ANALYSIS OF ALTERNATIVES

Legal name of applicant(s):	*Instrumentation Laboratory S.p.A*
Submitted by:	*Instrumentation Laboratory S.p.A*
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol ethoxylated (OPE, EC 618-541-1, CAS 9036-19-5)
Use title:	*Use as a lysing agent for red blood cells in blood analysis diagnostic device.*
Use number:	*1*

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LIST OF ABBREVIATIONS

ER – *Emergency room*

ICU – *Intensive care Unit*

IQM – *intelligent quality management. A proprietary process of the applicant allowing for devices to be free of operator or expert maintenance.*

SVHC – *Substance of Very High Concern*

tBili - *total bilirubin*

tHb – *total hemoglobin*

sO_2 – *Oxygen saturation*

O_2Hb - *hemoglobin fractions including oxyhemoglobin*

HHb – *deoxyhemogobin*

COHb – *carboxyhemoglobin*

MetHb - *methemoglobin*

PCS - *Process Control Solutions – an automated method that ensures a smooth functioning of the device in all circumstances*

POC – *point of care – the place near the patient where the applicant's device is meant to be used*

OPE - *4-(1,1,3,3-tetramethylbutyl)phenol ethoxylated (OPE, EC 618-541-1, CAS 9036-19-5). The authorizable substance.*

V & V – *Verification and Validation*

DECLARATION

The Applicant [Authorisation holder] is aware of the fact that evidence might be requested by ECHA to support information provided in this document.

Also, we request that the information blanked out in the "public version" of the Analysis of Alternatives is not disclosed. We hereby declare that, to the best of our knowledge as of today ([DATE]) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature  21 June 2019, Bedford, MA (USA)

Jim Richard

Director of Quality Engineering, Instrumentation Laboratory Company

SUMMARY

The applicant is a leading manufacturer of in vitro diagnostic/scientific research equipment for point-of-care (near patient) blood gas tests. The applicant has already started the substitution process but requires more time than the sunset date allows to substitute the substance. The justification of the requested review period can be found in the substitution plan included in this analysis of alternatives.

The analysis of alternatives therefore focusses on the absence of drop-in substitution and the absence of competing products that could substitute in the market. The conclusion of the analysis of alternative are:

- A drop-in substitute is not available. Even if it were available it would be impossible to implement before the sunset date due to technical challenges and regulatory requirements;
- There are other blood gas analyzers on the market. All of them present different characteristics that make them imperfect substitutes for the applicant's device. The issues being both technical and economical;
- There is a considerable number of devices installed in Europe today. These devices would need to be phased out immediately at the sunset date leading to considerable cost for the European health care sector.

The applicants use does not create any emissions to the environment. The substitution effort detailed in the relevant section will ensure that at the end of the review period the substance will have been substituted throughout the EU in the applicant's devices without any detrimental effects for health care customers, patients or the European economy.

THE APPLICANT

Instrumentation Laboratory – part of Werfen - develops, manufactures and distributes instruments, related reagents and data management solutions, for hospitals around the world—at the point-of-care and in the laboratory. Their solutions include Hemostasis and Acute Care Diagnostic products and services, all designed with a common goal: to help healthcare providers enhance patient care and efficiency. The products affected by the authorization is the GEM series point-of-care blood analyzers, which offer a full panel of blood gas tests in less than a minute and fully automates all quality management, maintenance and data management aspects of testing.

Data from the GEM Premier family of blood gas analyzers are used daily in hospitals around the world to make life-saving decisions regarding patient health. It is imperative that these data have the highest possible reliability and accuracy. The use of OPE in the GEM Premier analyzers is currently critical to the performance of the CO-Oximetry system, providing results for total hemoglobin, oxyhemoglobin, carboxyhemoglobin, methemoglobin, deoxy-hemoglobin, oxygen saturation and total bilirubin.

CONSULTATIONS

The applicant started an internal process of consultation shortly after the substances were added to the annex XIV of REACH. This involved the gathering of the knowledge on uses of OPE within the company, potential alternatives and different suppliers of alternative surfactants. The conclusion of these consultations was that substitution is possible but requires extensive feasibility, design, and development that can pose challenges during implementation. Furthermore there are regulatory approvals and homologations required that require a considerable amount of time to fulfill. The applicants took a decision to implement a company-wide substitution plan which was kicked off in March 2019.

ANALYSIS OF THE SUBSTANCE FUNCTION AND TECHNICAL REQUIREMENT FOR THE PRODUCT

The OPE performs the cell lysis when the blood sample is introduced into the analyzer. Triton X-100 is the surfactant used as a lysing agent to rupture the cell membranes of the red blood cells in a whole blood sample. The blood measurement algorithms of the GEM Premier analyzers require complete and fast lysis (1 to 2 seconds) for accurate measurements and reporting results in 45s to diagnose and treat critically ill patients.

DESCRIPTION OF THE TECHNICAL FUNCTION PROVIDED BY THE ANNEX XIV SUBSTANCE

The only technical function of the substance is to perform cell-lysis within 1 to 2 seconds.

TECHNICAL REQUIREMENTS

THE INSTRUMENTATION LABORATORY DEVICE: GEM PREMIER ANALYZERS

The GEM Premier analyzers are portable critical care systems for use by health care professionals to rapidly analyze whole blood samples. They serves as key diagnostic analyzers in hospital labs, operating rooms, emergency rooms and other Point-of-Care at locations across the Global and EU Health Care Sector.

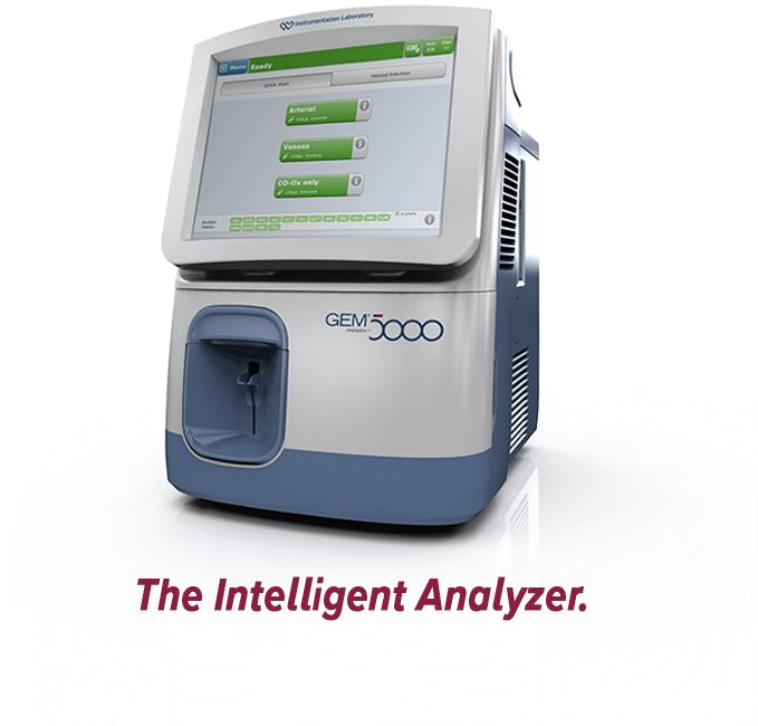


Figure 1 The GEM Premier 5000 analyzer

Blood gas testing using critical care analyzers such as GEM Premier 4000 or GEM Premier 5000 is a core element of diagnostic and treatment procedures carried out in the Health Care Sector today for blood gas, electrolyte, metabolite, and CO-Oximetry measurements.

One of the measurement methodologies employed in the GEM series analyzers is CO-Oximetry:

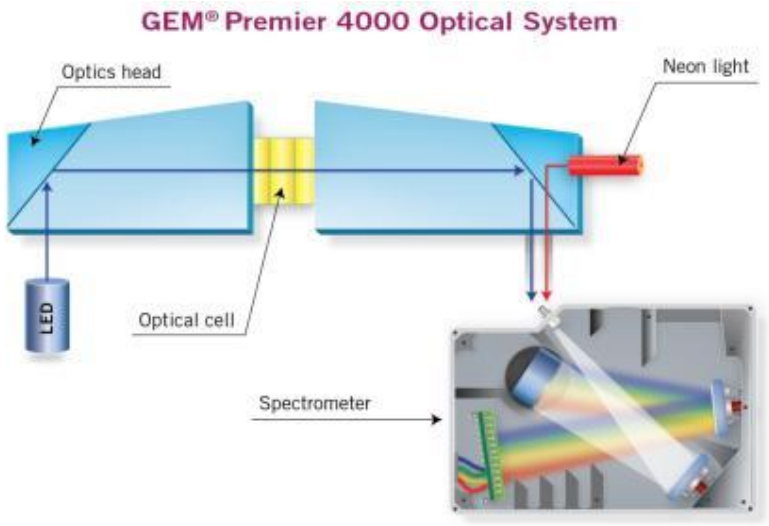


Figure 2 Basics of CO-Oximetry

- CO-Oximetry is based on optical absorbance measurements of the sample (the hemoglobin species have specific absorbance patterns).
- Optical measurement is performed following chemical lysing, where the whole blood sample is homogeneously mixed with the lysing solution. The sample spectrum is measured simultaneously at about 2000 wavelengths from 475 to 650 nm.
- The chemical lysing of the sample is implemented to minimize the light scattering effect of the blood cells and to make the spectral measurement more reliable.

The instrument then analyzes the absorption spectra, measuring concentrations of the individual components shown in Figure 3:

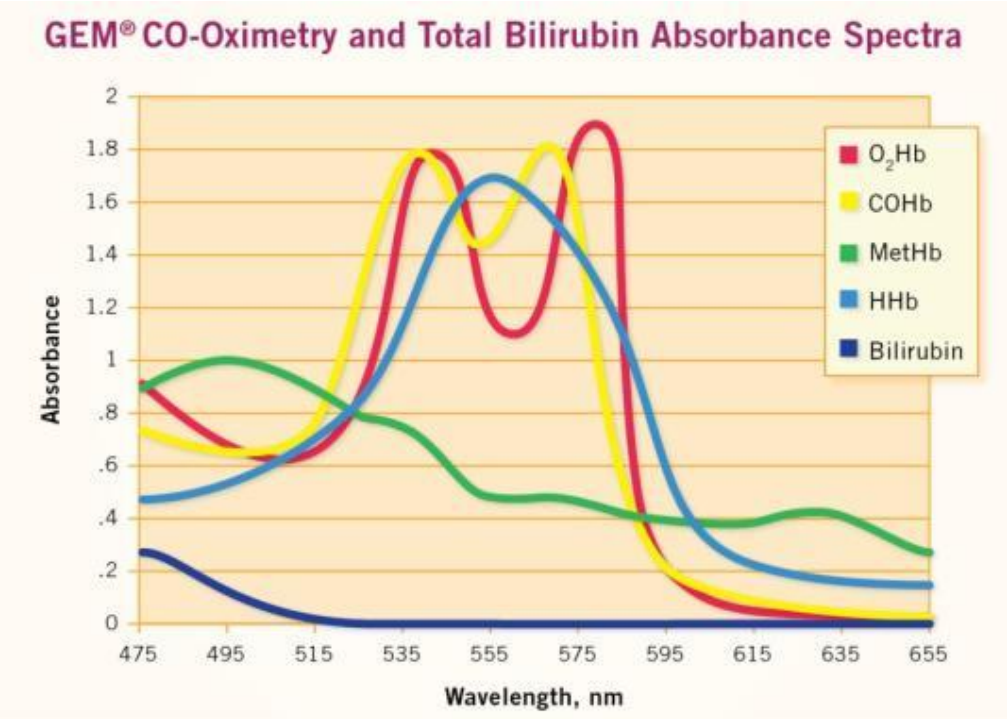


Figure 3 CO-Oximetry absorbance spectra

The CO-Oximetry module of the GEM series analyzers is an optical measurement device and any factor (e.g. change in chemical composition of the lysing solution) that impacts the absorption spectrum of the sample will change the outcome of the analysis. Hence the change in surfactant would require modification of the analytical algorithms and require a significant software modification to account for the new optical properties of the reagents.

The GEM Premier analyzer is comprised of an instrument housing and a disposable cartridge (PAK) that can measure the following parameters: pH, pCO_2, pO_2, sodium, potassium, ionized calcium, chloride, glucose, lactate, hematocrit, total bilirubin (tBili), total hemoglobin (tHb), oxygen saturation (sO_2), and hemoglobin fractions including oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), carboxyhemoglobin (COHb) and methemoglobin (MetHb). These analytes, along with derived parameters, aid in the

diagnosis of a patient's acid/base status, electrolyte and metabolite balance and oxygen delivery capacity.

The cartridge contains all the components required to perform whole blood testing. This includes a sensor card, an oximetry module and individually packaged process control and lysing solutions. The sensor card provides a low volume, gas tight chamber in which whole blood samples are presented to the sensors. The process control solutions are utilized in performing quality management and other assay specific functions. The lysing solution is used to lyse the whole blood cells prior to optical measurements.

The sensor values of the GEM Premier cartridge are measured and monitored with Process Control Solutions (PCS). These solutions are pre-tonometered to specific levels of pO_2 and pCO_2, and contain known quantities of analytes and dyes tested against NIST traceable reference standards when applicable. All process control solutions are used to monitor and correct performance of the system during use, as part of the Intelligent Quality Management (iQM) system.

Key applications of CO-Oximetry at the Point-of-Care:

Table 1 Key applications of CO-Oximetry at Point-of-Care

ER	•**COHb**: Patients suspected of Carbon Monoxide and other poisoning •**MetHb**: Variety of poisons, chemicals •**tHb/sO_2/Hct:** Internal bleeding, trauma & other anemias
CVOR	•**tHb/sO_2**: Helps in avoiding unnecessary blood transfusions during cardiac surgery
ICU	•**O_2/Hb & O_2 content**: Tissue oxygenation status •**tHb/sO_2**: Measurement of conditions that affect RBC in clinical ill patients (i.e. anemia)
NICU	•**MetHb**: Monitoring of Nitric Oxide therapy to babies with pulmonary conditions (avoid toxicity) •**tBilirubin**: High amounts can lead to Jaundice and Kernicterus •**tHb/sO_2:** Oxygentation status
Cardiac Cath	•SO_2 values for shunt studies •GEM 4000/5000 offer full Blood Gas for emergent situations

The GEM Premier analyzers have the following characteristics (partially) due to the use of the OPE:

- Single, self-contained cartridge able to meet all measurement functions and is stored at room temperature;
- Maintenance-free—operators cannot change or manipulate the cartridge;
- Self-correcting after every analysis checking for both machine failures, operator error or sample issues through iQM;
- Designed for operators at the point-of-care, without the need of specific laboratory technician skill-sets;
- Very fast (45s) results;
- 9 months reagent shelf-life (which is long);
- 100% capture of all effluent in a sealed bag inside the disposable cartridge.

TECHNICAL REQUIREMENTS

The following are technical requirements that must be met for a substitute lysing agent:

- A low degree of foaming;

- Compatibility with the equipment; notably non-interference with the optical analysis method;
- Meet stability and shelf-life targets of the current substance (9 months at room temperature).

As long as the above function and requirements are met, the products, software and algorithms can be modified to obtain identical function to the current product that uses OPE.

RESEARCH AND DEVELOPMENT

The applicant has launched a feasibility project to determine a potential substitute for OPE and is currently evaluating two [redacted] substances [redacted]. This step is part of the substitution plan below. Preliminary results indicate that it is possible to achieve comparable cell lysis as with OPE. However, due to the optical interaction of OPE with other reagent components used in the GEM system as described above, development of new algorithms and a system software change would be required to release these hypothetical substitutes.

Additional analytical testing is required to assess the above mentioned reagent and analytical risk factors – timeline estimated in the substitution plan - to resolve analytical risks and algorithm development due to early stage of feasibility. The implementation timeline is dependent on analytical and regulatory risk assessment by public authorities. The R&D is ongoing and the applicant is confident that a solution will be found amongst commercially available non-ionic surfactants. However the implementation of the change will require further substantial modifications to the equipment and a production process.

The quality management, auto-error reporting & correction system is dependent on historical data collected from a wide range of patient samples representing different clinical conditions. The pattern recognition algorithms employed in the iQM system, such as sensor clot patterns, CO-Oximetry clot patterns, and interference patterns, are dependent on this historical data. Since this system is dependent on a large amount of patient data, modification of the surfactant may alter the functionality of the pattern

recognition algorithms, and new patient data will be required to validate the functionality of iQM. This work is feasible, but takes time and cannot be accelerated without potential impact to the accuracy of patient results.

DATA SEARCHES

N/A

IDENTIFICATION OF KNOWN ALTERNATIVES
SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

There are two possibilities to look at substituting the substance:

- Substituting the substance in the current products – this is the subject of the annex substitution plan;
- Substitution through a different lysis method – this is the subject of the present analysis of alternatives.

The applicant concurs that technical substitution of OPE within its products is possible. However it requires 12 years as described in the substitution plan detailed at the end of the analysis of alternatives.

DIFFERENT ANALYSIS OR LYSIS METHODS

There is no instrument available on the market that is identical in all its features to the GEM series analyzers. There are however other instruments that perform blood-analysis that do not use chemical lysis and therefore do not use an SVHC (substance of very high concern) for that purpose. The analysis below covers the three products that come closest to performing the same function as the GEM analyzer. Even then the Siemens, Radiometer, and Roche products cannot perform the iQM of the applicant.

HEALTH CARE CUSTOMER NEEDS WHEN PURCHASING AN ANALYZER

The health care professional wants to achieve the highest quality results under all circumstances. Patient care is the central focus in the choice of any analyzer but there are several top concerns that are consistently reported by customers:

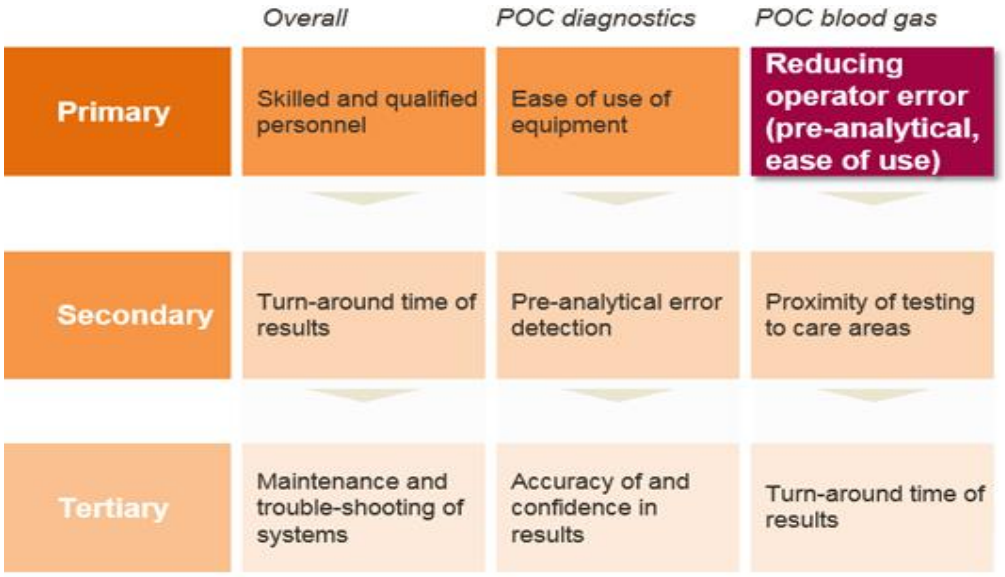


Figure 4 Health care priorities for blood analyzers

As a laboratory director commented – staff competency is one of the biggest challenges as it introduces quality issues. In other words, if the operator needs to be able to make decisions on whether a test has run correctly, the instrument operated within standard parameters or need to manipulate a sample to ensure a correct run; the risk of errors is introduced.

Combine this with a staff that – at point-of-care – should be primarily patient focused and therefore less trained in analytical equipment as well as the inevitable urgency within an Emergency Room, Intensive Care Unit or other critical care areas and it should be obvious that operator related intervention in the testing process should be reduced and facilitated as much as possible.

Laboratory errors cost money, lives and time – between 1.1%[1] and 1.4%[2] of tests contain errors causing tens of thousands of complications every day. Research[3] has shown that:

- 61.9% of errors are pre-analytical – i.e. wrong sample preparation, operator manipulation errors, micro-clots etc…

[1] Binita Goswarmi et al. Clinical Chemistry Lab Med 2010; 48 (1): 63-66

[2] Mario Plebani et al. Clinical Chemistry 2007; 53:7; 1338-134-1342

[3] Ibid above.

- 15% of errors are analytical – i.e. the instrument is malfunctioning for example due to a clot;
- 23.1% are post analytical – i.e. errors in interpretation or reporting.

At worst death can occur, at best delays in optimal treatment are incurred. Instrumentation Laboratory has attempted to reduce all these errors and in particular the pre-analytical and analytical ones to a minimum. The GEM analyzer series also avoids the need for maintenance, automates quality management and can operate with a single cartridge for all functions. This is not only convenient it reduces the chances of errors and reduces impact on staff time to manage multiple consumables or cartridges to perform testing. Finally the GEM Analyzer provides reviewable online data to the health care provider about the tests and performance of the analyzer allowing for improvements in patient care. All these functions are inherent to the design of the GEM analyzer and the implementation of iQM - Intelligent Quality Management.

IQM - INTELLIGENT QUALITY MANAGEMENT

WHAT IS IQM?

The applicant believes that other blood gas analysis instruments are not alternatives to the applicant's instruments in terms of simplicity and error detection. In the present analysis we aim to show that:

- The error detection, reporting, solution inherent in the GEM series analyzers makes them uniquely suitable to critical Point-of-Care (ICU, ER etc) environments;
- The iQM system unique to the GEM series analyzers is not implemented in the other analytical instruments;
- The integrated single cartridge/no maintenance aspect of the GEM series analyzers provides concrete operational and ease-of-use advantages.

IQM provides real time quality assurance in that every sample, every test, every cartridge is continuously tested to see whether it is within known correct parameters. Why is this important?

Systemic error detection is reduced from hours to minutes[4][5] and transient sample specific errors are detected immediately. In other words using iQM the corrective action is faster, while a fault in a classical analyzer may only be discovered much later. When that occurs it calls into question all the tests since the moment the classical analyzer was previously established to be functioning correctly.

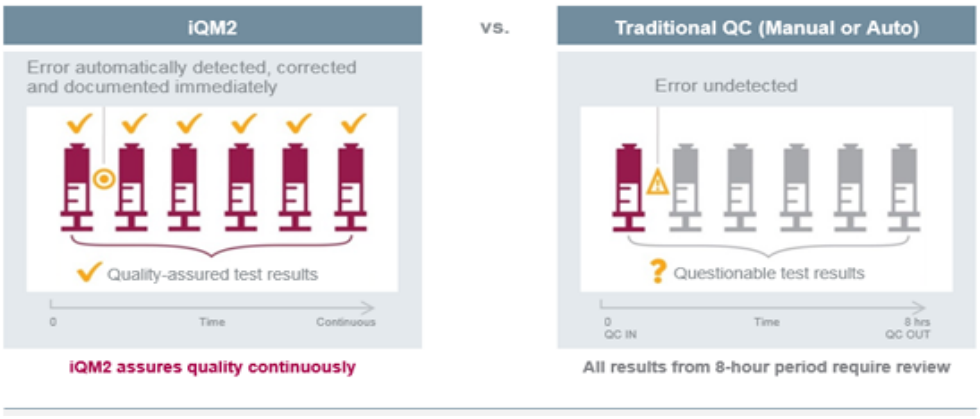


Figure 5 Quality assured tests vs. Questionable tests

The monitoring covers sample, sensor, reagent and CO-Oximetry errors.. The most important differentiating ones with other analyzers are:

- Micro-clots, which can occur from inadequate anti-coagulant or improper mixing
- Benzalkonium Chloride, utilized in skin sanitation and intravascular-access devices, is a positive ion that can cause positive bias with Na^{+} and Ca^{++}

[4] Westgard JO, *et al*. Validation of iQM active process control technology. *Point of Care, The Journal of Near-Patient Testing and Technology*. 2003:Vol. 2, No. 1.

[5] Toffaletti JG, *et al*. Validation of a quality assessment of blood gas and electrolyte testing. *Clinica Chimica Acta*. 2007:382:65–70.(Together with James Westgard, PhD, IL established the methodology for optimizing high probability of error detection and low probability of false rejection of drift limits. Method performance, in terms of Mean and Standard Deviation, of measured PCS values were obtained from the data of 276 GEM PAK cartridges used in Proof-of-Performance and Beta trials for the GEM Premier 5000 analyzer.)

- CO-Ox/tBili spectral errors, resulting from turbidity or endogenous/exogenous dyes

All analyzers are able to detect major clots – but micro-clots are a real issue that would require maintenance by an operator or qualified person in other analyzers.

In summary the GEM Analyzer provides the following functions not comprehensively provided by other analyzers:

- **Automatic real-time detection**
    - Performs continuous checks—**before**, ***during*** and **after** every sample, using:
    - Five types of **continuous** quality checks performed throughout GEM PAK use-life
    - IntraSpect™ technology– quality checks **during** every sample analysis
- **Immediate, automatic correction**
    - Initiates intelligent corrective actions, if any sensor, CO-Ox, system-stability or sample error, is detected *specific to source of error*
- **Automatic documentation**
    - Documents all actions in real-time; no manual documentation required, *minimizing regulatory requirement efforts*

SINGLE CARTRIDGE DEVICE

The GEM Series analyzer uses only one cartridge that can be used for all functions and can be stored at room temperature:

Figure 6 Cartridge view – note the transparent bag at the end is the waste bag, containing all samples and reagents that have been used

The system is not only convenient but provides a real financial saving for the users of the instruments compared to devices with multiple cartridges. This benefit translates in several ways:

- Other devices all use multiple cartridges for different readings and this needs to be documented which is always challenging for the POC operator and therefore, taking their valuable time from patient management ;
- In point-of-care situations the need – even infrequent – of changing a cartridge when the need for a measurement is urgent leads to delay and therefore higher cost for the health care provider.

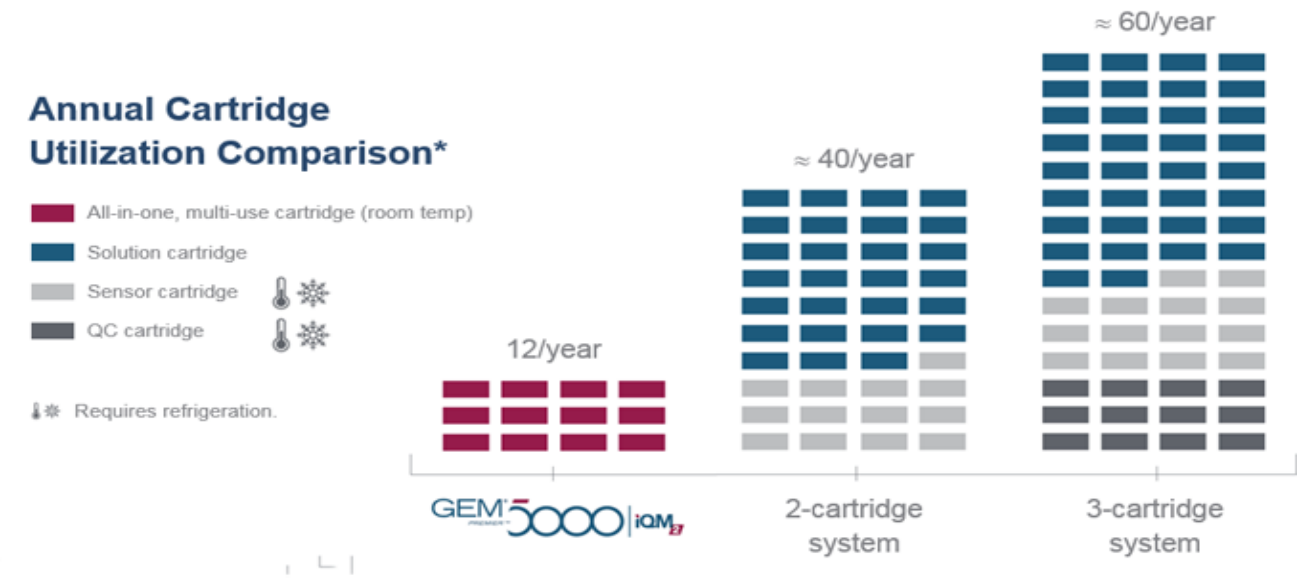


Figure 7 Comparison of cartridge uses

GENERAL ASSESSMENT

There are many blood analyzers on the market and each of them have relative benefits and drawbacks. Their optimal use depends on what and where you want to use the devices. In 2012 a very rare comparison was made by the College of American Pathologists. The article confirms the claims of the applicant that their devices are different from other devices on the market and none of them are perfect substitutes for each other.

http://www.captodayonline.com/Archives/0812/0812_in_vitro_blood_gas_analyzers_guide.pdf

The article is interesting in that all the three major manufacturers interviewed concur that patient and point-of-care data will be requirements in the future. The article is now seven years old but the current market confirms that the predicted development took place. The applicant was the first to offer these functionalities and as a consequence has maintained a lead over its competitors due to historical patient data going back further than those of its competitors.

Other competing technologies approach CO-Oximetry measurements in various ways, including ultrasonic lysis and measurement of whole blood without hemolysis. One distinct advantage of the current chemical lysis method employed by GEM Premier analyzers is that

the Triton X-100 is contained in a solution that buffers the pH of the sample, eliminating the potentially extreme effect of pH on measured Methemoglobin. Thus, the GEM analyzers are better able to provide an accurate result in the presence of varying pH.

Some of the competing technologies (e.g. ultrasonic lysing) require exposing the blood samples to analyser components for measurement of CO-Oximetry parameters. On the GEM Premier systems blood is exposed only to the disposable cartridge components, allowing for simplicity in biohazard waste disposal and easy analyser decontamination.

To the applicant's knowledge the following blood analysis instruments present similar analytical capabilities to its GEM analyser. There are other blood analysis devices on the market but the applicant believes that they are not equivalent substitutes for its devices due to either single use application or limited market share in EU.

- Siemens' RapidPoint 500;
- Radiometer's ABL 90 / ABL 800,
- Roche diagnostics' Cobas 123.

Feature	**Radiometer**		**Siemens**	**Roche Diagnostics**
	ABL 700/800	**ABL 80/90**	**Rapidpoint 400/500**	**Cobas 123**
Sample	Whole Blood	Whole Blood	Whole Blood	Whole Blood
Method of Hemolysis	Ultrasonic	Ultrasonic	Whole Blood (no lysis)	Ultrasonic
Optical System	White LED and spectrometer	White LED and spectrometer	Halogen Lamp with spectrometer	White LED with High-Resolution Spectrometer
Wavelengths	478– 672 nm	478– 672 nm	unpublished	470–670 nm
tHb Calibration	Every 30 days	Calibration schedule	Calibration schedule	Calibration schedule

Zero Calibration	Yes (Automatic)	Calibration schedule	Calibration schedule	Calibration schedule
QC Requirements Liquid QC Frequency Optical QC	Daily per regulations N/A	Internal QC	Internal QC	Internal QC

Table 2 Other blood analyzers available in the EU

It's difficult to compare such equipment because some differences follow from the nature of the design. Radiometer's ABL 800 is primarily focussed on laboratory applications due to its size and maintenance requirements, which are not ideal for point-of-care applications. The Cobas 123 (Roche), ABL 90 (Radiometer), and RapidPoint 500 (Siemens) need multiple cartridges, which have shorter shelf/use life and require refrigerated storage. This is a difference that is pertinent in the market and means that whilst the products are partial substitutes of one another it is not correct to conclude that the substitution would be seamless in all cases. The fact that all of them find a place in the market shows that the different capabilities are valued by the customers.

The one unavoidable cost associated with a non-use scenario is that the existing installed base of Instrumentation Laboratory GEM analysers used in the European market will need to be withdrawn on the sunset date. This will have a capital cost for health care institutions across the European Union and require retraining of personnel in the operation of substitute machines.

WHOLE BLOOD ANALYSIS (NO LYSIS) – SIEMENS' RAPIDPOINT 500

ALTERNATIVE TECHNIQUE DESCRIPTION

The Siemens competing product performs an optical measurement of whole blood without lysis.

The Siemens competing product functions on the basis of a multiple cartridge system containing various mixes of reagents and chemicals. The exact composition of these

cartridges is unknown although the Siemens SDS[6] gives some indication. The following warnings are given with regard to the reagents contained in the different bags inside the cartridge:

Full text of classifications [CLP/GHS]

LS Zero Cal	
Eye Irrit. 2, H319	SERIOUS EYE DAMAGE/ EYE IRRITATION - Category 2
Skin Irrit. 2, H315	SKIN CORROSION/IRRITATION - Category 2
STOT SE 3, H335	SPECIFIC TARGET ORGAN TOXICITY (SINGLE EXPOSURE) (Respiratory tract irritation) - Category 3
Reagent C Pouch	
Acute Tox. 3, H301	ACUTE TOXICITY (oral) - Category 3
Acute Tox. 3, H311	ACUTE TOXICITY (dermal) - Category 3
Aquatic Acute 1, H400	ACUTE AQUATIC HAZARD - Category 1
Aquatic Chronic 1, H410	LONG-TERM AQUATIC HAZARD - Category 1
Aquatic Chronic 3, H412	LONG-TERM AQUATIC HAZARD - Category 3
Skin Corr. 1B, H314	SKIN CORROSION/IRRITATION - Category 1B
Skin Sens. 1, H317	SKIN SENSITIZATION - Category 1
STOT SE 3, H335	SPECIFIC TARGET ORGAN TOXICITY (SINGLE EXPOSURE) (Respiratory tract irritation) - Category 3

Figure 8 Source SIEMENS SDS

The SDS further indicates the contents of the cartridge qualify as PBT and vPvB. As regards disposal the Siemens cartridges must be treated as chemical waste (as per the SDS).

TECHNICAL FEASIBILITY

The Siemens competing product delivers comparable analytical options to the GEM series devices of the applicant with some drawbacks:

- There are multiple cartridges (3) required for different functions of the machine – this increases the use of the number of cartridges as well as user manipulation during use;
- Some (not all) of the cartridges must be stored in a refrigerated environment.
- Each cartridge has to be changed out at different intervals based on different metrics (stability, number of tests, etc.), all which requires management
- The instrument requires operator troubleshooting in case of issues (replacement of clot catchers);

- The Siemens device does not offer comprehensive quality management program with intelligent sample-specific error detection, correction and documentation capabilities

THE COST OF MULTIPLE CARTRIDGES

These issues in particular are problematic for a number of users of the analyzers. In intensive care, emergency treatment surroundings limit the ability to store cartridges safely (and document that storage). Patient primary care will always supersede the control of the equipment so that the Siemens device presents important practical disadvantages. These are particularly acute in warmer climates or mobile care locations. Furthermore the regular calibration/maintenance schedule means when a fault is discovered during this process all measurements made from that point to the last known calibration/maintenance are suspect and may need to be repeated.

REQUIRED OPERATOR INTERVENTION IN MAINTENANCE, CALIBRATION AND QC OF THE DEVICE

The Siemens device requires frequent and repeated operator intervention. In this sense it is less suited to point-of-care use than the applicant's device. The device's operating manual makes this clear:

- Wash/Waste cycle – the Siemens device requires the use of a special Wash/Waste cartridge whenever a cartridge is at end of life or almost depleted. (Section 5-2 of the Rapid point 500 operating manual);
- Whilst the system performs routine automatic calibrations every 30 min[7] (section 3-2 of the Rapid point 500 operating manual) there is a special procedure if the automatic calibration fails twice in a row (section 3-4). This is noted as requiring special operator to intervene and therefore cannot (normally) be performed at point of care.
- Quality Control can be performed automatically (sections 4-5 and 4-6 of the manual) but the default setting is 'unscheduled' which means operator assisted. It involves: 'Insertion of an ampule with a special syringe' (section 4-7) and therefore again a maintenance operation that would not be possible at the Point-of-Care.

[7] The GEM analyser performs such calibrations after every measurement so that no result can be invalidated after it has been acted upon.

- The manual contains an extensive section on trouble-shooting and several of these require technical manipulation of the device (sections 6-1 to 6-64). Particularly telling is the section on the replacement of the sample port which is necessary if there are 'fibrin clots' (section 6-54). Such clots will occur with some frequency and require a special technical intervention which the applicant's device would never require.

The Siemens RapidPoint 500 is a very good device but less suited for the point-of-care use that the GEM analyser has been designed for.

CONCLUSION ON TECHNICAL FEASIBILITY

The applicant believes that their market share in Europe shows that the GEM product has an added value over and above that of the competing Siemens product. The conclusion must therefore be that a substitute with a method that avoids lysis is available but has compromises in terms of quality and is less suited to a point-of-care environment.

ECONOMIC FEASIBILITY AND IMPACTS

In case the authorisation is not granted for the requested review period, European customers will need to stop using the GEM series analyser by the end of 2021. These machines generally have a life time of about 15 years and are in many cases not fully depreciated at the sunset date nor at a considerable time thereafter. There would therefore be an immediate capital cost involved for healthcare institutions around the EU if they were removed from service.

Based on an installed base of [redacted] devices and the type of contracts customers are using (purchasing vs. renting), it is estimated the capital write off for EEA customers would be more than € [redacted], as detailed in the SEA.

Furthermore there are one-off training costs equal to more than € [redacted] ([redacted] times € [redacted]; see Table 2 in the SEA for details).

REDUCTION OF OVERALL RISK DUE TO TRANSITION TO THE ALTERNATIVE

As the applicant's use avoids emissions of OPE and the competing Siemens technology is subject to similar restrictions on environmental emission, the applicant contends there

is no risk reduction due to the alternative. There is a shift from a chemical already on the Annex XIV to known PBT/vPvB/Long term aquatic 1 level substances. Both substances are recovered 100% and treated in the same manner as chemical waste – perforce the conclusion must be that the Siemens technology adds no benefit.

AVAILABILITY

The applicant concedes that Siemens would be able to service the applicant's market. However this could certainly not be done immediately as the number of devices to be substituted is very large.

CONCLUSION ON SUITABILITY AND AVAILABILITY FOR ALTERNATIVE 1

The applicant concludes that the alternative is technically imperfect as a substitute, would bring considerable societal costs and bring no benefits in terms of risk or hazard. Therefore the alternative is deemed to be unsuitable.

NON CHEMICAL LYSIS – RADIOMETER ABL 90 / ABL 800

ALTERNATIVE TECHNIQUE DESCRIPTION

Radiometer's device uses ultrasound to lyse the cells and otherwise functions in an analogous manner to the applicant's device.

TECHNICAL FEASIBILITY

The main differences between the applicant's device and both Radiometer devices:

- Limited shelf-life (4 months) of the consumable cassettes;
- Storage must be under controlled conditions. Some cartridges require refrigeration;
- Multiple consumables (sensor cassette, solution pack, sampler assembly) required to perform different functions;
- User initiation ofinitiated external calibration for total hemoglobin;
- ABL 800 requires routine maintenance and troubleshooting to perform testing – not ideal for point-of-care operation.

Radiometer has made claims that it is equivalent in some ways to the GEM analyzer series. In particular on two aspects:

1) 'No maintenance'
2) Patient data system called AQM ™.

A simple examination of the Radiometer ABL90 Operators Manual shows that included in the device are instruments meant to be used by the operator to manually troubleshoot errors (flushing the fluidics of the system). The manual also indicates a requirement to substitute various other parts at regular intervals:

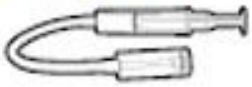
Consumables	Default tests or activities per day	Recommended replacement interval after installation
Solution Pack	10	Maximum 30 days or when the number of activities is zero
Sensor Cassette	10	Maximum 30 days or when the number of tests is zero
Inlet Gasket Holder	10	12 months
Inlet Connector Gasket	10	12 months

Figure 9 P. 33 of Radiometer ABL 90 manual

The manual has no less than 15 pages of explanations on the various consumables and how they should be replaced during operation. Sometimes this requires some specific tools. The device also requires manual calibration using specific tools (pp. 75-79 of the Radiometer manual):

The device also requires cleaning and sterilization on a regular schedule (as set out in pp. 47-48 of the manual). There are specific instructions for flushing the device in the event of e.g. micro-clots (p. 83):

Prerequisites:



An ABL90 FLEX Flush Device

A paper tissue or a cloth

The device would then go into 'intervention required mode' and a number of more or less complex manipulations are needed (pp. 84-86) requiring the use of special tools. The manual lists over (pp. 86-121) 20 pages of error codes that may occur and a substantial number of them would require the intervention of a specialist, e.g.:

- Recalibration required;
- QC errors requiring repeating the analysis on a new sample;
- Mechanical interventions c.q. repairs to the device.

Such manipulations are not excessive if the operator is a specialized lab technician but is not suitable for point-of-care situations where the user is a health care professional with primary focus on patient care. The device serves a different purpose than the applicant's device which does not require such interventions. Such items would not be included if the device could automatically maintain itself like the GEM analyzer does. This is not a criticism of the quality of the device, it was simply developed to be managed by laboratory-trained operators where there is less stress than at point-of-care where the GEM analyzer is meant to be used.

The Radiometer device also does not offer comprehensive quality management program with intelligent sample-specific error detection, correction and documentation capabilities that the applicant's device can offer.

ECONOMIC FEASIBILITY AND IMPACTS

At the point-of-care use the Radiometer device has higher operating costs to operate than the applicant's device. The GEM features a single, all-in-one PAK that contains all components required for testing and ensuring quality over 31 days or 450 tests. In

contrast, the competing Radiometer products require electrodes, membranes, reagents, solutions, gas tanks, QC ampule materials and maintenance programs which can amount to hundreds of components over the course of a year vs a dozen for the GEM. The number of consumables is considerably higher for Radiometer's device. This translates into significant operator/technician hands-on time and analyser unavailability for patient testing.

As has been averred above the down-time and maintenance needs of the devices is also considerably higher. With a factor of 10 higher downtime, the Radiometer ABL800 device is less suitable in critical care areas as emergency rooms and intensive care units as well as other high stress, time sensitive environments. Substitution of the applicant's device with the Radiometer device would therefore deliver neither the standard of care that is available from the GEM series nor be equivalent on a cost basis. Thereby yielding poorer patient care for greater uncertainties and greater inefficiencies.

In case the authorisation is not granted for the requested review period, European customers will need to stop using the GEM series analyser by the end of 2021. These machines generally have a life time of about 15 years and are in many cases not written off. There would therefore be an immediate capital cost involved for healthcare institutions around the EU.

Based on an installed base of [redacted] devices and the type of contracts customers are using (purchasing vs. renting), it is estimated the capital write off for EEA customers would be more than € [redacted], as detailed in the SEA.

Furthermore there are one-off training costs equal to more than € [redacted] ([redacted] times € [redacted]; see Table 2 in the SEA for details).

REDUCTION OF OVERALL RISK DUE TO TRANSITION TO THE ALTERNATIVE

As the applicant's use avoids emissions of OPE there is no difference in risk between the two alternatives. Whilst the use of OPE may be avoided, the waste treatment is identical due to the bio-hazard nature of the samples and the other chemicals used in the process. As OPE does not present a risk to the operator the outcome is therefore the same: no emission of OPE to the environment.

AVAILABILITY

The applicant concedes that Radiometer would be able to service the applicant's market. However this could certainly not be done immediately as the number of devices to be substituted is very large.

CONCLUSION ON SUITABILITY AND AVAILABILITY FOR ALTERNATIVE 2

The applicant concludes that the alternative is technically imperfect, would bring considerable societal costs and bring no benefits in terms of risk or hazard. Therefore the alternative is deemed to be unsuitable.

NON CHEMICAL LYSIS – ROCHE COBAS 123

ALTERNATIVE TECHNIQUE DESCRIPTION

Roche's device uses ultrasound to lyse the cells and otherwise functions in an analogous manner to the applicant's device.

TECHNICAL FEASIBILITY

The Roche device presents the same issues as the Radiometer and Siemens devices:

- Multiple cartridges required – included sensor cartridges;
- The Roche device is not equivalent to the GEM Premier analyser in terms of analytical functionality and quality management.
- The maintenance and quality controls is comparable to that of the Siemens and Radiometer devices and not equivalent to that of the applicant.

The Roche device is therefore an imperfect substitute to the applicant's device as its purpose is to be a laboratory device for blood gas analysis rather than a point-of-care used device with a data management system aimed at assisting health-care decisions.

ECONOMIC FEASIBILITY

Same as for the other alternatives – the existing devices of the applicants would need to be written off by European health care providers if this device was used to substitute the GEM series analyser.

Based on an installed base of [redacted] devices and the type of contracts customers are using (purchasing vs. renting), it is estimated the capital write off for EEA customers would be more than € [redacted], as detailed in the SEA.

Furthermore there are one-off training costs equal to more than € [redacted] ([redacted] times € [redacted]; see Table 2 in the SEA for details).

REDUCTION OF OVERALL RISK DUE TO TRANSITION TO THE ALTERNATIVE

As the applicant's use avoids emissions of OPE there is no difference in risk between the two alternatives. Whilst the use of OPE may be avoided due to the possible bio-hazard of the samples and the other chemicals used in the process, the waste treatment is identical. As OPE does not present a risk to the operator the outcome is therefore the same: no emission of OPE to the environment.

AVAILABILITY

The applicant concedes that Roche would be able to service the applicant's market. However this could certainly not be done immediately as the number of devices to be substituted is very large.

CONCLUSION ON SUITABILITY AND AVAILABILITY FOR ALTERNATIVE 3

The applicant concludes that the alternative is technically imperfect, would bring considerable societal costs and bring no benefits in terms of risk or hazard. Therefore the alternative is deemed to be unsuitable.

OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES FOR USE 1

The applicant concludes that there are no substitutes available at this time for its device in the market. Furthermore the applicant cannot implement a substitute surfactant before the sunset date due to the constraints outlined below in the substitution strategy.

SUBSTITUTION EFFORTS TAKEN BY THE APPLICANT IF AN AUTHORISATION IS GRANTED

The applicant is a manufacturer of acute care diagnostic tools. The devices are the GEM family of blood gas analyzers and are used for patient level analysis of blood samples. The

diagnostic processes for CO-Oximetry and associated intelligent quality management (iQM) processes, which are the core of the machines' function, are designed around the use of Triton-X100 (OPE) and its fluidic and optical interactions with patient blood and aqueous process control solutions. The use of an alternative lysing agent will require a redesign and reimplementation of iQM processes for CO-Oximetry.

The present plan outlines the steps that will result in the substitution.

FACTORS AFFECTING SUBSTITUTION

There are five main factors in the substitution of the surfactant in the process:

1) Finding an alternative surfactant;
2) Developing the software and algorithm changes required to adapt the devices to the new optical properties of the solutions being tested;
3) Internal verification, validation and introduction of manufacturing changes on production site;
4) Regulatory submissions and approval process;
5) New product launch;

FINDING AN ALTERNATIVE SURFACTANT

The use of Triton X-100 in the GEM Premier analyzers is currently critical to the performance of the CO-Oximetry system, providing results for:

- total hemoglobin,
- oxyhemoglobin,
- carboxyhemoglobin,
- methemoglobin,
- deoxy-hemoglobin,
- oxygen saturation,
- total bilirubin.

Triton X-100 is the surfactant used as a lysing agent to rupture the cell membranes of the red blood cells in a blood sample. The blood measurement algorithms of the GEM Premier analyzers require complete and fast lysis for accurate measurements and reporting results in 45 seconds to diagnose and treat critically ill patients. In order for the GEM Premier analyzers to continue to provide patient blood data with uncompromised reliability and accuracy, an alternate lysing agent must be:

1) Carefully selected and validated for use;
2) The alternative lysing agent must be capable of quickly lysing the blood cells (in 1-2 seconds, a capability not exhibited by all surfactants);
3) The alternative lysing agent must be capable of fully lysing red blood cells (a capability not exhibited by all surfactants);
4) Must not interfere with the intended optical measurements;
5) Must not interact with blood haemoglobin chemistry or chemistry of other analytic measurements;
6) Must exhibit a low degree of foaming;
7) Must meet established product claims for the GEM Premier analyzers over the claimed reagent shelf life (up to 9 months at room temperature) and use life (up to 31 days in the analyzer).

The applicant believes that a suitable candidate as alternative surfactant is commercially available. At this time there is no reason to believe that a new surfactant would have to be invented to meet the above criteria.

SOFTWARE AND ALGORITHM CHANGES

Data from the GEM Premier critical care analyzers are used daily in hospitals around the world to make life-saving decisions regarding patient health. It is imperative that these data have the highest possible reliability and accuracy. The GEM lysing solution is directly mixed with the sample prior to optical measurement. Triton X-100 interacts optically with the dyes in GEM Process Control Solutions, and analyzer functionality is optimized based on such interaction through algorithms. Its replacement will require major changes to the GEM algorithms through software update to the analyzer.

Whatever change is made to the lysing agent will have consequences for optical properties of the solution that is being analysed. The software and detection algorithms of the GEM analyser device must therefore be changed to reflect the new optical properties of lysing solution. Finding a suitable lysing agent is only a first step towards making it work inside the GEM analytical devices.

INTERNAL VALIDATION AND INTRODUCTION IN THE MANUFACTURING PROCESS

Once the alternative is found and the software/algorithms are re-optimized changes must be introduced in the manufacturing process. This will require modifications to the current process:

- Filling the reagent bags for the GEM analyzer devices;
- Set-up and manufacture of the new analytical devices;
- Training of the customer support, marketing and trainers for the devices (required if a device function were to change which will hopefully be avoided).

REGULATORY SUBMISSIONS AND PRODUCT LAUNCH

At this stage it is not yet possible to say with absolute certainty whether Regulatory review of the devices will be required by external authorities such as the FDA in the United States or notified body in the European Union.

Nevertheless the applicant believes that a regulatory review is very likely based on his experience implementing changes in the past. As any type of software change is usually subject to regulatory review and may require both clinical assessments and updated regulatory dossier submissions.

Once an alternate substance is identified, its impact on GEM calibration and patient sample measurement will be determined and reported to regulatory authorities. Their response and the level of additional tests required will impact the substitution period but the applicant is confident that barring surprises the requested review period will suffice under all realistic best case scenarios.

As has been outlined above a central part of the added value brought by the GEM analysers is the IQM. The IQM allows the device to autocorrect both internal faults of the device and of each tested sample. It will then automatically repair itself or adapt the result of the test to take into account the deviation that was noted or indicate an invalid test result. The present system was validated[8] by Professor James Westgard[9] the renowned quality control expert.

The system was designed based on large amount of historical data collected from a wide range of patient samples representing different clinical conditions. Data is globally collected to assist the operator in getting the best result from the test on the sample but also allow the machines to record monitor measurement variations, signal drifts, (micro) clot errors, etc…

The self-corrective mechanism runs a pattern recognition algorithm on any data from analyzers in operation allowing for the machines to correct all errors. Since this system is dependent on a large amount of patient data, modification of the surfactant may alter the functionality of the pattern recognition algorithms, and new patient data will be required to validate the functionality of iQM. There is no substitute for the development of this database than to run many machines for an extended period. As the substitution of the surfactant touches the core technology of the device (CO-Oximetry) the database needs to be substantially repopulated with data from machines operating with the alternative.

The collection of this patient data can be performed in partial parallel with the development of the substitute and its implementation. It may, however, cause some delays in implementation at set mile-stones in the process as the completeness of the patient dataset is validated.

8 Point of Care – vol. 2 no. 1 03/2003. Validation of IQM Active Process Control Technology, *Westgard, Fallon, Mansouri*.

9 https://james.westgard.com/about.html

UPDATING AND VALIDATING PRODUCTS IN THE MARKET

There is a large park of devices currently in use at European healthcare centres. These devices (which are often the property of the local healthcare centre) will need their software to be updated. This process cannot be implemented immediately.

LIST OF ACTIONS AND TIMETABLE WITH MILESTONES

The present milestones are estimated on a realistic best case scenario. The applicant is very certain with regards to the timelines for the first four milestones. The last two are (partially) dependent on external agencies and customer cooperation in the field. It is reasonable to presume that some slippage will occur in the time-frames of those steps.

MILESTONE 1: CHOICE OF ALTERNATE SUBSTANCE (Q4 2020)

This stage is already in progress – the deliverable will be an alternative substance that performs the technical functions and is compatible with the devices.

Table 3 Choice of alternate substance

Item	Category	Activity	Deliverable	Responsible	Notes
1	Feasibility	Compare available surfactants and identify potential substitutes	Technical Review	[redacted]	In Progress
2	Feasibility	Lysing functionality assessment of multiple alternatives	Technical Review	[redacted]	In Progress
3	Feasibility	Reagent shelf life risk assessment comparing multiple alternatives	Technical Review	[redacted]	n/a
4	Feasibility	Cartridge use-life/ EC sensor stability assessment comparing multiple alternatives	Technical Review	[redacted]	n/a

5	Feasibility	Dye/process control solution compatibility risk assessment comparing multiple alternatives	Technical Review	[redacted]	n/a
6	Feasibility	On-analyzer assessment of blood panel performance of multiple alternatives	Technical Review	[redacted]	n/a
7	Feasibility	Develop mitigations to address observed analytical risks	Technical Review	[redacted]	n/a
8	Feasibility	Down selection to final choice	Technical Review	[redacted]	n/a
9	Design Input	Update design inputs as necessary	Updated requirements (reagents, software [redacted] [redacted]	[redacted]	n/a

Expected Completion: Q4 2020

Resources Required:

- 2 FTE [redacted]
- 0.25 FTE [redacted]
- 0.5 FTE [redacted]
- 0.25 FTE [redacted]

MILESTONE 2: COMPLETE DESIGN AND DEVELOPMENT (Q4 2021)

This is a product development stage optimize the required technical changes and prepare the technical work to be done at production. These steps are described below.

Table 4 Complete Design and Development

Item	Category	Activity	Deliverable	Responsible	Notes
1	Planning	Plan the required activities for the design and process changes	Design and Development Plan	[redacted]	n/a
2	Planning	Periodically update and distribute the project schedule	Project Schedule	[redacted]	n/a
3	Design Output	Develop the manufacturing documentation	Updated Reagent Manufacturing Procedures Data Review/Report	[redacted]	n/a
4	Design Output	Develop the design documentation	Updated Software Functional Specifications Data Review/Report	[redacted]	n/a
5	Risk Management	Perform incremental risk management assessment, if required, per QMDD300001-04	Risk Review	[redacted]	n/a
6	Regulatory	Perform regulatory assessment across all notified bodies	Regulatory Plan	[redacted]	n/a
7	Design Review	Perform Design Reviews per QMDD20001-00 as required. The number of design reviews is TBD	Signed Designed Review Records	[redacted]	n/a

Expected Completion: Q4 2021

Resources Required:

- 1 FTE [redacted]
- 1 FTE [redacted]
- 0.5 FTE [redacted]
- 0.5 FTE [redacted]
- 0.25 FTE [redacted]
- 0.25 FTE [redacted]

MILESTONE 3: DESIGN TRANSFER TO MANUFACTURING (Q3 2022)

This stage is the first step towards manufacturing the new lysing bags.

Table 5 Design Transfer to Manufacturing

Item	Category	Activity	Deliverable	Responsible	Notes
1	Design Transfer	Manufacturing Process Qualification	Technical Review	[redacted]	n/a
2	Design Transfer	Production of a minimum of 3 pilot lots of lysing bags	Availability of pilot bags	[redacted]	n/a

Expected Completion: Q3 2022

Resources Required:

- 1 FTE [redacted]
- 0.25 FTE [redacted]

MILESTONE 4: COMPLETE DESIGN VERIFICATION AND VALIDATION (Q3 2024)

This stage finalises the internal verification and validation and completion of the design process implementation.

Table 6 Complete Design verification and validation

Item	Category	Activity	Deliverable	Responsible	Notes
1	Planning	Plan the required verification and validation activities	V&V Plan	[redacted]	Planning based on risk assessment and regulatory assessment
2	Design Verification	Execute design verification specified in the V&V plan	V&V Protocols and Reports	[redacted]	n/a
3	Design Validation	Execute design validation specified in the V&V plan	V&V Protocols and Reports	[redacted]	Up to 1.5 yr if clinical trials are required per regulatory assessment
Expected Completion: Q3 2024 Resources Required: • 1 FTE [redacted] • 1 FTE [redacted] • 0.25 FTE [redacted] • 0.5 FTE [redacted]					

MILESTONE 5: REGULATORY SUBMISSIONS AND PRODUCT LAUNCH (Q2 2025)

The product is at this moment verified and validated from an internal perspective but the approval of the regulatory authorities must be obtained. The timing for this is arbitrarily set at 9 months but could be much longer.

Table 7 Regulatory submissions and Product launch

Item	Category	Activity	Deliverable	Responsible	Notes
1	Regulatory Submissions	Prepare and submit applicable regulatory submissions	Completed regulatory submission	[redacted]	As applicable based on Regulatory Plan
2	Product Launch	Product Launch	Released Product	[redacted]	n/a
Expected Completion: Q2 2025 Resources Required: • 1 FTE [redacted] • 0.5 FTE [redacted] • 0.5 FTE [redacted] • 0.25 FTE [redacted]					

MILESTONE 6: UPGRADE LEGACY EQUIPMENT (Q4 2029)

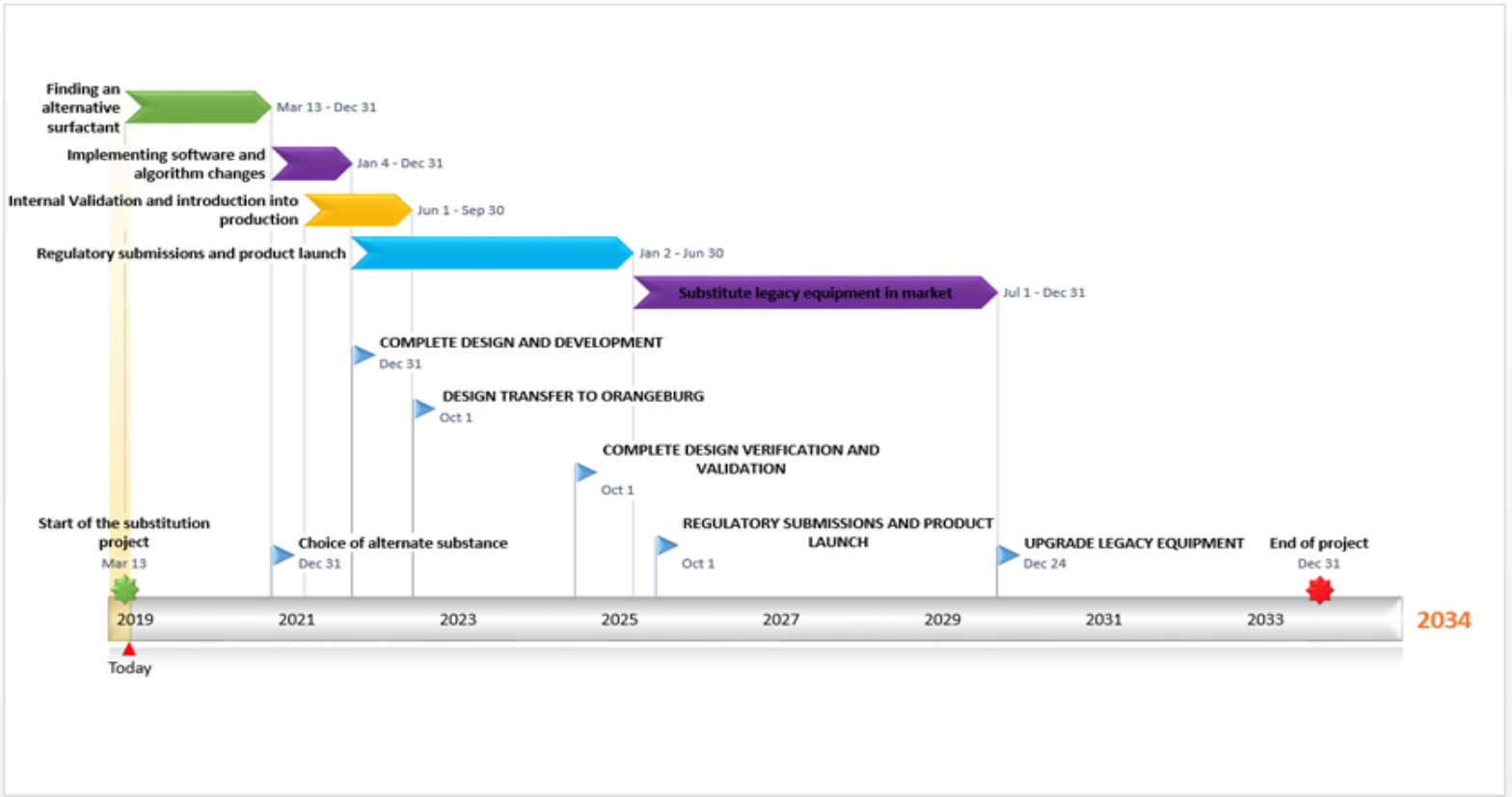
There are over [redacted] devices in the European market that need to be modified to use the new lysing bags. This requires an estimation of devices that need replacement (obsolescence) and those that can be upgraded either on the spot or at Instrumentation Laboratory sites.

These upgrades need to take place in agreement with the customer and therefore planned well ahead.

Table 8 Upgrade legacy equipment

Item	Category	Activity	Deliverable	Resources	Notes
1	Customer outreach	Inventory devices in market – triage for obsolescence, refit or upgrade	Client List with time line for substitution	[redacted]	n/a
2	Upgrades on site	Customer visit/Return and refit of equipment	Upgrade devices per customer	[redacted]	n/a
Expected Completion: Q4 2029 Resources Required: • 1 [redacted] • 3 [redacted] • 0.5 [redacted]					

SCHEMATIC OVERVIEW OF SUBSTITUTION



MONITORING OF THE IMPLEMENTATION OF THE SUBSTITUTION PLAN

Instrumentation Laboratory Company utilizes a robust quality management system that is certified to comply with the ISO 13485:2016 standard. In addition, the company operates using a sophisticated business system to manage the worldwide distribution and support of products. Both include established processes and tools to manage, deploy and monitor product updates for customer instruments in clinical use. This includes deployment and tracking of software updates and control of which products are distributed to which customers and instruments.

Instrumentation Laboratory is required by regulation to monitor and respond to customer complaints in a timely manner and take all appropriate actions to ensure safety and efficacy of our products including, when warranted, product removal from the field. All of these processes are documented in our Quality System, training to these procedures is provided to appropriate personnel and we are regularly audited for compliance to these regulations as part of our certification process.

The substitution plan can therefore be fitted within the regular design control process that Instrumentation Laboratory performs on a regular basis. The management and control structure is part and parcel of normal operation. Progress can be checked by enforcement authorities and internal accountability is laid down.

CONCLUSIONS OF THE SUBSTITUTION STRATEGY

The substitution process from start to finish will require 14 years. However as the process started in 2019 the actual review period required to complete the process is 10 years to complete the process. To prevent the need to apply for a review of authorisation 18 months ahead of the deadline it is proposed that 12 years be granted so that the success or failure of the substitution process can be established 18 months before the deadline for submitting a review report.

CONCLUSION

The applicant will substitute the substance.

ANNEX – JUSTIFICATIONS FOR CONFIDENTIALITY CLAIMS

Blanked out item reference	Page number	Justification for confidentiality
Blanks # 1 & 2	*17*	*The information regarding alternative surfactant being tested is a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 3-8	*29*	*The information regarding the number of devices sold and their value in the market are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 9-14	*33*	*The information regarding the number of devices sold and their value in the market are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 15-20	*35*	*The information regarding the number of devices sold and their value in the market are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 21-34 *Table 1*	*40-41*	*The information regarding the resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is*

		claimed confidential in line with Article 119 of the REACH Regulation.
Blanks # 35-48 *Table 2*	*42-43*	*The information regarding resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 49-52 *Table 3*	*43*	*The information regarding resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 53-56 *Table 4*	*44*	*The information regarding resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 58-65 *Table 5*	*45*	*The information regarding resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*
Blanks # 66	*46*	*The information regarding the number of devices sold are a business secret whose publication could harm the interests*

		of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.
Blanks # 67-74 *Table 6*	*46*	*The information regarding resources and departments involved in testing and implementing the alternative surfactant are a business secret whose publication could harm the interests of the applicant. The information is claimed confidential in line with Article 119 of the REACH Regulation.*