Functional Analysis to Drive Research and Identify Regulation Requirements: An Example with a Lithium Monitoring Device

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Abstract: Medical device development is often understood as a linear process with design stages occurring sequentially. First stages are usually performed in order to specify the future device definition through interviews/meetings of the end-users, researchers and manufacturers. Because the medical device is original, these first stages mainly involve end-users and researcher. However, regulation constraints and economic reality sometimes makes manufacturers hesitant to base the industrial development on this initial basis. Functional analysis, well known by manufacturers, is a method used to accurately define the final functions of a medical device. In this conference, we estimate that the functional analysis can be put to profit in a more efficient way if researchers and end-users get familiar with it prior to the interview/meeting stages. Although the results of such knowledge democratisation is not demonstrated here, we present the function analysis conducted on a lithium monitoring device according to this multidisciplinary approach. We also show that function analysis can be used not only to drive research actions but also to identify regulation requirements.

1 INTRODUCTION

Research and development actions in technologies for health are usually driven by discussions and experience exchanges between practitioners, researchers and industrial partners. Because the need to be addressed involves innovations that have never been studied before, first discussions are often led by practitioners and researchers with an academic point of view. However, in the case of medical devices developments, the main goal is neither to increase knowledge nor to invent new technologies. The goal is to answer the need as quickly as possible while

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proposing a new medical device which not only addresses the need but also meets the manufacturer interests and end-users wishes.

User driven medical device development is now widely applied in different collaborative formats likes Living Labs (Korman, 2016) or Hacking Health organizations (Chowdhury, 2012). These approaches have been more or less conceptualized a while ago. In a well-organized and well-documented paper (Money, 2011), it is recall that user-centred usability engineering methods have already been proposed to improve the Medical Device Design and Development (MDDD) (Gosbee, 2002). Money and co-workers describe the MDDD using 4 main development stages, each of them involving distinct actions. They can be summarized as follows. **Stage 1** identifies the user's need and involves enquiries and interviews, both dealing with contextual and usability issues. This forms the basis for the initial concept which is further defined during **stage 2** which uses reduced focus groups deepening the initial concept ideas. This produces requirements documents leading to **stage 3**, fully oriented to the device manufacturing. The device can then be evaluated during **stage 4** in order to check whether or not the users' requirements are satisfied. We assume that prototyping actions are present between stages 2 and 3 or completely included in stage 3.

In (Money, 2011), what manufacturers think of the user-driven approach is analysed through interviews. Instead of trying to rewrite their conclusion, we simply reproduce the main points they report. "*The findings reveal that despite standards agencies and academic literature offering strong support for the employment formal methods, manufacturers are still hesitant due to a range of factors including: perceived barriers to obtaining ethical approval; the speed at which such activity may be carried out; the belief that there is no need given the 'all-knowing' nature of senior health care staff and clinical champions; a belief that effective results are achievable by consulting a minimal number of champions. Furthermore, less senior health care practitioners and patients were rarely seen as being able to provide valuable input into the process*".

More generally, what is mentioned above also applies to researchers who often misunderstand both the manufacturer economic constraints and patients/practitioners possibilities. Indeed, some technical or scientific solutions can be incompatible with a practical use or they can lead to an over-expensive device. In these 2 cases other and more realistic solutions must be explored, otherwise, conditions to be safe, efficient and to match with the local regulation will be difficult.

Indeed, since the very beginning of the MDDD, discussions between end-users, researchers and manufacturers must be somehow oriented/guided towards realistic solutions. For this a conceptual tool must be employed and this tool should ideally be known (even partially) by all the stakeholders.

Functional analysis is a technology design tool already well known by manufacturers but very rarely by researchers and the reduced number of end-users interviewed during the above mentioned stage 2. We believe that functional analysis should be pedagogically presented to end-users and researchers prior to any enquiry. This pedagogical effort should be clearly codified to allow beginners quickly understanding main issues of this method and how it can be used to drive the research and development actions and to identify the corresponding regulation issues. In this way interviews conducted to set-up the initial prototype design can be focused on functional analysis key points and the "expert" users can be efficiently involved in stage 3 of the MDDD. At the end, we think that what was called "end-users' wishes" at the beginning of this introduction will become "end-users' highlights", that researchers will directly focus on realistically translatable solutions and that manufacturers will be less hesitant to these data into account.

In this conference, we do not present a retrospective study on how this pedagogic effort is put to profit to enhance MDDD, but we describe the functional analysis which has been conducted in the frame of the H2020 R-LiNK project (grant agreement n°754907) according to this multidisciplinary concept. The goal is to present how this analysis accounts for end-users' requirements, how it drives the research actions to be privileged and how it allows identifying regulation requirements. In the next section, we rapidly presents the main goals of the R-LiNK project. The functional analysis is described in section 3. A short discussion is then proposed in section 4 before some conclusive remarks are given.

2 THE R-LiNK PROJECT

The consortium of this European project led by Pr. Franck Bellivier (INSERM UMR-S1144) is composed of 22 European partners including research institutes, hospitals, clinical investigation centers and companies.

The main objective of R-LiNK is to identify the eligibility criteria for treatment with lithium in bipolar

disorder type 1 (BD1) patients in terms of response, safety and tolerability. Research actions conducted to find lithium response biomarkers involve multidisciplinary research fields like "omics" investigations, blood analyses, nuclear magnetic resonance imaging and activity assessment. The functional analysis presented in this paper is related to treatment adherence as explained below.

2.1 Origin of the Project

Bipolar disorders (BD) are prevalent mental disorders and a leading cause of suicide. Bipolar disorders are lifelong lasting, with an episodic course of the illness in most cases. Mood stabilizers are the mainstay of treatment of BD and lithium is the gold standard (Sani, 2017).

Indeed, a substantial minority of individuals remain asymptomatic for years on lithium (about 20%) but most show only partial response and up to one third do not respond (Burgess, 2001). Furthermore, in current clinical practice, lithium exposure is poorly controlled using laboratory tests. First, it is usually verified only once or twice a year. Second, adherence to chronic treatment is known to be poor. Meanwhile, the prescription of lithium remains delicate. For the treatment to be effective, serum concentrations 10-14 h after the last dose taken must reach 0.5 to 1.0 mEq/L. If plasmatic concentration exceeds 1.2 mEq/L, toxic effects are likely to occur (Amdisen, 1967; Baldessarini, 2013; Bauer, 2016; Tondo, 2019).

Therefore, there is an important medical need to first, provide the patients/practitioners with a simple tool which could allow patients to become actor of her/his treatment, hence improving the adherence to treatment and second, to increase the frequency with which the lithium level can be assessed in a non-invasive manner. To this end, the device is intended to be used at home by patients, so it's a class C in vitro medical device, according the European regulation (EU 2017/746). The idea is not to replace laboratory lithium dosing techniques but to create a simple home-based lithium level indicator so that the patient can check if her/his lithium level is below, within or above the therapeutic window. A rapid analysis of the home-based usability possibilities led us to consider the detection of lithium in saliva. Also, because it will be used at home by patients or by non-specifically trained medical staff, the device must be carefully designed and a complete functional analysis must be performed.

3 FUNCTIONAL STATEMENT OF THE NEED

Functional specifications documents are well codified, even if different methodologies can be used to write them. They can be separated in three parts:

- need analysis
- functional analysis
- technical specification

Before and during constitution of functional specifications, studies are carried out to better understand the needs of potential customers.

3.1 Analysis of the Need

Analysis of the need is an essential phase because it dictates the direction of the future work. The needs and the objectives should be clearly identified and formalized.

To do this, different tools can be used; one of them is the APTE® method (see for example (APTE, no date)). This method starts from the expression of a need, without considering any technical solutions. It constitutes the first phase of design leading to the edition of the functional specifications. Three questions have to be considered.

- To whom is the "product" useful?
- What does the "product" acts on?
- What is the purpose of the "product"?

3.1.1 Expression and Characterization of the Need for R-LiNK Monitoring Device

In our project, the "product" is the monitoring device. To whom is the "product" useful? The R-LiNK monitoring device is useful to patients suffering from bipolar disorder and the medical staff. What does the "product" acts on? It acts on patients' saliva to assess lithium levels. What is the purpose of the "product"? It aims at improving treatment adherence and to avoid relapse by self-monitoring and self-management. Furthermore, it aims at minimizing (avoid if possible) the risk of lithium overdose. This is illustrated in figure 1.

This first expression of the need is of course essential but not sufficient. Indeed, the need will be correctly addressed only if the expected performances of the device are obtained. Therefore, the need has to be clearly characterized specifying qualification and quantification to estimate measurable quantities.

For the R-LiNK monitoring device, the need will be satisfied if the device allows lithium detection

between 0.5 and 4 mM, with 0.2 mM accuracy and improve treatment adherence, among others.

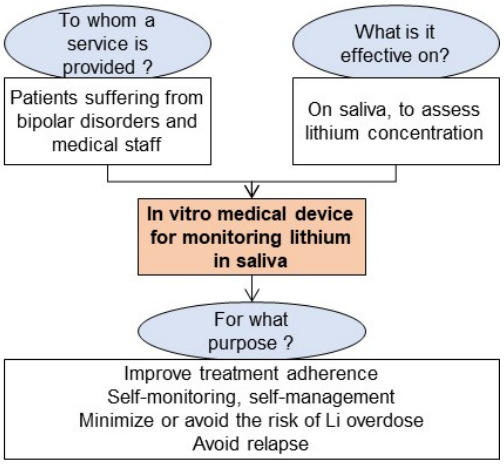

Figure 1: R-LiNK monitoring device: expression of the need.

3.1.2 Validation of the Need

Here, the questions to be answered are defined as follows. What is the origin of the need or why is the device wanted? What can change the need or even makes the need disappear?

The need of detecting lithium with a simple monitoring device comes from practitioner facing some clinical issues.

First, as described above, 30-55% of individuals selected for treatment with lithium will not have the predicted outcome. One possible cause to the non-efficacy of the treatment is the non-adherence to treatment. Second, lithium can be toxic and the therapeutic window is limited, between 0.5 and 1.2 mM in plasma with toxic effects above the maximum value.

These two issues will not disappear but technological or pharmaceutical developments may change clinical practices. One major evolution has been identified: emergence of new medicine for bipolar disorder leading to stopping the use of lithium therapy.

Taking these elements into account, it is therefore unlikely that the need for a new lithium monitoring device disappears completely.

3.2 Establishment of Service Functions and Constraints

Since the need has been validated, the functional analysis can continue and a list of functions can be established. First, it's important to better understand what a function is. Looking normative definition issued from the French Association for Standardization (AFNOR), a function is an action of a product or one of its constituents expressed exclusively in terms of purpose.

Therefore, it is required to disregard technological solutions. In order to help defining these functions, an interactions diagram of the device with its environment can be drawn. The diagram defines the limits of the device and specifies the life situation being studied. This is presented in figure 2. In this figure, bubbles represent the **physical elements** of the environment that have impact on the device. Lines characterize **functions** linking the system to its environment.

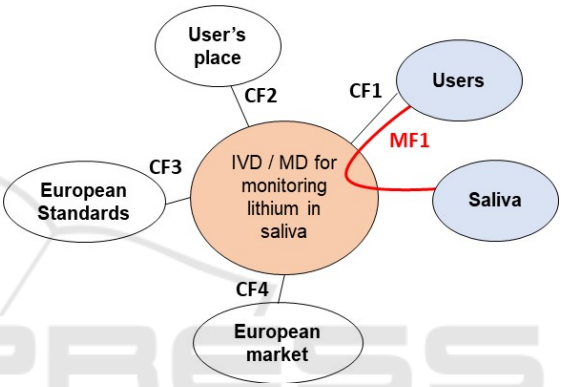

Figure 2: R-LiNK monitoring device interaction diagram for the "normal use" life situation.

Two types of functions exist: the main function and constraint functions. The main function reflects actions performed by the device, the constraint functions reflect an adaptation of the device to its environment. Therefore, the environment has to be defined for a specified life situation. In our R-LiNK example, the diagram represents the life situation "normal use".

Environment of the R-LiNK monitoring device consists of:

- users
- biological sample
- user's place
- European standards (IVD MD 2017/746)
- European market

Functions are defined as follows.

Main function:

- MF1: the device indicates the level of lithium in the biological sample.

Constraint functions:

- CF1: the device is suitable for all users
- CF2: the device is suitable for home use
- CF3: the device respects the regulations in force
- CF4: the device integrates the European market at a reasonable cost

Note that the market is not a physical element, but cost is really a constraint to take in account at the beginning of the development. That's why we chose to include this notion in our functional analysis of the need.

3.2.1 Justifications of Functions

To ensure the function is really necessary, it's possible to ask, as for the need: what is the purpose, the origin and the probability to disappear for each function?

For the R-LiNK device, the purpose of MF1 is to improve treatment adherence by self-monitoring and to minimize or avoid the risk of lithium overdose or under dosing. New medicine for bipolar disorder leading to the stopping lithium therapy can make the function disappear. Eliminating the function is unlikely. **The function is validated**.

The purpose of CF1 is to meet the expectations of user comfort whatever the patient's physical condition is because: the patient can use the product easily and quickly so they can monitor themselves without demotivation, the patient is looking for effective products that provide him with a certain comfort of use. Eliminating the function is unlikely. **The function is validated**.

The purpose of CF2 is to meet the expectations of user comfort whatever the place of use because patients have to regularly monitor themselves at home or at their place of holiday, during their work travels. Eliminating the function is unlikely. **The function is validated**.

The purpose of CF3 is to be able to commercialize the device and to assure the user that the product has been approved and that he can therefore use. The products sold must be certified by standards of quality and safety. Eliminating the function is unlikely. **The function is validated**.

The goal of CF4 is to enable the use of the device throughout the European Union at a reasonable cost because all patients are concerned and reimbursement rules are not identical for the entire European community. Eliminating the function is unlikely. **The function is validated.**

3.2.2 Functional Analysis and Usability

At this stage of the functional analysis, details can be provided to really meet the end-users' need. It is often made by brainstorming or interview with the various stakeholders. In our project, these investigations led to the conclusions given below.

- The device must measure lithium quickly (5 minutes if patients have to wait for results, more if the result is recorded).
- The device must to detect lithium in the therapeutic window (ideally 0.5 mM to 5 mM, with an accuracy of 0.2 mM in saliva).
- The device must be non-invasive (use of saliva instead of blood).
- The device has to deliver the results in an understandable manner.
- The device must be easy to use, compact and mobile.
- Finally, the device must be easily stored after use.

3.2.3 Characterization of Service Functions and Constraints

Based on all these indications, the functions are then defined with criteria, levels, and tests to be performed. This is summarized in table 1.

Note that in table 1, we inserted a column titled "flexibility". This estimates how negotiable can be the results expected in columns "criteria" and "levels". Flexibility is defined as follows:

- F0 means zero flexibility, imperative level
- F1 means low flexibility, little negotiable level
- F2 means good flexibility, negotiable level
- F3 means strong flexibility, very negotiable level.

After this functional analysis of the need, technological solutions can be envisaged. At this stage, it is essential to think about the solutions objectively and without restrictions. To do this, a Functional Analysis System Technique (FAST) is useful (FAST1, FAST2, FAST3, no date). Among other methods, the use of FAST allows a highly multidisciplinary consortium to speak the same language. Structured analysis and design technique, also termed SADT (Ross, 1985), may be used too, but we think it is more adapted when the technical solution is already chosen.

Table 1: Definition of the functions.

N°	Function	Criteria / standard	Levels	Flexibility	Tests
MF1	**Monitor the level of salivary lithium**	Indicate the level of lithium in saliva comprehensively for the patient	0,5 mM to 5 mM 100 µL saliva Without contamination Accuracy 0.2 mM	F1	Performance tests in the laboratory on artificial samples then on real calibrated samples. Tests in real conditions of use
CF1	**Suitable for all users**	The patient easily uses the device without errors	Pass the aptitude to use tests	F0	Formative and summative evaluation tests
CF2	**Suitable for home use**	The device works in the patient's environment: home, holidays	Pass the aptitude to use tests	F0	Formative and summative evaluation tests
CF3	**Respect the regulations in force**	Complies with the new European IVMD regulation (auto-monitoring)	UE 2017/746	F0	Respect the regulation in force
CF4	**Integrate the European market at a reasonable cost**	The cost is not a hindrance for the patient or the institutions	Consumable 10 € Cartridge reader 300 €	F1 F2	Estimated costs by item, including raw materials and an estimate of manufacturing costs

FAST allows, among other things, organizing and understanding relationship between functions. It helps identifying missing or redundant functions. All functions can be analyzed in the same way. The method consists in asking, for each of them: why do you do [Function], how do you do [Function] and when you do [Function] is there another function that occur together with or as a result of [Function]? This can be formalized using the codified diagram presented in figure 3.

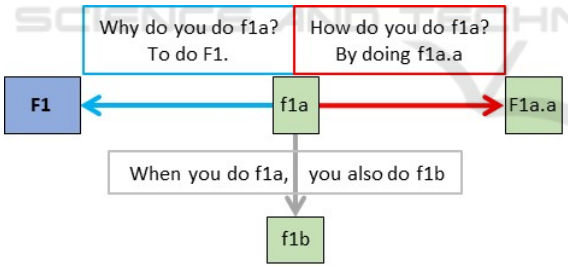

Figure 3: General principle for establishing a FAST diagram.

The FAST diagram corresponding to the device developed in the frame of the R-LiNK project is presented in figure 4. In this figure, the first column (on the left hand side) corresponds to functions. Identification of these functions should ideally take place during the stage 1 of the MDDD described in the introduction of this document. The identification of the items presented in the second columns should be made during stage 2. The third and fourth columns should be filled during the end of stage 2 or the beginning of stage 3 depending on where the prototyping actions are performed. The idea of this conference is not to go through each items depicted in figure 4. However, we shortly describe how the main function analysis lead to "usability" solutions. The MF1 function is analyzed as follows.

- In order to assess the lithium level in the biological sample it is necessary to put the saliva in contact with the sensor's reagents.
- For this, the user must be able to collect the saliva.
- In order to collect the saliva, different technical solutions can be used: use an existing saliva sampling device (Salivette® type) or spit in a recipient.

Here, we recall that the scientific or technological solutions are listed in column 4 but the final choice is not yet made. This is because, in the frame of our functional analysis, the goal is not yet to select the final solutions but to identify all of them as we already mentioned above while writing that we should disregards technological solutions.

Indeed, when the FAST diagram is finalized, practical work can start. This is the prototyping phase which should take place during stage 2 or 3 of the MDDD method already mentioned. Choice of the technical solutions or specialty areas where research efforts should be put can now be finalized in accordance with the end-users' "highlights" and regulation constraints. Because our device is intended to be used in the European community, the regulation documents listed in figure 4 correspond to a part a part of required standards to comply with the European Regulation.

4 A BIT OF DISCUSSION

We have seen that the functional analysis allows defining what a medical device should be in order to meet requirements of end-users, researchers and manufacturers in accordance with the regulation constraints. The FAST diagram summarizes these aspects. Including this diagram in the general MDDD plane proposed elsewhere, we understand that the functional analysis takes place at the beginning of the development, mainly during stages 1 and 2.

In order to be efficiently conducted, the functional analysis must involve all the stakeholders which includes not only manufacturers who already know this kind of analysis but also end-users and researchers. For this, a pedagogic effort must be made which is not in the scope of this conference.

However, if we only stick to this understanding, there is a risk that the functional analysis is considered as a background task which extends over the beginning of the MDDD process. The consequence could likely be that important information highlighted during the functional analysis are under-estimated during the prototyping phase, if not simply forgotten. It is therefore crucial that actors try to consider the development of a medical device not like a process linear in time but as a whole.

The linear perception of technological developments is nowadays probably due to the importance that the TRL scale has gained these last decades. This "Readiness Technology Level" scale was originally proposed by the NASA to improve technology developments. However, the NASA proposed a more general and less linear development model with the so-called CML scale, namely the "Concept Maturity Level" scale (Ziemer, 2013). Readers interested in this method can refer to (CML1, CML2, no date). The CML scale has recently been adapted to the medical device development (Béjean, 2019). The development is now not only described but also driven through 3 main dimensions: need, science and technology, programmatic.

We think that the functional analysis can efficiently be used to link the above mentioned 3-dimensional development descriptions.

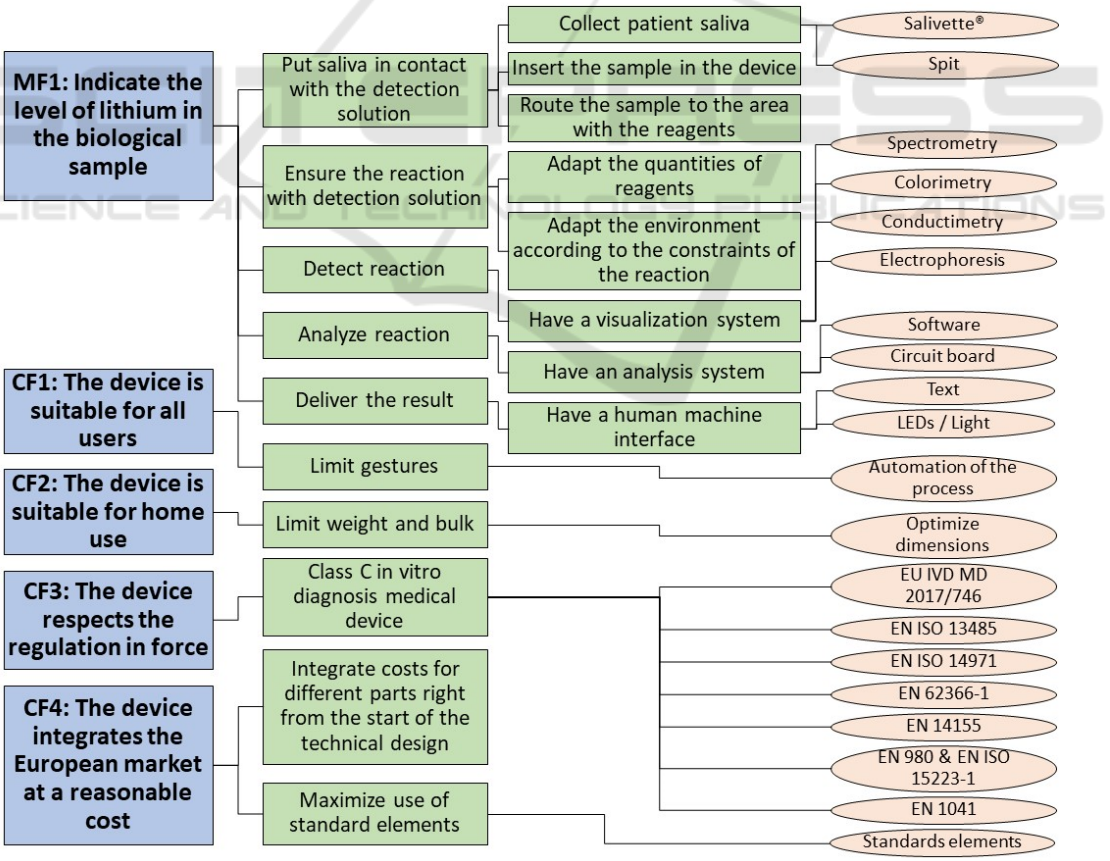

Figure 4: FAST diagram obtained for the home-based lithium monitoring device of the R-LiNK project.

5 CONCLUSION

In this paper, we have presented how function analysis can be used to drive research and development actions and to identify regulation constraints during the development of medical devices. An example of functional analysis conducted to design a home-based lithium monitoring device is given. It is shown that function must be identified and characterized and that technological solutions and regulation constraints arise from this analysis. At this stage, scientific or technological techniques used in the final medical device are not yet chosen. They will be chosen during the subsequent prototyping phase according to the identified regulation constraints.

But, beyond the only description of a functional analysis, we pointed out that an efficient design of a medical device implies controlled discussion between end-users, researchers and manufacturers. In order to ensure these fruitful discussions and exchanges of experience, a common innovation frame must be adopted. The idea here is that functional analysis can be this common frame to the condition that it is pedagogically explained and presented to stakeholders less familiar with it than manufacturers. Functional analysis can then be regarded as a common thread in the design and development process.

This methodology is currently applied to the lithium monitoring device developed in the frame of the H2020 R-LiNK project and results of this development will be available soon.

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