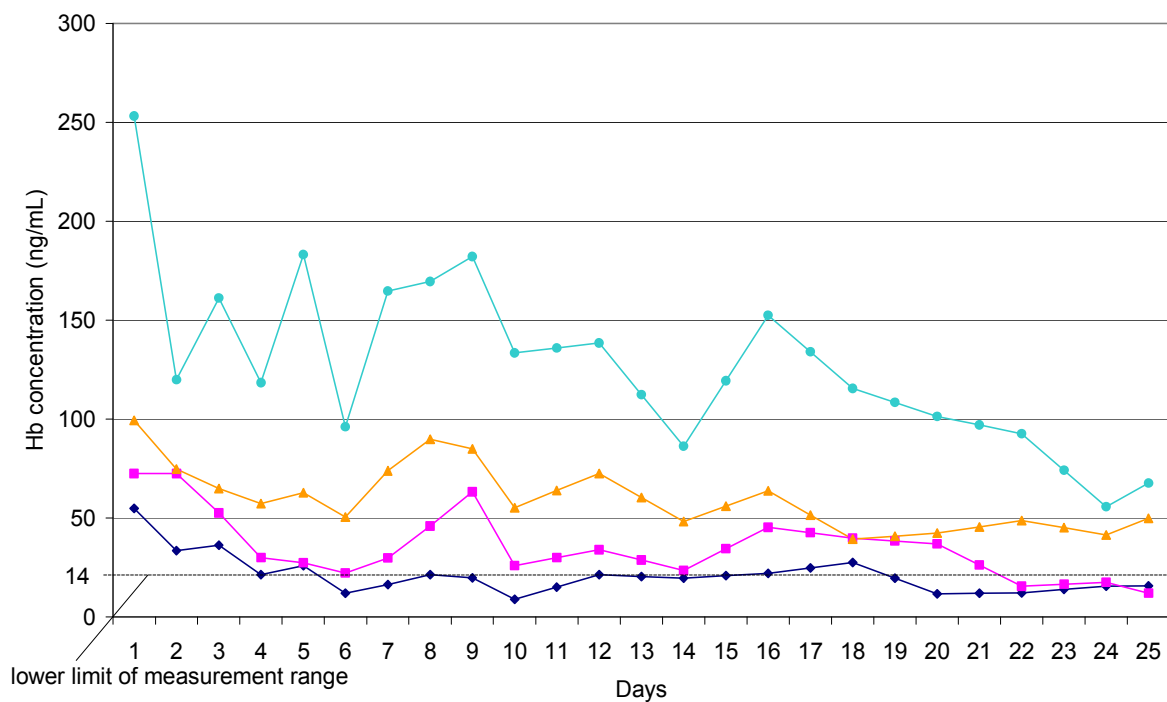
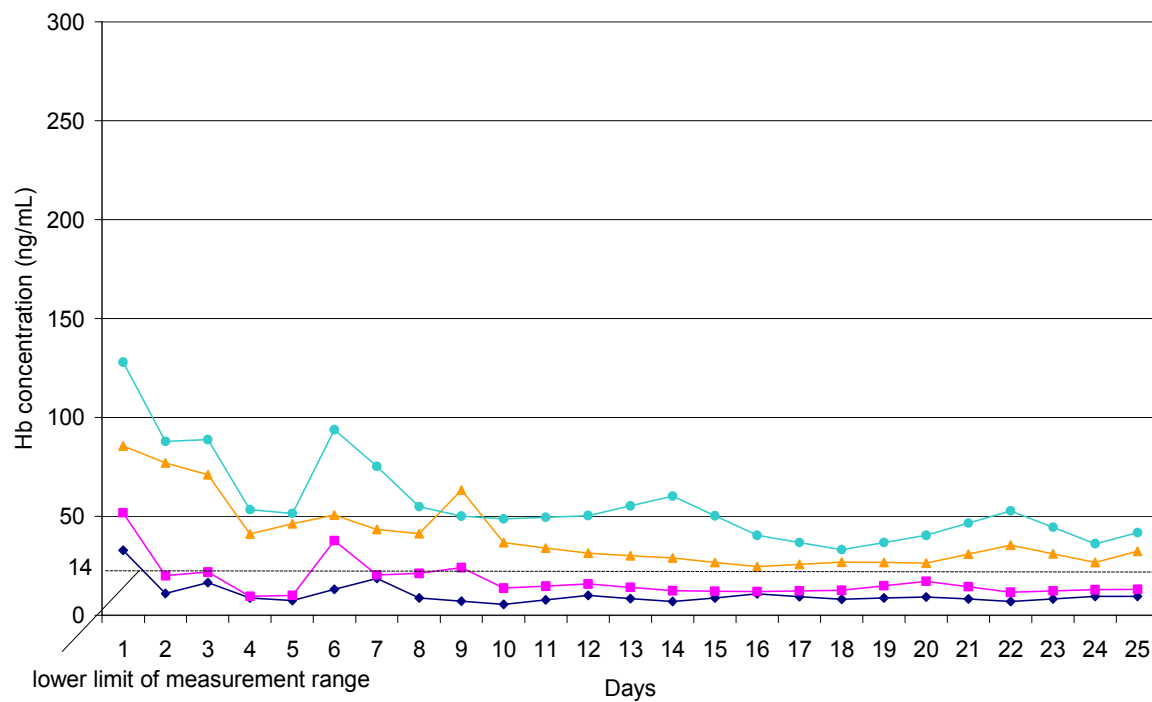


Figure 25. DEVEL-A-TAB card 29 to 34°C stability data



Sample collection device user questionnaire

Instructions for loading testing devices

Hema-screen card

1. Lift the front flap of the hema-screen DEVEL-A-TAB card
2. Using applicator stick provided, stab faeces in 4 different areas and then apply sample to circle number 1
3. Repeat the above process **using the same faecal sample** for circle number 2.
4. Close the flap and return the card to the foil envelope
5. Discard the applicator stick in a rubbish bin, do not flush down the toilet.

New Hemtube (very thin tube)

1. Insert the pointed tip of the sampling stick into 5 or 6 different sites of the faecal sample and then scrape the surface of the specimen several times horizontally.
2. Insert the sampling stick all the way into the open end of the sampling tube until you hear a click. Ensure the stick clicks into place, fits tightly and does not leak.
3. Place in plastic bag

Green cap tube

1. Twist the green cap on the bottle 180 degrees and pull to open.
2. Use green probe attached to the lid scrape some faeces from the surface of the sample so that the screw thread is covered in faeces.
3. Return the probe back into the bottle and push down to snap shut.
4. Place in plastic bag

Purple FOB gold tube

1. Unscrew and remove the purple cap from the bottle with the internal probe attached.
2. Insert the purple probe into 5 or 6 different sites on the faecal sample.
3. Return the probe back into the bottle and screw tightly into place
5. Place in plastic bag

Questionnaire for devices collection system

To help us obtain information on the samples collection systems we would be grateful if you could complete this questionnaire after you have used each device.

Hema-screen card

Collecting the faecal sample onto the applicator stick

Easy Tricky

Applying the sample to the window

Easy Tricky

Any additional comments

New Hemtube (very thin tube)

Removal of the collection probe from the device

Easy Tricky

Collecting the faecal sample on the probe

Easy Tricky

Reinserting the probe into the sample tube

Easy Tricky

Closing the device

Easy Tricky

Overall impression of the system

Excellent Satisfactory Unsatisfactory

Any additional comments

Green cap tube

Removal of the collection probe from the device

Easy Tricky

Collecting the faecal sample on the probe

Easy Tricky

Reinserting the probe into the sample tube

Easy Tricky

Closing the device

Easy Tricky

Overall impression of the system

Excellent Satisfactory Unsatisfactory

Any additional comments

Purple FOB gold tube

Removal of the collection probe from the device

Easy Tricky

Collecting the faecal sample on the probe

Easy Tricky

Reinserting the probe into the sample tube

Easy Tricky

Closing the device

Easy Tricky

Overall impression of the system

Excellent Satisfactory Unsatisfactory

Any additional comments

Laboratory user survey



Centre for Evidence-based Purchasing

User survey for immunochemical faecal occult blood tests

Name

Contact details

Please answer the questions by clicking into the grey areas. Some offer drop-down lists, others are free text and some are tick boxes. Some have help text which appears in the status bar at the bottom of the screen.

About the system you are using

1. System manufacturer Please select
2. Analyser Please select Other Please specify
3. How many analysers do you have? Please select
4. How long have the analysers been in use? Please select
5. How often is each analyser serviced? Please select
6. What is the total number of samples processed (average samples/week)?
7. What is the maximum throughput (test/hour) you can achieve on each analyser?
8. What percentage of samples need to be repeated and for what reason?

Samples

9. Sample identification. Please select all the identification markers put onto each sample, when and how this is done and by whom.

	How	By whom	When
9.1. Participant name (If 'Other' is selected, please describe in free text box)	Please select Free text	Please select Free text	Please select Free text
9.2. Sample identification number. (If 'Other' is selected, please describe in free text box)	Please select As a barcode? <input type="checkbox"/> As a number? <input type="checkbox"/> Free text	Please select Free text	Please select Free text
9.3. Date of sample collection. (If 'Other' is selected, please describe in free text box)	Please select Free text	Please select Free text	Please select Free text
9.4. Any other identification data?	Please describe	Please describe	Please describe

10. Have you had any problems with the sample collection devices? Please select

10.1. If Yes, please describe the problems and give their frequency

11. How are the devices distributed to the participants?

12. How are the samples transported back to the laboratory?

13. Have you had any difficulties with transportation? Please select

13.1. If Yes, please describe.

14. What percentage of samples received are unsuitable for testing?

14.1. What are the reasons for their unsuitability?

15. What advice is given to participants on storage of the collected sample until it is returned to the laboratory?

16. How many samples is the participant requested to provide for each screening ? Please select

16.1. What do you do when the results from the same participant are different? Please select If 'Other', please describe

Connectivity

17. We are interested in the import and/or export of data and how this is accomplished with each analytical system.

17.1. How does the analyser identify the sample?

From its rack position only

By external hand-held barcode reader and rack position

By internal barcode reader

Other, please give details

17.2. Does the analyser hold any participant data other than the sample barcode and the result? Please select If 'Yes', what data?

17.3. How is the analytical result from the sample linked to the participant identification data, ready for reporting?

The analytical system

18. Does the analytical system have an uninterrupted power supply? Please select

18.1. Please give details of any problems which have arisen from power cuts or fluctuations:

Patient data lost

Reagent management data lost

Calibration data lost

Other . Please describe

19. Have there been any losses of electronic data for reasons other than power failure? Please select

19.1. If Yes, please give details of frequency and causes.

20. Do you analyse internal quality control (QC) samples? Please select

20.1. Has QC fallen outside of acceptable range? Please select

20.2. Please give reasons for QC failures

21. Do you participate in external quality assessment scheme/proficiency testing? Please select

21.1. If Yes, which scheme?

21.2. Have any results been unacceptable? Please select

21.3. Please give any known causes of unacceptable results

22. Have you ever used telephone technical support from the manufacturer/supplier? Please select

22.1. How would you rate this service for quality? Please select

And response time? Please select

22.2. Any further comments about this service

23. Have you had to call in the service engineer? Please select

23.1. How would you rate this service for quality? Please select

and response time? Please select

23.2. Any further comments about this service?

24. Have you had any days when no results were possible due to assay or instrumentation failures? Please select

24.1. If Yes, how frequent were they and what were the causes of these failures.

25. Has it been necessary to replace the analyser? Please select

25.1. If Yes, please give the reason for replacement

25.2. If Yes, how long did replacement take (from when the analyser failed to when the new one was put into routine use)?

26. Have you had to replace any parts of the analyser? Please select

26.1. If Yes, how long did they take to arrive?

27. Have you had any problems with the performance of the assay (eg. unexpected results or positivity rate)? Please select

27.1. If Yes, please give details, including the frequency of the problem

28. How would you describe the overall reliability of the analytical system? Please select

Reliability of consumable delivery:

29. Do you have a regular standing order for consumables? Please select

29.1. Are the correct consumables delivered? Please select

29.2. Are they delivered on time? Please select

29.3. Are the 'Use by' dates suitable for your requirements? Please select

29.4. Any further comments about consumables

Health and safety

30. What are the health and safety risks associated with the use of the system?

Sample collection devices

Analyser

30.1. What measures have you taken to reduce these risks

31. Please give your overall impression of this analytical system when used for screening.

Evaluation report: Immunochemical faecal occult blood tests

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