QUESTIONNAIR FROM OEKO on

COCIR EXEMPTION REQUEST FOR

OEKO Question, received on 23 September:

Question 1:
Regarding the information provided along the evaluation process, we would still like to clarify a couple of aspects from which we are missing some details:

- In order to evaluate the relevance of the need of the exemption for existing devices already on the market, we would like to have an idea of the average lifetime of the ISE PoC analysers to which this exemption refers.
- In terms of alternative methods to ISE PoC analysers you provide information about ion chromatography, flame photometry, atomic adsorption spectroscopy and glass pH electrodes for pH. For these you refer to differences between required time, materials, measurement procedure and calibration in comparison to ISE PoC anaylsers. It would be useful for the evaluation if you could provide more detailed information (by means of a comparative table) about the specifics of all of these aspects, so the critical limitation and reasons why they fail to perform the required function can be clearly visualized.

Question 2:
With the intention of assessing the technical practicability of the DEHP substitution in ISEs for blood analysers, we also reached out to technical experts in the field that could be able to provide independent technical comments to inform the evaluation process.
In the context of this specific request we were in contact with Prof. Mark Meyerhoff from the department of chemistry of the University of Michigan who is an expert on biological sensors. He provided technical comments regarding the use of DEHP as plasticizer in ion-selective membrane electrodes (ISEs).

So far, the declarations contained in this document are considered a significant input to the evaluation report. Given that at the moment it cannot be stated which of the manufacturers for such devices are currently in need of this exemption, we would like to give COCIR the opportunity to comment Prof. Meyerhoff's declarations (please see attached document).

Answer to Question 1.1 : Average lifetime of ISE

The average life-time of ISE PoC Analyzer is 9.7 years, with >50% of the install base older than 10 years

Answer to Question 1.2 : Comparison of analytical techniques for ISE PoC analytes

Method	Ions that can be analysed	Analysis time per sample	Limitations	Total elapsed time from taking sample to results	Analyse whole blood	Measure ion activity	No maintenance needed	Automatic calibration	Automatic quality control	Can analyse all analytes (Na+, K+, Ca2+, H+, pCO2, Cl-, Glu, Lac, pO2, total haemoglobin, hematocrit) simultaneously	Positive ID of patient	Connection to hospital IT system
ISE PoC analyser	Na+, K+, Ca2+, H+, pCO2 (bicarbonate), Cl-, Glu, Lac, pO2, total haemoglobin, hematocrit	1 minute for all analytes simultaneously. It is important to note that measuring blood gases (pO2) and metabolites (glu, lac) together is critical for a full and rapid diagnosis of the patient.	All ions can be analysed simultaneously and rapidly from a very small quantity of fluid.	1 minute	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ion chromatography	Na+, K+, Ca2+, total CO2 (bicarbonate), Cl-	Whole blood cannot be analysed as it will block the small capillary and so additional time (at least 15 minutes) is needed to	Cannot measure ion activity. Anions and cations must be analysed separately, either by using two	15 + (2 x 30) + 30 + 30 = ca. 2 hours for one sample, then >30 minutes for subsequent samples plus queuing time.	No	No	No	No	No	No	No	No

		separate blood to extract the clear plasma that contains the ions (e.g. by centrifuge). Analysis requires calibration with at least at two standards (these contain for example all cations Na+, K+, Ca2+,) each standard taking typically 30 minutes. Recalibration is advisable every 2 – 3 hours. Analysis time per sample is up to 30 minutes and in addition is data processing time of up to another 30 minutes. Note that Ca2+ ions take the longest time for analysis[1].	instruments or changing columns which will add at least one additional hour to the analysis time as the column has to equilibrate before it can be used. Ion chromatograph must be used by trained analysts and so are not suitable for PoC locations. Samples therefore need to be taken from PoC facilities to these labs, where the samples join a queue, which can typically add 1 hour.									
Atomic adsorption spectroscopy	Na+, K+, Ca2+,	If a sufficient volume of blood is available, it can be centrifuged to	Cannot measure ion activity This method is slow because whole	At least 2 hours including waiting time - 15 to 30 +	No	No	No	No	No	No	No	No

[1] See figure 4 in https://webcache.googleusercontent.com/search?q=cache:wI4xJ6tlCb8J:https://www.mdpi.com/2297-8739/5/1/16/pdf+&cd=1&hl=en&ct=clnk&gl=uk&client=firefox-b-d and figure 11 of https://www.unil.ch/idyst/files/live/sites/idyst/files/shared/Labos/Jackson_2000.pdf

		obtain the clear aqueous phase, which will take about 15 minutes to separate the phases. Alternatively, acid digestion is an option but will take at least one hour (it also determines total calcium which is not the same as the concentration of the ISE method). Calibration of the spectrometer requires analysis of the ion at least at two concentrations so will take at least 6 minutes[2] per ion and sample analysis about 3 minutes per ion[3]. Total elapsed time for four ions is 15 to 30 + 18 + (3x3) = 42 to 57 minutes. In addition, time is required to set up the	blood cannot be analysed directly and only one ion is analysed at a time. These instruments are fairly large and require gas cylinders of acetylene and oxygen. These are very hazardous and are unsuitable in an emergency hospital environment. They can therefore only be used at a different location away from patients and untrained staff. Samples therefore need to be taken from PoC facilities to these labs, where the samples join a queue, which	18 + (3x3) = 42 to 57 minutes									

[2] It is good practice to flush out the instrument after each sample for about 10 minutes to avoid cross-contamination, so this time would be in addition per sample.
[3] https://www.sciencedirect.com/topics/materials-science/atomic-absorption-spectrometry

		spectrometer and allow it to equilibrate (ca. 1 hour) before any analysis can be carried out.	can typically add 1 hour.									
Flame photometry	Na+, K+, Ca2+,	Very similar to atomic adsorption spectroscopy, but can be quicker as Na+, K+ and Ca2+ can be analysed simultaneously, but has to be calibrated for each ion has to be separate taking about 18 minutes for three ions. Total elapsed include blood separation time is 15 + 18 + 3 = 36 minutes plus 1 hour equilibration time.	Cannot measure ion activity Flame photometry is a type of atomic adsorption spectroscopy and so analysis time is similar and the limitations described above are the same	1 - 2 hours = 15 + 18 + 3 = 36 minutes plus 1 hour equilibration time.	No	No	No	No	No	No	No	No
pH electrode	H+ only	Requires at least 10cm^3. This quantity will not always be available, for example very little blood can be taken from premature babies.	Measuring blood analytes, particularly pH, needs to be done at 37C (body temperature) and the system/sample controlled to +/- 0.1C for	Ca. 1 plus time for temperature equilibration and recalibration, probably 30 minutes per sample, although not likely to be	Yes	Yes	Yes	No	No	No	No	No

			acceptable clinical performance. The electrode would need to be cleaned between each sample to remove adsorbed proteins. The adsorption of proteins can cause the sensor to drift, requiring calibration. In addition, exposure of the sample to air will change the pH. Taking these together, a bench top pH electrode would not be capable of achieving the minimum +/- 0.04 pH unit total analytical error expectation	sufficiently accurate									

Answer to Question2:

Thank you for providing the input from Prof. Mark Meyerhoff. He is well known to us and is a highly respected expert in the field of ion selective electrodes. His technical input on the ISE selectivity impact from changing plasticizers in sensor membrane formulations is correct. However this is only one requirement for a clinically useful blood analysis system.

There are complex interactions between the sensor membrane formulations, internal electrolyte formulations, system calibration reagent surfactants, calibration reagent preservatives and compatibility with internal system materials used to house the sensors. The membrane formulations are specifically optimized to function within the system and all components that contact the sensors. All these aspects need to be addressed to yield a stable, reproducible and useful system.

In our exemption request we also noted that the system utilizes mathematical formulas (algorithms) that are specifically designed for each sensor (membrane formulation). Therefore it is the total integrated system (instrument, reagents, sensor formulation, algorithms) that is the complete system device which yields clinically acceptable performance and results.

Overall system stability and availability is very important to enable quick treatment of patients. In our exemption request we showed data that alternative plasticizers do not enable a stable system and will result in delayed treatment of patients. This delay can negatively impact patient outcomes. We also showed data that alternative plasticizers yield sensors with more variability. This can cause low quality clinical results leading to improper treatment of patients.

The conclusion of our data was the following; DEHP exhibits the best balance of initial drift after one hour and reproducibility and is therefore the preferred plasticizer. This has allowed the technology to meet the needs of the critical care environment in particular a short period of time to obtain results and a short time before first measurement with a new cartridge.