REQUEST FOR ADDITIONAL INFORMATION

Submission number:	NR546252-21
Legal name of applicant:	SEBIA
Submitted by:	SEBIA
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated
Uses:	Use-1, Use-2, Use-3

Contents

1. AIM & GOAL

The present document synthesises the Applicant's answers to the Socio-Economic Assessment Committee's request for additional information (communication number: AFA-C-2114476591-42-01/F) received on 2019/07/01.

2. REQUEST FOR ADDITIONAL INFORMATION

2.1. Question 1

2.1.1. Committees' question

> *In relation to use 1, the number of kits and techniques quoted in the text are 133 and 25 respectively. However, we understand from your newly provided spreadsheet that there are 142 different kits and 26 different techniques associated with use 1. Please clarify.*

2.1.2. Applicant's answer

Please find below the table displaying SEBIA's products concerned by Use-1 (from page 31-32):

HYDRAGEL® RANGES	NATURE OF THE SOLUTION	NUMBER OF SOLUTIONS REFERENCES INVOLVED	NUMBER OF KITS REFERENCES IMPACTED
HYDRAGEL® PROTEIN(E)	Dye	1 (ref. 56046)	7
	Strip buffer	1 (ref. 56187)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® HR	Dye	2 (ref. 56106 & 56046)	7
	Strip buffer	1 (ref. 56196)	
	Anti-serum diluent	1 (ref. 56222)	
	Coated support	1 (ref.56302)	
HYDRAGEL® PROTEINURIE	Dye	1 (ref. 56106)	2
	Coated support	1 (ref. 56302)	
HYDRAGEL® β1-β2	Dye	1 (ref. 56046)	4
	Strip buffer	1 (ref. 56218)	
	Coated support	1 (ref.56302)	
HYDRAGEL® LIPOPROTEIN	Strip buffer	1 (ref. 56184)	3
	Coated support	1 (ref. 56302)	
HYDRAGEL® LIPOPROTEIN (E)+LP(A)	Strip buffer	1 (ref. 56186)	4
	Coated support	1 (ref. 56302)	
HYDRAGEL® LDL/HDL CHOL. DIRECT	Strip buffer	1 (ref. 56028)	4
	Substrate solvent	1 (ref. 56056)	
	Coated support	1 (ref.56302)	
HYDRAGEL® IF PENTA	Dye	1 (ref. 56046)	8
	Colouring base	1 (ref. 56328)	
	Fixing solution	1 (ref. 56600)	
	Strip buffer	1 (ref. 56191)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® IF	Dye	2 (ref. 56046 & 56106)	18
	Colouring base	5 (ref. 56132, 56133, 56134, 56136, 56137)	
	Fixing solution	1 (ref. 56600)	
	Strip buffer	1 (ref. 56191)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® IF/BENCE JONES	Dye	1 (ref. 56106)	2
	Colouring base	5 (ref. 56135, 56136, 56137, 56138, 56139)	
	Fixing solution	1 (ref. 56600)	
	Strip buffer	1 (ref. 56232)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® BENCE JONES	Dye	1 (ref. 56106)	9
	Colouring base	5 (ref. 56135, 56136, 56137, 56138, 56139)	
	Strip buffer	1 (ref. 56191)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® OUCHTERLONY	Coated support	1 (ref. 56302)	1
HYDRAGEL® HEMOGLOBIN(E)	Dye	1 (ref. 56046)	3
	Strip buffer	1 (ref. 56194)	
	Coated support	1 (ref.56302)	
HYDRAGEL® ACID(E) HEMOGLOBIN(E)	Dye	1 (ref. 56046)	3
	Strip buffer	1 (ref. 56290)	
	Coated support	1 (ref.56302)	
HYDRAGEL® APO E IF	Anti-serum diluent	1 (ref. 56222)	2
	Coated support	1 (ref.56302)	
HYDRAGEL® IEP	Dye	2 (ref. 56046 & 56106)	3
	Coated support	1 (ref. 56302)	
HYDRAGEL® CSF	Strip buffer	1 (ref. 56232)	4
	Anti-serum diluent	1 (ref. 56239)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® CSF ISOFOCUSING	Anti-serum diluent	1 (ref. 56222)	2
	Coated support	1 (ref. 56302)	
HYDRAGEL® ISO-LDH	Strip buffer	1 (ref. 56240)	4
	Coated support	1 (ref. 56302)	
HYDRAGEL® ISO-PAL	Substrate solvent	1 (ref. 56040)	3
	Strip buffer	1 (ref. 56271)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® ISO-CK	Strip buffer	1 (ref. 56240)	-1 4
	Coated support	1 (ref. 56302)	
HYDRAGEL® A1AT ISOFOCUSING	Antiserum diluent	1 (ref. 56380)	2
	Coated support	1 (ref. 56302)	
HYDRAGEL® URINE PROFILE	Dye	1 (ref. 56106)	6
	Colouring base	2 (ref. 56140 & 54141)	
	Strip buffer	1 (ref. 56191)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® β2 TRANSFERRINE	Strip buffer	1 (ref. 56194)	1
	Anti-serum diluent	1 (ref. 56239)	
	Coated support	1 (ref. 56302)	
HYDRAGEL® VON WILLEBRAND	Anti-serum diluent	1 (ref. 56327)	-1 3
OTHER PRODUCTS SOLD SEPARATELY	Colouring base	10 (ref. 56132, 56133, 56134, 56135, 56136, 56137, 56138, 56139, 56142, 56328)	29 separate solutions & 4 solutions boxes
	Fixing solution	1 (ref. 56600)	
	Dye	2 (ref. 56046 & 56106)	

Table 5. SEBIA's products concerned by Use-1 (• *REXOR product*)

As for the number of kits, the rapporters are right, the number of kits were not properly inventoried for HYDRAGEL® ISO-CK (4 instead of 3) and HYDRAGEL® VON WILLEBRAND (3 instead of 1). This brings the total numbers of kits at 109+33 other products sold separately either **142 kits in total.**

Regarding the different techniques, the rapporters must only take into account the 25 first lines of the newly provided spreadsheet as the last row relates to the other products sold separately. **In total, 25 techniques are listed.**

2.2. Question 2

2.2.1. Committees' question

> *According to your answer to question 18, the overall functionality is the same for all kits but the requirements of functionality and performance are specific. You go on to say that you have at least 50 different functionalities and therefore 50 different substitution processes. Please clarify what kind of differences there are in functionalities within the use applied for and in what way this affects the substitution processes.*

2.2.2. Applicant's answer

There was a misunderstanding in the meaning of the functionalities. The main functionality of substance (inside one use) remains the same within all kits. However, depending on the kit and the molecule to be analysed, a specific balance needs to be scrupulously respected in every single component of the kit so the kit can be effective.

The electrophoretic separation of the proteins of interest is based on the migration of these proteins, by the application of an electric field according to their electric charge density and / or their molecular weight (kDa).

The various techniques listed in the file allow to analyse different proteins of interest that all have different electrical charges/molecular weights. As a result, the migration media (the different reagents: gel, buffer, etc.) are all different according to the techniques and their physico-chemical balance (pH, ...) is adapted according to the charge density/molecular weight of the proteins to be analyzed.

Changing a parameter (replacing a chemical or changing concentration) will break the balance (fine and precise) of the migration medium. So, on the one hand, this precarious balance will be complicated to find and on the other hand, it is different for each technique so substitution work is absolutely not applicable from one technique to another in all SEBIA's products. This explains why the substitution process will differ:

- ***From a technology to another (capillary vs gel electrophoresis).***
- ***From a technique to another.*** For every technique within one functional requirement related to one use, it may exist different dissociative power or solubilization power.
  Other example, in a particular case such as that defined in usage 2 (lysis), in capillary technology, once the lysis has been obtained, the substitution product may impact the migration and the quality of the analyses carried out, differently according to the technique. Hence, the product to be used has to be carefully determined, technique by technique.
- ***From a kit to another (among a same technique).*** Example of the kits "standard mask" (MS) and "dynamic mask (MD) have different the Triton X-100 balance in their components.

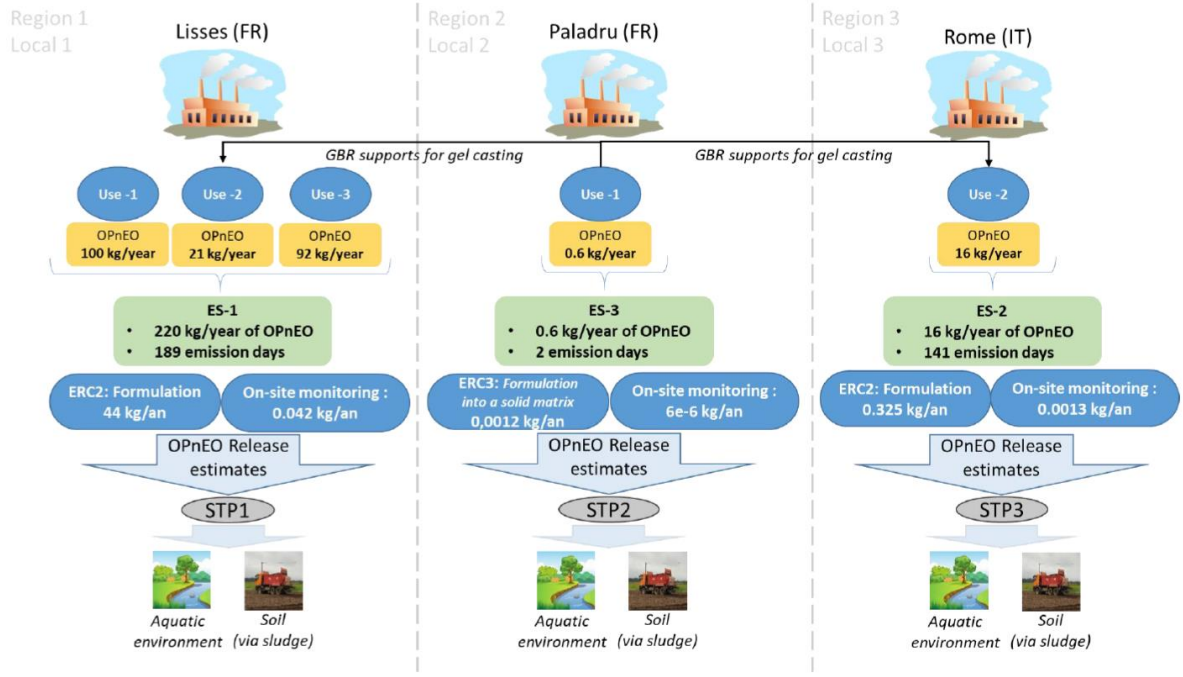
2.3. Question 3

2.3.1. Committees' question

> *In your answers to questions 20, 30 and 41, you say that the quantities of Triton TX-100 are expected to increase over time since a growth of 8% per year is expected. Later in the answer you state that there will be a decline. Please confirm whether the tonnages applied for are the maximum tonnages expected over the review periods applied for.*

2.3.2. Applicant's answer

Please find below the overview of the relationships between Uses/Exposure Scenarios/Sites.



In the site of Lisses (ES-1), a total maximum quantity of 220 kg of OPnEO per year is expected to be used during the review period for all uses.

In the site of Paladru (ES-3), a maximum quantity of 0.6 kg of OPnEO per year is expected to be used during the review period.

In the site of Rome (ES-2), a maximum quantity of 16 kg of OPnEO per year is expected to be used during the review period.

Hence, the applicant confirms that the total maximum amount applied for during the review period is 236.6 kg/year (any sites and uses combined).

2.4. Question 4

2.4.1. Committees' question

> *Your answer to question 21c-d are difficult to understand and you have not answered SEAC's question about what the processes in Table 20 mean in practice. Please explain clearly how you have derived at the conclusion that 9 years would be required for the industrialisation stage. Please outline any assumptions or calculations that this conclusion is based on.*

2.4.2. Applicant's answer

Please see below the mentioned Table 20 :

PHASES 5 : INDUSTRIALIZATION DESCRIPTION (IN WEEKS)							
PROCESS	PRELIMINARY STUDY	DEVELOPMENT	EQUIPMENT QUALIFICATION	PROCESS VALIDATION	SUMMARY	TOTAL TIME REQUIRED FOR EACH PROCESS	IMPACT LEVEL
Semi-automatic distribution	2	4	6	-	2	14	Minor impact
Bottling (small volumes)	2	4	12	-	2	20	Minor impact
Strips manufacturing	14	28-40	48	32	8	142	Minor impact
Solutions preparation	16	32-48	48	32	8	152	Minor impact
Fluid system for transfer from storage ranks room to process lines	2	4	6	-	2	14	Major impact - Qualification time proportional to equipment complexity
Bottling (larger volumes – 100, 250, 700 mL)	10	20-24	36	24	10	104	Variable impact regarding the line and thus the equipment complexity
Software bars manufacturing	8	16-20	40	24	6	88	Variable impact regarding the line and thus the equipment complexity
Gel casting in clean rooms	20	40-60	72	40	20	202	Major impact regarding the equipment complexity

Table 20. Industrialization processes, impacts and timeline

This table displays the estimated time required for the substitution process applied on industrial processes. The substitution process is divided in 5 steps which aim are detail below :

PRELIMINARY STUDY	Organization of the working group
	Risk analysis related to the replacement of Triton X-100 for each equipment or part of equipment related to the process
DEVELOPMENT	Study the substitution impact
	Set up of the equipment settings necessary for the shift of new formulas on process devices
	Definition of the new ranges of controls
EQUIPMENT QUALIFICATION	Drafting of qualification dossiers (Installation Qualification, Operational Qualification, Performance Qualification) for each process equipment taking into account the impact of the substitution on the equipment - new settings - new ranges of controls

PROCESS VALIDATION	Drafting of validation dossier (Installation Qualification, Operational Qualification, Performance Qualification) taking into account the qualification of equipments and workers
	Provide proof of the process's ability to reproducibly achieve the expected functional results
	Define the revalidation criteria of the modified process
SUMMARY	Review of risk analyzes
	Project report

Finally, a typo mistake has been made ; industrialisation stage would not take 9 years but 7 years. The total time required is the sum of the weeks need for each industrial parts, 736 weeks or 14 years. Considering that only 2 people are currently able to carry out the tests and draft the corresponding files, **7 years of continuous work** was approximated.

2.5. Question 5

2.5.1. Committees' question

> *According to your response to question 21f, the commercial deployment relates more to the registration process. At the same time, you have allocated 6 years to the registration process and four years to the commercial deployment stage (corrected in your answer to 4 from 5, as stated in the application). While part of these two stages run in parallel, it is not clear what all of these years are required for. Therefore, please explain clearly what activities are required in the following two stages and how much time those activities would need:*
>
> *a. Regulatory registration*
>
> *b. Commercial deployment*

2.5.2. Applicant's answer

a. Regulatory registration

The field of *in vitro* diagnostics, and health are very controlled and standardized fields. The marketing authorization of a finished product depends on the registration in the country of commercialization. At present, Sébia markets in 120 countries.

For the registration, countries require very specific files to validate the entry of a kit on their territory. Many tests have to be realized (replaceability, reproducibility, several on different batchs, ...) with results and documents to provide.

These records must provide the expected reliability of the product. The time required to perform these tests is important and some steps are incompressible such as, for example, the achievement of stability tests that last several months.

Once the validation data obtained by the R&D laboratories, the technical file and the CE marking file can be updated. This operation takes 3 months for a product range.

The regulation of in vitro diagnostic medical devices is different in each country.

Please refer to the excel file "Countries-Regulatory Affairs.xlsx" enclosed to get more about the time required for the registration. In this document, in the tab "Synthèse", are displayed realistic time required for the registration of each technique obtained from the technique following technique tabs where are calculated the time according to the countries of sales.

For each country, the files are constructed from the data in the technical file according to their requirements.

As an example, China has very high requirements. All validation studies must be done with several batches of reagents. Studies in Chinese hospitals are needed. The time indicated takes into account the time of a person in the Regulatory Affairs Department in France added to the time of a person in the Regulatory Affairs Department at the Shanghai Representative Office.

In order to be able to sell our products in the United States, we have to register them in the FDA, if the modification is major, a correlation study done in the United States is necessary. The presentation of the results of the studies and the submission file is very framed. The time indicated takes into account the time of a person in the Regulatory Affairs Department in France added to the time of a person in the Regulatory Affairs Department of the American subsidiary.

The time given takes into account the recording of each product line independently. It is possible that this time is slightly shortened in the countries where the registration is simple if we can group several ranges of products.

The time indicated is that of registrations according to the regulations in force today. It is likely that some regulations will increase their requirements in the future.

Today the Regulatory Affairs department is already at the maximum occupancy rate, for the moment it could not absorb such a workload.

The regulatory phase is forcing prior to the commercial deployment phase and the two phases cannot be performed at the same time.

Finally, this is not 74 years but 47 years calculated.

b. Commercial deployment

Commercial deployment is the validation of new commercial products at the customer's premises. This validation is carried out in France by SEBIA's application engineers. The time required for commercial deployment is difficult to be precisely estimated. The estimation was made from the around 1800 equipments sold in France (with a mean of 4 techniques per apparatus).

The average time required for a re-validation is estimated at 1 day for 4 techniques (realistic estimation taken from practice). **Hence, the commercial deployment only performed in France, would require 1800/221=8 years for 1FTE either 4 years for 2FTE.**

Knowing that the equipment sales in France represents around 10% of Sebia worldwide sales, 20 FTE would be required to cover all the commercial deployment.

2.5.3. Committees' question

> *You have not responded to question 42a in enough detail (the response is recorded under 42b). Please be more concrete in explaining why the different technologies require different timelines when you clarify why the activities outlined in Tables 19, 20 and 21 are different between the HYDRAGEL and CAPILLARYS ranges. One way of presenting this could be to add an extra column to the tables where the reasons for the differences (where relevant) are outlined.*

2.5.4. Applicant's answer

Tables 19, 20 and 21 are different between the HYDRAGEL and CAPILLARYS ranges as these ranges are based on different technologies.

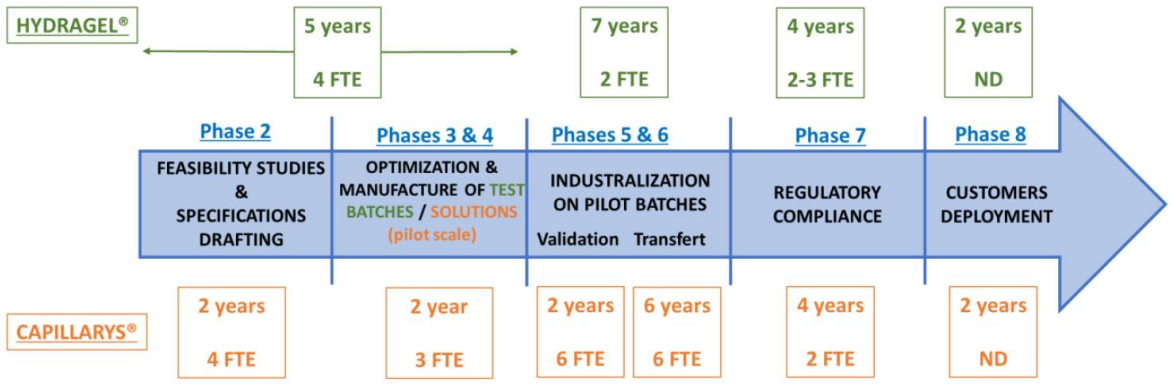
Electrophoresis allows the separation of molecules within biological samples. This separation is driven by electric field applied on the sample.

In gel electrophoresis (HYDRAGEL), the molecules to be separated are deposited on a gel support in contact with a buffer solution. Depending on the kit, Triton™ X-100 may intervene at several component (i.e. buffer or gel supports).

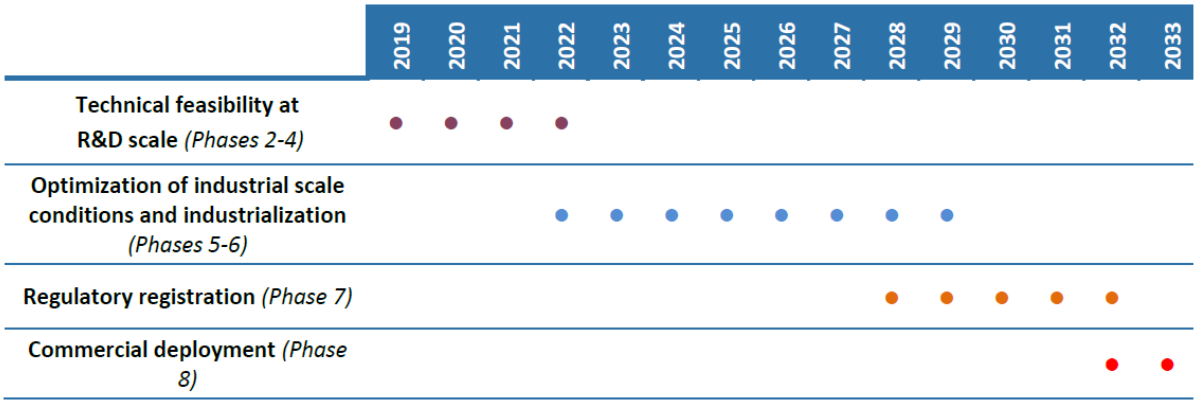
In capillary electrophoresis, the conducting buffer is contained within a capillary tube. Samples are injected into one end of the capillary tube. As the sample migrates through the capillary, its components separate and elute at different times.

Migration media in gel technology and in capillary technology have different physicochemical characteristics and are not identical. As a result, substitution searches cannot be enforced from one technology to another.

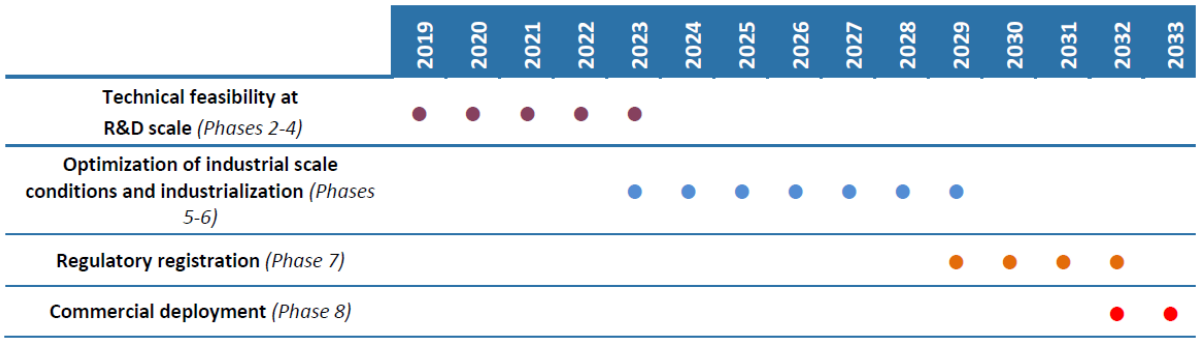
Although the functional and performance requirements of the Triton™ X-100 are the same within Use-3 in both technologies, technical substitution will be different between the HYDRAGEL and CAPILLARYS ranges. The estimated periods dedicated to each phase for HYDRAGEL® and CAPILLARYS® ranges are represented below:



18 years were estimated for the substitution of Triton™ X-100 for each technology. However, SEBIA provided a shortened timeline of 12 years for each of these CAPILLARYS® / MINICAP® and HYDRAGEL® products in order to replace as quickly as possible (please see the following timelines).



General substitution timeline for CAPILLARYS® / MINICAP® products concerned by Use-3



General substitution timeline for HYDRAGEL® products concerned by Use-3

The two technologies are totally different. Besides, for the capillary electrophoresis, the characteristic sought for the product to be substituted only affects Use-3 (among the 4 defined uses), lysis of red blood cells, so as to release the proteins of interest, namely hemoglobins. The characteristics sought in gel technology are more varied and cover all four defined uses. Thus, the properties required for the substitute product are very different between the two technologies, impacting the R&D approach of the process. **Consequently, an extra column to the tables where the reasons for the differences would be outlined seems not relevant to the applicant as the two technologies are totally different.**

2.6. Question 7

2.6.1. Committees' question

> *Based on the responses provided, SEAC understands that for each of the uses applied for, it would in theory be possible to substitute within 7 years if the additional required staff was hired to deal with the high number of kits simultaneously. To support your claim that 12 years is needed for uses 1-3, please estimate what the cost would be of undertaking the substitution in 7 years, rather than in 12 years (for which you have already estimated the costs in the application for authorisation). Please include any calculations that you undertake to derive the cost of substituting in 7 years.*

2.6.2. Applicant's answer

Please find below the tables summarizing the methodology applied for the estimation of the recruitment cost engaged if the substitution would be undertaken in 7 years, rather than in 12 years:

Use-1									
Review period		12				7			
	Average gross wage	$Time_{12year}$	$FTE_{12years}$	Recruitement cost (NV)	Recruitement cost (NPV)	$Time_{7years}$	FTE_{7years}	Recruitement cost (NV)	Recruitement cost (NPV)
R&D	58000	4,5	27	7 071 167,00 €	6 295 916,00 €	2,6	46,3	7 047 000,00 €	6 518 688,84 €
INDUSTRIALIZATION	58000	7	2	812 000,00 €	807 066,38 €	4,1	3,4	812 000,00 €	893 788,94 €
REGULATORY	45000	6	12,4	3 341 625,00 €	2 218 612,00 €	3,5	21,3	3 348 000,00 €	2 597 085,16 €
TOTAL				11 224 792,00 €	**9 321 594,38 €**			11 207 000,00 €	**10 009 562,94 €**

Use-2									
Review period		12				7			
	Average gross wage	$Time_{12year}$	$FTE_{12years}$	Recruitement cost (NV)	Recruitement cost (NPV)	$Time_{7years}$	FTE_{7years}	Recruitement cost (NV)	Recruitement cost (NPV)
R&D	58000	4,45	21	5 423 000,00 €	4 828 447,00 €	2,6	36,0	5 420 100,00 €	5 013 756,97 €
INDUSTRIALIZATION	58000	7	2,6	1 058 784,00 €	627 718,00 €	4,1	4,5	1 055 600,00 €	885 659,53 €
REGULATORY	45000	5	11,4	2 562 750,00 €	1 444 972,00 €	2,9	19,5	2 565 000,00 €	1 950 188,78 €
TOTAL				9 044 534,00 €	**6 901 137,00 €**			9 040 700,00 €	**7 849 605,28 €**

Use-3									
Review period		12				7			
	Average gross wage	$Time_{12year}$	$FTE_{12years}$	Recruitement cost (NV)	Recruitement cost (NPV)	$Time_{7years}$	FTE_{7years}	Recruitement cost (NV)	Recruitement cost (NPV)
R&D	58000	4,35	11	2 777 958,00 €	2 473 395,09 €	2,5	18,9	2 775 300,00 €	2 567 236,71 €
INDUSTRIALIZATION	58000	7,5	14,6	6 354 412,00 €	4 225 956,29 €	4,4	25,0	6 351 000,00 €	5 228 092,39 €
REGULATORY	45000	4	4,7	837 375,00 €	342 238,95 €	2,3	8,1	846 000,00 €	643 220,16 €
TOTAL				9 969 745,00 €	**7 041 590,33 €**			9 972 300,00 €	**8 438 549,26 €**

$Time_{7years}$ is the period of activity strictly dedicated to a substitution step (e.g. R&D). This period was basically calculated with a proportionality relationship from the **$Time_{12years}$**, the **12 years** review period and the **7 years** review period.

N.B: $Time_{12years}$ related to the industrialization in the Use-1 table has been updated from 9 to 7 years for more consistency with question 4.

FTE_{7years} is the additional FTE to be recruited along **$Time_{7years}$**. This value was obtained with the following relationship:

$$FTE_{7years} = \frac{Time_{12years}}{Time_{7years}} \times FTE_{12years}$$

The recruitment cost (nominal value) over 7 years was obtained by with:

$$\sum (FTE_{7years} \times Time_{7years} \times Average\ gross\ wage)$$

Finally, the recruitment cost as Net Present Value was obtained by applying the discounting rate over the recruitment periods dedicated to each step. These table can be found in the enclosed excel file named "**Recruitment cost over 7 years versus 12 years.xlsx**".

Recruitment costs (already significant over 12 years, and even more over 7 years) have a significant impact on operating costs and lower revenues and profits - lower profitability of the company: less income to pay off debt and pay shareholders. This cost will weigh on the applicant's profitability and be a major impediment to the pursuit of objectives growth.

It may also be argued that the company is made up of 580 employees, half of whom are in France. And that the recruitment of 107 FTE over 12 years is already huge (in percentage) compared to the payroll of the company.

If the company reports over 7 years, it will generate an even bigger increase in payroll. In addition to the high cost of recruitment, the increase in operating costs, the difficulty of managing a significant

increase in the payroll, Sebia will have to expand its premises. This is another very important cost that will be added because technically adapted premises (lab, ...) are needed which amounts to several tens of millions of euros. **In conclusion, Sebia will not be able to absorb the recruitment cost within only 7 years.**

2.7. Question 8

2.7.1. Committees' question

> *For each of the uses applied for, please provide a public range of the average profit losses for one year (rather than the whole review period applied for).*

2.7.2. Applicant's answer

In the first answers session, the applicant provided an estimation of lost of profits based on the average of profit between 2015 to 2018. The applicant understands from the question asked that SEAC is more interested on forecasted annual range of the profits lost during the review period. Please find below the table gathering the requested information.

Profits	Average on 2015-2018	Range estimated for 2022
Use-1	[redacted]	[60-70 M]
Use-2	[redacted]	[60-70 M]
Use-3	[redacted]	[20-30 M]

This is of course just an estimation based on 8% annual growth, taking into account 4% discounting rate and assuming no change in the market trends during the review period.

2.8. Question 9

2.8.1. Committees' question

> *Regarding your agreement with the French Government which designates SEBIA as a strategic firm, please provide details of when this agreement came into force and is there a time at which this contract expires/must be renewed? Any other supporting information that would clarify this relationship would be helpful.*

2.8.2. Applicant's answer

Such an agreement was existing with the previous shareholders of SEBIA and to allow the change of control in February 2018 the new shareholders had to sign a new agreement with the French government. There is no expiring period. This agreement's purpose is to ensure that the Company's assets, technology and employees are remaining located in France. Finally, it is a strictly confidential agreement that can only be communicated with the approval of the Ministry of Finance and the

shareholders. A request for approval can be done for this agreement proof, however, this document could not be obtained in such short term and without guarantee of acceptance.