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 3
2. REQUEST FOR ADDITIONAL INFORMATION 3

General question for all uses applied for by SEBIA: 3

2.1. Question 13 3
2.2. Question 14 3
2.3. Question 15 4
2.4. Question 16 4

Specific questions related to use 1: 5

2.5. Question 17 5
2.6. Question 18 5
2.7. Question 19 6
2.8. Question 20 7
2.9. Question 21 9
2.10. Question 22 10
2.11. Question 23 11
2.12. Question 24 12
2.13. Question 25 12

Specific questions related to use 2: 14

2.14. Question 26 14
2.15. Question 27 14
2.16. Question 28 14
2.17. Question 29 15
2.18. Question 30 16
2.19. Question 31 17
2.20. Question 32 18
2.21. Question 33 19
2.22. Question 34 20
2.1. Question 35 20
2.1. Question 36 21

Specific questions related to use 3: 22

2.2. Question 37 22
2.3. Question 38 22
2.4. Question 39 22
2.5. Question 40 23
2.6. Question 41 24
2.7. Question 42 24
2.8. Question 43 26
2.9. Question 44 26
2.10. Question 45 27
2.11. Question 46 27

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-2114473062-56-01/F) received on 2019/05/24.

2. REQUEST FOR ADDITIONAL INFORMATION

General question for all uses applied for by SEBIA:

2.1. Question 13

2.1.1. Committees' question

> *Please clarify the relationship between all the uses applied for. In particular, please provide:*
>
> *a. An illustration or table presenting which kits are covered by which use(s).*
>
> *b. The number of kits produced for each use and at which site*
>
> *c. A clarification of whether the different uses depend on each other (apart from the fact that they all have an economic importance for SEBIA). E.g. would the kits covered under each of the uses typically be used on their own or would some of them be used as a pre-step to the kits covered under one of the other uses?*
>
> *d. The market share occupied by each range*

2.1.2. Applicant's answer

Please refer to the attached excel file named "Techniques and kits.xlsx".

2.2. Question 14

2.2.1. Committees' question

> *Please clarify whether there is any difference between the terms assays, tests and kits?*

2.2.2. Applicant's answer

The kit is the consumable-reactive pack that allows the realization of the tests / assays (synonyms) on the automates.

2.3. Question 15

2.3.1. Committees' question

> *The applicant mentions the use of 2 discount rates. However, only the rate of 4% is quoted. Please clarify if another discount rate is used in the analysis, to what exactly is it applied and what the rate is. (E.g. page 40 of Use 1).*

2.3.2. Applicant's answer

In section 2.7.2.1. It is stated that two distinct discount rates are used: one used to consider economic impacts and another related to human health costs. As the 4-tert-OPnEO is classified under REACh due to Endocrine disrupting properties for the environment, the discount rate related to human health costs is thus not applicable. Hence only one discount rate was considerated.

2.4. Question 16

2.4.1. Committees' question

> *Please clarify the relationship that is in place with the French Ministry of Finance? Does the applicant receive tax incentives or subsidies as part of this agreement?*

2.4.2. Applicant's answer

As SEBIA is a French Group with contractual relations with public hospitals (including military hospitals), it has been classified as strategic by the French State and as such financial investors have been forced to make commitments not to relocate the company. activity and continuity of supply contracts.

Specific questions related to use 1:

2.5. Question 17

2.5.1. Committees' question

> *On p.8, the products covered under use 1 are said to cover around 30% of the applicant's global turnover. On p.77, the products are said to represent around 35% of the global turnover. On p.86, the use is said to represent 40% of the company's income. Please clarify what share of the applicant's turnover the products covered under use 1 represent.*

2.5.2. Applicant's answer

The kits covered by Use-1 represent 40 % of SEBIA's turnover.

2.6. Question 18

2.6.1. Committees' question

> *Please provide more information about the diversity of the 133 kits covered by the use applied for. In particular, please clarify:*
>
> *a. whether the functional and performance requirements are the same for all 133 kits and their solutions?*
>
> *b. whether the substitution process would be the same for all 133 kits and their solutions. For example, would the implementation of an alternative in any of them require the same validation and regulatory registration phases?*

2.6.2. Applicant's answer

a. The title of this use has been written in the simplest possible way but it is actually very complex because it concerns several types of components and intervenes at several stages of the test.

   This partly explains that the functional and performance requirements are multiple for the 133 kits.

   So yes, it can be said that the use and overall functionality is the same but the requirements of functionality and performance are specific, at least from one technique to another and sometimes within the same technique.

   In addition, each technique corresponds to several years of development (in order to develop the analysis of the parameters corresponding to this technique).

   Then, each technique is declined in different kits (procedure and automaton different, n analysis possible different ...).

   In each kit, there is one or more components that contain the ONPEs.

For some components, the ONPE only corresponds to one use, for others to several uses.

Hence the fact that we find several uses in the same kit.

Within the same technique, the functional and performance requirements are globally the same.

But there may be specificities when within the same technique, the kits have differences in procedure (eg standard mask / dynamic mask, amido / purple dye ...) or are available on several machines.

So no, the functional and performance requirements are not the same we have at least 50 different functionalities and therefore 50 different substitution processes.

For validation and registration, it's a little similar because validation tests will be based on specificities (and these are the tests that take the most time).

In addition, most kits have several uses, it will be necessary to ensure that the substitute works for each use separately and also combined. The products provided by SEBIA, meet specific requirements of high technical science. Substitution processes and solutions will have to meet the same requirements.

b. The time required for the validation and regulatory process may differ from a kit to another. Indeed, as mentioned p71: “the regulation of in vitro diagnostic medical devices varies with countries. For each country, the files are constructed from the data in the technical file according to their requirements. As a result, the time required for the regulatory procedure can dramatically vary from one country to another.”

2.7. Question 19

2.7.1. Committees’ question

> *Please clarify whether you do aim to try to substitute within 12 years if an authorisation is granted. This remains unclear since the substitution is said to represent a significant cost also under the 12-year review period applied for but yet you say that you would pursue the substitution process described in section 4.2 if the authorisation is granted.*

2.7.2. Applicant’s answer

SEBIA do intend to substitute. The comments about the substitution cost were aimed to emphase the fact that only a long review period would allow SEBIA to absorb the costs.

2.8. Question 20

2.8.1. Committees' question

> *Related to the above, could you please clarify why the consumption of Triton TX-100 is expected to decrease from 2021 onwards "by engaging in substitution" (p.48)? You have stated that it would take at least 12 years to substitute so it is unclear why consumption would start going down from 2021 onwards.*
>
> *Also, please clarify whether the expected growth would be within the current range of solutions or whether the applicant foresees that the use applied for would cover also the development of new solutions.*

2.8.2. Applicant's answer

The quantities used will increase over time since a growth of 8% per year is expected.

However, some alternative processes without Triton will be implemented shortly (i.e. the washing process sponges). These processes, have not been taken into account in the current AfA.

Moreover, some references that contain Triton for that sales are low will surely be stopped in the coming years because their substitution would be too expensive.

These two reasons explain the decline of the consumption of Triton even though the overall trend is to growth.

2.9. Question 21

2.9.1. Committees' question

The substitution plan outlined on pages 66-74 has several inconsistencies and there are certain issues that need clarification. Specifically:

a. Tables 17-19 outline the phases to be carried out on "each HYDRAGEL® technique, individually". However, it is not explained what a "technique" refers to and there seems to be different meanings of this terms used throughout the document. Based on the assumptions outlined in Table 21, more than 40 different techniques appear to be covered by the use applied for so it can also not refer to the individual kits or product ranges. Please provide an explanation of what these different techniques are.

b. On p.73 it is stated that 27 FTEs will have to be recruited for the phase of R&D and technical feasibility. But Table 21 on the previous page states that 3 FTEs are to be recruited for R&D. Could you please clarify?

c. The industrialization stage (9 years on this table) is very long and it is not clear how it is connected to the figures from tables 19 and 20. Could you explain more on this?

d. It is difficult to understand the timelines and justifications provided in Table 20. While the total weeks in the table add up to 736 (~14 years), the accompanying text refers to 534 weeks (~10 years). And yet, you conclude that with 2 FTEs, nine years would be required. Please clarify how this has been estimated in further detail. Furthermore, please clarify what the eight processes in Table 20 mean in practice and what the durations are based on (e.g. are they in line with similar substitution efforts previously undertaken?).

e. Table 21 states that 4 years would be required for commercial deployment while Table 22 states that five years would be required. Which one is correct?

f. Could you elaborate more why up to five years is needed for commercial deployment, having in mind that SDS and labelling preparation per product is not extremely time consuming, and it can be done in parallel for different products?

g. The purpose of Table 21 is unclear and some of the calculations do not seem to add up (e.g. 74 years for regulatory compliance). However, we understand this table to be more of an illustrative example of how long the substitution could take without time pressure and that the timeline in Table 22 is the timeline that should be used as the basis for the evaluation. Could you please confirm this?

h. The additional recruitment costs seems to be expressed as the nominal value. Please provide the cost estimation of additional recruitment costs expressed as NPV. Also, please clarify whether the average annual gross wage is the average wage paid by the industry sector or the average wage paid by the applicant.

2.9.2. Applicant's answer

a. Usage 1 has 133 kits spread over 25 different techniques. Terms range refer to HYDRAGEL or CAPILLARIS. Many techniques exist among gel electrophoresis (Immuno-electrophoresis, Immunofixation, Isoelectric focusing). Some of them were introduced in section 2.3.1. Those are the techniques mentioned in the use, knowing that one technique can incorporate several kits. Please refer to "Technique and kits.xlsx.

b. According to table 21, with 3 FTE, 122 years would be required. The 27 FTE relates to the same worked performed with 12 years (the review period requested).

c. There is no direct correlation between the assumption of 9 years required for the industrialization stage and the figures tables 19 and 20. Tables 19 and 20 aim to estimate the time required for the process whereas the 9 years relate to continuous work with an uncompressible and maximum

number of 18 major and 9 minor equipment employed simultaneously, justifying a first R&D work carried out on 9 kits in parallel.

d. The correct duration is 736 weeks (~14 years). The value of the last line has been forgotten in the total time required for each process table 20. The durations mentioned here represent project durations but SEBIA do not has the resources to conduct all these projects in parallel. Only 2 FTE are currently able to carry out the tests and to carry out the corresponding files. This means that only 2 MAJOR equipment or 4 MINOR equipment can be made in parallel. We have in first approach 14 MAJOR equipment and 9 MINOR equipment: an approximation of 9 years of continuous work.

e. A dot were unintentionally added in Table 22. 4 years are actually required.

f. According to the applicant, the commercial deployment relates more to the registration process which could last up to 5 years depending on the country the registration is requested for. For exemple, this process takes at least 5 years in China.

g. The reviewers are right. The applicant confirms that the timeline displayed Table 22 should only been taken into account for the evaluation.

h. Indeed, the additional recruitment costs were expressed as the nominal values. Please see in the following table, the additional recruitment costs as NPV.

R&D	*6,295,916 €*
INDUSTRIALIZATION	*808,721 €*
REGULATORY COMPLIANCE/REGISTRATION	*2,218,612 €*

The total cost is 9,323,249 €. These figures were calculated under the assumption that the costs are the same over the years. Besides, the average annual gross wage is the average wage paid by the applicant.

2.10. Question 22

2.10.1. Committees' question

> *In the section on environmental impacts of continued use, you state that measurements in the lower Rhône have shown an average annual flow of nonylphenols and para-tert-octylphenols of 197,135 grams per year and 12,621 grams per year. Do you mean ~197.1 kg and ~12.6 kg or ~197.1 g and ~12.6 g?*

2.10.2. Applicant's answer

The applicant meant ~197.1 kg and ~12.6 kg.

2.11. Question 23

2.11.1. Committees' question

> *The economic impacts are based on revenue losses over 12 years. However, revenue is not a good indicator for benefits to society as it does not take into account saved costs when operations cease. Could you therefore please provide information on the expected profit losses for this use instead? A public range of the average profit in previous years would be enough.*
>
> *Relatedly, it would be good to anticipate the market consequences of a non-authorisation — you state that "SEBIA offers its products and services in the context of competitive bidding" yet you don't think competitors would be in a position to supply the market in the short or medium term in case of a non-authorisation. Please clarify whether there would be direct competitors who produce similar products without using the SVHC and, if so, where would they be based? Could they be expected to supply the market before the end of the review period applied for? In that case, profit loss to the applicant would be partially compensated by gains to the competitors and this should be discussed as well.*

2.11.2. Applicant's answer

The Group reached an average Profit Before Tax at [0-10%] of its sales for the period 2015-2018.

The variable costs are mainly made of raw material costs, transport costs and a limited part of the overheads due to the highly centralized structure of the Group. Therefore, it is estimated that the non-authorization would leave about 78% of the total costs before taxation (obviously 100% of the depreciations and interests).

Impact related to Use 1: the average loss of profit would be [10-100M€] (based on the previous years).

This would inevitably put SEBIA in a huge loss-making position and would force the Group to a massive restructuring of its activities. It would also force SEBIA to try to renegotiate its financial debt in already a difficult context of highly leveraged financial structure.

A sales or a profit approach are coming to the same conclusion that a non-authorization would lead SEBIA to bankruptcy.

It is important to remind that SEBIA's instruments are running only on SEBIA's reagents and no competitor can replace these reagents with their current range of products. The only way to supply the customers would be to replace all SEBIA's instruments by other instruments which is almost impossible to do in a short or medium term due to the number of instruments having to be produced and installed as well as the quantities of reagents to be produced.

2.12. Question 24

2.12.1. Committees' question

> *While the application contains useful background information on the major diseases that can be diagnosed by the applicant's kits, the medical impacts which could specifically be anticipated from the non-use scenario are not discussed in much detail. In particular:*
>
> *a. The AoA/SEA states that approximately 84 million patients' samples could have been tested with kits concerned by this use. However, it is unclear what time period this refers to. Please clarify how many patients are expected to be tested by kits concerned by this use per year.*
>
> *b. Are there alternatives for the end product, i.e. diagnosis tools that are not based on gel electrophoresis? If so, please describe what that means for the impact on patients.*

2.12.2. Applicant's answer

a. The 84 million patients mentioned is based on the survey performed for 2017. So about 80 million patients are expected to be tested by kits concerned by this use per year.

b. Most of the technologies for IVD are based on gel electrophoresis using 4-tert-OPnEO.

2.13. Question 25

2.13.1. Committees' question

> *The presented non-use scenario is the cease of manufacturing of HYDRAGEL kits and the economic impacts are based on the lost revenues for those kits solely. However, in the presentation of social impacts (p.86), it is stated that the non-use scenario would actually be closure of the whole company. The unemployment impacts are presented for the shut-down of the whole company, rather than for the staff directly concerned by the HYDRAGEL kits. Can you give a justification for this inconsistency between the economic and social impacts?*

2.13.2. Applicant's answer

The whole activity of SEBIA rely on the 4-tert-OPnEO. Every single kit relates to several Uses of the AfA. If one authorization for one Use is not granted, this could impact not only the employees directly related to 4-tert-OPnEO but all the company. Besides, the company operates with an LBO system. Part of the company is owned by shareholders and the other part is financed by bank. To repay this debt, the company must maintain its turnover at a level, at least equivalent to the CA announced in the file, and at best with a constant growth rate. It is obvious that with a loss of 40% turnover (turnover related to all the reagents containing ONPE and which does not take into account the turnover related to the sale of the automates), the financial income necessary for the reimbursement of the debt would be insufficient. The non-repayment of his debt would lead the company to bankruptcy.

Specific questions related to use 2:

2.14. Question 26

2.14.1. Committees' question

> *The use of 4-tert-OPnEO by INTERLAB only covers the gel buffers included in the gel electrophoresis kits. Is 4-tert-OPnEO not used in the other solutions and buffers (i.e. those products covered by use 1 for SEBIA) included in the gel electrophoresis kits of INTERLAB? If not, what alternative do they use and could SEBIA use the same?*

2.14.2. Applicant's answer

No. 4-tert-OPnEO is the solutions and buffers included in the gel electrophoresis kits of INTERLAB.

2.15. Question 27

2.15.1. Committees' question

> *On p.32 the electrophoresis kits concerned by use 2 are said to account for around 65% of the total gel electrophoresis range manufactured by SEBIA and INTERLAB. On p.78, they are said to represent 75% of the gel ranges concerned. Please clarify what this difference refers to. Please also clarify what share of the applicant's turnover the kits covered by use 2 represent.*

2.15.2. Applicant's answer

The kits covered by the Use-2 represent 40 % of SEBIA's turnover.

2.16. Question 28

2.16.1. Committees' question

> *Please provide more information about the diversity of the 102 kits covered by the use applied for. In particular, please clarify:*
>
> *a. whether the functional and performance requirements are the same for all 102 kits and their solutions?*
>
> *b. whether the substitution process would be the same for all 102 kits and their solutions. For example, would the implementation of an alternative in any of them require the same validation and regulatory registration phases?*

2.16.2. Applicant's answer

a. The title of this use has been written in the simplest possible way but it is actually very complex because it concerns several types of components and intervenes at several stages of the test. This partly explains that the functional and performance requirements are multiple for the 102 kits. So yes, it can be said that the use and overall functionality is the same but the requirements of functionality and performance are specific, at least from one technique to another and sometimes within the same technique. The products provided by SEBIA, meet specific requirements of high technical science. Substitution processes and solutions will have to meet the same requirements.

b. The time required for these steps may differ from a kit to another. Indeed, as mentioned p71: "the regulation of in vitro diagnostic medical devices varies with countries. For each country, the files are constructed from the data in the technical file according to their requirements. As a result, the time required for the regulatory procedure can dramatically vary from one country to another."

2.17. Question 29

2.17.1. Committees' question

> *Please clarify whether you do aim to try to substitute within 12 years if an authorisation is granted. This remains unclear since the substitution is said to represent a significant cost also under the 12-year review period applied for but yet you say that you would pursue the substitution process described in section 4.2.2 if the authorisation is granted.*

2.17.2. Applicant's answer

SEBIA do intend to substitute. The comments about the substitution cost were aimed to emphase the fact that only a long review period would allow SEBIA to absorb the costs.

2.18. Question 30

2.18.1. Committees' question

> *Related to the above, could you please clarify why the consumption of Triton TX-100 and Triton X-405 is expected to decrease from 2021 onwards "by engaging in substitution" (p.46)? You have stated that it would take at least 12 years to substitute so it is unclear why consumption would start going down from 2021 onwards. Also, please clarify whether the expected growth would be within the current range of solutions or whether the applicant foresees that the use applied for would cover also the development of new solutions.*
>
> *Finally, it seems that the expected consumption may exceed the tonnage applied for in 2022 (even if only very slightly). Please note that the tonnage applied for (for this use 37kg) would be the maximum tonnage allowed under the authorisation, if granted.*

2.18.2. Applicant's answer

The quantities used will increase over time since a growth of 8% per year is expected.

Some alternative processes without Triton will be implemented shortly (i.e. the washing process sponges). These processes, have not been taken into account in the current AfA.

Moreover, some references that contain Triton for that sales are low will surely be stopped in the coming years because their substitution would be too expensive.

These two reasons explain the decline of the consumption of Triton even though the overall trend is to growth.

According to the CSR the quantity applied for is 37 kg (21 kg for SEBIA and 16 for Interlab). The significant figures should have been taken into account in the SEA.

The quantities used will increase over time since a growth of 8% per year is expected.

2.19. Question 31

2.19.1. Committees' question

The substitution plan outlined on pages 66-75 has several inconsistencies and there are certain issues that need clarification. Specifically:

a. Tables 21-23 outline the phases to be carried out on "each HYDRAGEL® technique, individually". However, it is not explained what a "technique" refers to and there seems to be different meanings of this terms used throughout the document. Based on Table 25, the use covers "around 25 different techniques", which means that the term can also not refer to the individual product ranges. Please provide an explanation of what these different techniques are. Also, since the substitution plan is done on the basis of techniques, please explain why the exact number of techniques is not given (rather than saying "around 25").

b. On p.73 it is stated that 21 FTEs will have to be recruited for the phase of R&D and technical feasibility. But Table 21 on the previous page states that 3 FTEs are to be recruited for R&D. Could you please clarify?

c. It is difficult to understand the processes, timelines and justifications provided in Table 24. While the total weeks in the table add up to 736 (~14 years), the accompanying text refers to 534 weeks (~10 years). And yet, you conclude that with 2 FTEs, seven years would be required. Please clarify how this has been estimated in further detail. Furthermore, please clarify what the eight processes in Table 24 mean in practice and what the durations are based on (e.g. are they in line with similar substitution efforts previously undertaken?).

d. The purpose of Table 25 is unclear and some of the calculations do not seem to add up (e.g. 74 years for regulatory compliance). However, we understand this table to be more of an illustrative example of how long the substitution could take without time pressure and that the timeline in Table 26 is the timeline that should be used as the basis for the evaluation. Could you please confirm this?

e. The industrialization and commercial deployment stages seem really long, having in mind that the process for different products could at least partially run in parallel. Tables 23-26 are not consistent and create confusion (as in use-1). Further explanation in needed.

f. The additional recruitment costs seems to be expressed as the nominal value. Please provide the cost estimation of additional recruitment costs expressed as NPV.

2.19.2. Applicant's answer

a. Terms range refer to HYDRAGEL or CAPILLARIS. Many techniques exist among gel electrophoresis (Immuno-electrophoresis, Immunofixation, Isoelectric focusing). Some of

them were introduced in section 2.3.1. Those are the techniques mentioned in the use, knowing that one technique can incorporate several kits. Please refer to "Technique and kits.xlsx.

b. According to table 21, with 3 FTE, 122 years would be required. The 21 FTE relates to the same worked performed with 12 years (the review period requested).

c. The correct duration is 736 weeks (~14 years). The value of the last line has been forgotten in the total time required for each process table 20. The durations mentioned here represent project durations but SEBIA do not has the resources to conduct all these projects in parallel. Only 2 FTE are currently able to carry out the tests and to carry out the corresponding files. This means that only 2 MAJOR equipment or 4 MINOR equipment can be made in parallel. We have in first approach 14 MAJOR equipment and 9 MINOR equipment: an approximation of 9 years of continuous work.

d. The reviewers are right. The applicant confirms that the timeline displayed Table 26 should only been taken into account for the evaluation.

e. Table 26 should only been taken into account.

f. Indeed, the additional recruitment costs were expressed as the nominal values. Please see in the following table, the additional recruitment costs as NPV.

R&D	4,828,447 €
INDUSTRIALIZATION	627,718 €
REGULATORY COMPLIANCE/REGISTRATION	1,444,972 €

The total cost is 6,901,137 €. These figures were calculated under the assumption that the costs are the same over the years. Besides, the average annual gross wage is the average wage paid by the applicant.

2.20. Question 32

2.20.1. Committees' question

> *The economic impacts are based on revenue losses over 12 years. However, revenue is not a good indicator for benefits to society as it does not take into account saved costs when operations cease. Could you therefore please provide information on the expected profit losses for this use instead? A public range of the average profit in previous years would be enough.*
>
> *Relatedly, it would be good to anticipate the market consequences of a non-authorisation — you state that "SEBIA offers its products and services in the context of competitive bidding" yet you don't think competitors would be in a position to supply the market in the short or medium term in case of a non-authorisation. Please clarify whether there would be direct competitors who produce similar products without using the SVHC and, if so, where would they be based? Could they be expected to supply the market before the end of the review period applied for? In that case, profit loss to the applicant would be partially compensated by gains to the competitors and this should be discussed as well.*

2.20.2. Applicant's answer

The Group reached an average Profit Before Tax at [0-10%] of its sales for the period 2015-2018.

The variable costs are mainly made of raw material costs, transport costs and a limited part of the overheads due to the highly centralized structure of the Group. Therefore, it is estimated that the non-authorization would leave about 78% of the total costs before taxation (obviously 100% of the depreciations and interests).

Impact related to Use 2: the average loss of profit would be [10-100mn€] (based on the previous years).

This would inevitably put SEBIA in a huge loss making position and would force the Group to a massive restructuring of its activities. It would also force SEBIA to try to renegotiate its financial debt in already a difficult context of highly leveraged financial structure.

A sales or a profit approach are coming to the same conclusion that a non-authorization would lead SEBIA to bankruptcy.

It is important to remind that SEBIA's instruments are running only on SEBIA's reagents and no competitor can replace these reagents with their current range of products. The only way to supply the customers would be to replace all SEBIA's instruments by other instruments which is almost impossible to do in a short or medium term due to the number of instruments having to be produced and installed as well as the quantities of reagents to be produced.

2.21. Question 33

2.21.1. Committees' question

> *While the application contains useful background information on the major diseases that can be diagnosed by the applicant's kits, the medical impacts which could specifically be anticipated from the non-use scenario are not discussed in much detail. In particular:*
>
> *a. The AoA/SEA states that approximately 41.7 million patients' samples could have been tested with kits concerned by this use. However, it is unclear what time period this refers to. Please clarify how many patients are expected to be tested by kits concerned by this use per year.*
>
> *b. Are there alternatives for the end product, i.e. diagnosis tools that are not based on gel electrophoresis? If so, please describe what that means for the impact on patients.*

2.21.2. Applicant's answer

a. The 41.7 million patients mentioned is based on the survey performed for 2017. So about 42 million patients are expected to be tested by kits concerned by this use per year.

b. Most of the technologies for IVD are based on gel electrophoresis using 4-tert-OPnEO.

2.22. Question 34

2.22.1. Committees' question

> *Why are there references to 133 kits in the spreadsheet for use 2 as only 102 kits are involved? Also the use of comma in figures quoted is not correct, e.g. the time taken between 102 and 133 kits.*

2.22.2. Applicant's answer

The reviewers are right. Typo mistakes have been made. 102 kits are involved.

2.1. Question 35

2.1.1. Committees' question

> *The number of man-hours concerned by "Use-3" is mentioned in the spreadsheet. This table is only for Interlab. There is no table detailing how you reach the number of 19.3 – please provide this.*

2.1.2. Applicant's answer

Typo mistakes have been made. The Use concerned in the spreadsheet is Use-2. Futhermore, 19.3 means nothing. 137 jobs are potentially impacted as explained in the spreadsheet.

2.1. Question 36

2.1.1. Committees' question

> *There is no table for nominal value of revenue loss for Interlab in the spreadsheet. Is the assumption that Interlab will also grow at 8% - Table 29 shows that this hasn't been the case.*

2.1.2. Applicant's answer

The spreadsheet integrates a tab this calculation for Interlab. It as been assumed that Interlab annual growth follows the 8% of SEBIA annual growth.

Specific questions related to use 3:

2.2. Question 37

2.2.1. Committees' question

> *Please clarify what the differences in end-uses are between capillary and gel electrophoresis. From pp. 28-30, we understand that there are some differences in terms of performance, ease and speed between the CAPILLARYS and the HYDRAGEL ranges. However, it is not clear whether they are used for the diagnosis of different diseases or whether they can be used for the same purposes.*

2.2.2. Applicant's answer

CAPILLARYS although more efficient is a less mature technology than HYDRAGEL in terms of diagnosed diseases. HYDRAGEL covers a lot more diagnosis.

2.3. Question 38

2.3.1. Committees' question

> *Please clarify what share of SEBIA's turnover and what share of INTERLAB's turnover the kits covered by use 3 represent.*

2.3.2. Applicant's answer

The share of SEBIA's turnover covered by Use-3 is 32 %.

The share of Interlab's turnover covered by Use-3 is 48 %.

2.4. Question 39

2.4.1. Committees' question

> *Please provide more information about the diversity of the 19 HYDRAGEL and 9 CAPILLARYS kits covered by the use applied for. In particular, please clarify:*
>
> *a. whether the functional and performance requirements are the same for all 28 kits and their solutions?*
>
> *b. whether the substitution process would be the same for all HYDRAGEL kits and their solutions, as well as for all CAPILLARYS kits and their solutions. For example, would the implementation of an alternative in any of them require the same validation and regulatory registration phases?*

2.4.2. Applicant's answer

a. The functional and performance requirements of the Triton™ X-100 in the 19 HYDRAGEL and 9 CAPILLARYS kits covered is the same. It can be said that the use and overall functionality is the same but the requirements of functionality and performance are specific, at least from one technique to another and sometimes within the same technique. In addition, each technique corresponds to several years of development (in order to develop the analysis of the parameters corresponding to this technique). Then, each technique is declined in different kits (procedure and automaton different, n analysis possible different ...). In each kit, there is one or more components that contain the ONPEs. For some components, the ONPE only corresponds to one use, for others to several uses. Hence the fact that we find several uses in the same kit. Within the same technique, the functional and performance requirements are globally the same.

   But there may be specificities when within the same technique, the kits have differences in procedure or are available on several machines.

   In addition, most kits have several uses, it will be necessary to ensure that the substitute works for each use separately and also combined.

b. Indeed, the implementation of an alternative in any of them would require the same validation and regulatory registration phases.

2.5. Question 40

2.5.1. Committees' question

> *Please clarify whether you do aim to try to substitute within 12 years if an authorisation is granted. This remains unclear since the substitution is said to represent a significant cost also under the 12-year review period applied for but yet you say that you would pursue the substitution process described in section 4.2 if the authorisation is granted.*

2.5.2. Applicant's answer

SEBIA do intend to substitute. The comments about the substitution cost were aimed to emphase the fact that only a long review period would allow SEBIA to absorb the costs.

2.6. Question 41

2.6.1. Committees' question

> *Related to the above, could you please clarify why the consumption of Triton TX-100 is expected to decrease from 2021 onwards "by engaging in substitution" (p.46)? You have stated that it would take at least 12 years to substitute so it is unclear why consumption would start going down from 2021 onwards. Also, please clarify whether the expected growth would be within the current range of solutions or whether the applicant foresees that the use applied for would cover also the development of new solutions.*

2.6.2. Applicant's answer

The quantities used will increase over time since a growth of 8% per year is expected.

However, some alternative processes without Triton will be implemented shortly (i.e. the washing process sponges). These processes, have not been taken into account in the current AfA.

Moreover, some references that contain Triton for that sales are low will surely be stopped in the coming years because their substitution would be too expensive.

These two reasons explain the decline of the consumption of Triton even though the overall trend is to growth.

2.7. Question 42

2.7.1. Committees' question

> *In relation to the substitution plan outlined on pages 67-75:*
>
> *a. Please 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.*
>
> *b. For the HYDRAGEL ranges, the assumptions regarding the timelines have been explained as part of the other uses applied for and we hope that our questions on those uses will help to clarify any open issues for those ranges. However, for CAPILLARYS, it is unclear how the timeline and FTE requirements outlined in Figure 33 have been derived. Please explain this in further detail. Also, please explain how much time would at a minimum be needed for the substitution for one CAPILLARYS kit or technique (whichever is more relevant).*
>
> *c. Similarly to the other uses, the plan refers to the number of different "techniques" without having explained what these techniques are. According to p.72, this use covers 19 different techniques and according to p.75, 9 of these techniques are associated with the CAPILLARYS range. Please provide an explanation of what these different techniques are.*
>
> *d. The additional recruitment costs seems to be expressed as the nominal value. Please provide the cost estimation of additional recruitment costs expressed as NPV.*

2.7.2. Applicant's answer

a. The quantities used will increase over time since a growth of 8% per year is expected.However, some alternative processes without Triton will be implemented shortly (i.e. the washing process sponges). These processes, have not been taken into account in the current AfA. Moreover, some references that contain Triton for that sales are low will surely be stopped in the coming years because their substitution would be too expensive.

   These two reasons explain the decline of the consumption of Triton even though the overall trend is to growth.

b. As explained before, HYDRAGEL and CAPILLARYS ranges as these ranges are based on different technologies. This implies that the technical substitution process will not be the same explaining the derivation of the timeline and FTE requirements outlined in Figure 33. SEBIA, estimated that 18 years would be required for the substitution in the CAPILLARYS range. However SEBIA aware that a special effort will have to be provided, and this, in order to replace as quickly as possible, has built a shortened timeline of 12 years for CAPILLARYS / MINICAP (Table 22).

c. Usage 2 has 90 kits spread over 26 different techniques. Terms range refer to HYDRAGEL or CAPILLARIS. Many techniques exist among gel electrophoresis (Immuno-electrophoresis, Immunofixation, Isoelectric focusing). Some of them were introduced in section 2.3.1. Those are the techniques mentioned in the use, knowing that one technique can incorporate several kits. Please refer to "Technique and kits.xlsx".

d. Indeed, the additional recruitment costs were expressed as the nominal values. Please see in the following table, the additional recruitment costs as NPV.

R&D	2,473,395 €
INDUSTRIALIZATION	4,225,956 €
REGULATORY COMPLIANCE/REGISTRATION	342,239 €

The total cost is 7,041,590 €. These figures were calculated under the assumption that the costs are the same over the years. Besides, the average annual gross wage is the average wage paid by the applicant.

2.8. Question 43

2.8.1. Committees' question

> *The industrialization stage seem long, having in mind that the process for different products could at least partially run in parallel. Please describe in more detail why this time is needed.*

2.8.2. Applicant's answer

The timelines displayed Tables 22 and 23 should only been taken into account for the assessment.

2.9. Question 44

2.9.1. Committees' question

> *The economic impacts are based on revenue losses over 12 years. However, revenue is not a good indicator for benefits to society as it does not take into account saved costs when operations cease. Could you therefore please provide information on the expected profit losses for this use instead? A public range of the average profit in previous years would be enough. Relatedly, it would be good to anticipate the market consequences of a non-authorisation — you state that "SEBIA offers its products and services in the context of competitive bidding" yet you don't think competitors would be in a position to supply the market in the short or medium term in case of a non-authorisation. Please clarify whether there would be direct competitors who produce similar products without using the SVHC and, if so, where would they be based? Could they be expected to supply the market before the end of the review period applied for? In that case, profit loss to the applicant would be partially compensated by gains to the competitors and this should be discussed as well.*

2.9.2. Applicant's answer

The Group reached an average Profit Before Tax at [0-10%] of its sales for the period 2015-2018.

The variable costs are mainly made of raw material costs, transport costs and a limited part of the overheads due to the highly centralized structure of the Group. Therefore, it is estimated that the non-authorization would leave about 78% of the total costs before taxation (obviously 100% of the depreciations and interests).

Impact related to Use 3: the average loss of profit would be [10-100M €] (based on the previous years).

This would inevitably put SEBIA in a huge loss making position and would force the Group to a massive restructuring of its activities. It would also force SEBIA to try to renegotiate its financial debt in already a difficult context of highly leveraged financial structure.

A sales or a profit approach are coming to the same conclusion that a non-authorization would lead SEBIA to bankruptcy.

It is important to remind that SEBIA's instruments are running only on SEBIA's reagents and no competitor can replace these reagents with their current range of products. The only way to supply the customers would be to replace all SEBIA's instruments by other instruments which is almost impossible to do in a short or medium term due to the number of instruments having to be produced and installed as well as the quantities of reagents to be produced.

2.10. Question 45

2.10.1. Committees' question

> *While the application contains useful background information on the major diseases that can be diagnosed by the applicant's kits, the medical impacts which could specifically be anticipated from the non-use scenario are not discussed in much detail. In particular:*
>
> *a. The AoA/SEA states that approximately 65.9 million patients' samples could have been tested with kits concerned by this use. However, it is unclear what time period this refers to. Please clarify how many patients are expected to be tested by kits concerned by this use per year.*
>
> *b. Are there alternatives for the end product, i.e. diagnosis tools that are not based on gel and capillary electrophoresis? If so, please describe what that means for the impact on patients.*

2.10.2. Applicant's answer

a. The 65.9 million patients mentioned is based on the survey performed for 2017. So about 66 million patients are expected to be tested by kits concerned by this use per year.

b. Most of the technologies for IVD based on electrophoresis are using 4-tert-OPnEO.

2.11. Question 46

2.11.1. Committees' question

> *There are references to man-hours of use 2 in spreadsheet for use 3. Please clarify if the heading is incorrect and the numbers are correct.*

2.11.2. Applicant's answer

Indeed, the heading is incorrect and the numbers are correct.