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The EU Medical Device Regulatory Process: The STAT-ON™

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Abstract

This chapter describes the complete regulatory process followed by STAT-ON™ product to comply with the actual European regulation. A complete idea of the steps to be followed, the associated estimated timing, and the material to be considered and prepared are presented. A complete discussion about the Quality Management System of the manufacturing company is also discussed.

4.1 Introduction

The regulatory process is one of the most important challenges that a manufacturer of medical devices must face. This process, which is costly and long, is essential and mandatory for maintaining the safety of patients whatsoever the field is being treated. In this chapter, we treat the main points and the pathway for achieving a medical device certificate for the European market based on the experience obtained in STAT-ON™.

4.1.1 Definition of a medical device

According to the Official Journal of the European Union (OJEU), where the regulations about medical devices are published, a medical device is defined as:

> *"…any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer*

to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or State,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means."

Given the importance of this statement, medical devices need to be controlled and regulated by strict rules in order to provide rigorous measurements that are applied in the field of health for several purposes.

Medical devices can be classified depending on the risk concerning the patient in several classes: class I (low risk), class IIa (medium risk), class IIb (medium/high risk), and ending with class III (high risk). Usually, the specific classification of a medical device must be done by an externally certified notified body, except for class I devices.

4.1.2 Directive MDD93/42 and the regulation MDR2017/745

In the recent past, since 1993, medical devices have been regulated under the Council Directive 93/42/EEC of June 14, 1993 (MDD93/42). This directive intended to harmonize the laws relating to medical devices within the European Union. However, medical devices have changed and progressed significantly, and several manufacturers demanded new regulations, notified bodies, and users of medical devices.

Since 2017, the new regulation MDR 2017/745 [1] on medical devices has prevailed in Europe, which derogates the MDD93/42/EEC. At the same time, the regulation set a 3-year moratorium after the date of entry into force, during which those devices certified under the previous regulation

continued to be valid. Due to the pandemic, this moratorium was extended until May 2021, the date from which a mandatory adaptation to the new regulatory framework is required.

According to the Legislative Act, the new regulation (MDR2017/745):

> *"…aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products. Both objectives are being pursued simultaneously and are inseparably linked whilst one not being secondary to the other. As regards Article 114 of the Treaty on the Functioning of the European Union (TFEU), this Regulation harmonises the rules for the placing on the market and putting into service of medical devices and their accessories on the Union market thus allowing them to benefit from the principle of free movement of goods."*

In other words, the new regulation improves the EU market functioning, ensuring safety for users and patients, and sets standards for the new quality management system, which empowers the companies to work with their products in the market.

Due to the moratorium application, Europe is living in a curious and exceptional situation since all manufacturers must adapt their medical devices. This has complicated the processes and logistics of the European Notified Bodies and manufacturers to accommodate their devices to the MDR 2017/745.

This, along with the Brexit situation, has made the manufacturers to also adapt their medical devices to the British authorities' requirements for obtaining the new UKCA certificate. This scenario has provoked a serious saturation in the notified bodies' activity, prolonging the periods to achieve a medical device certificate. Due to this situation, the period to certify a medical device can easily be 1 to 2 years.

It must be noted that STAT-ON™ is a medical device, class IIa, certified according to directive 93/42/EEC, that requires an adaptation to the new regulation. This process must be done before May 2024 to comply with the MDR 2017/745.

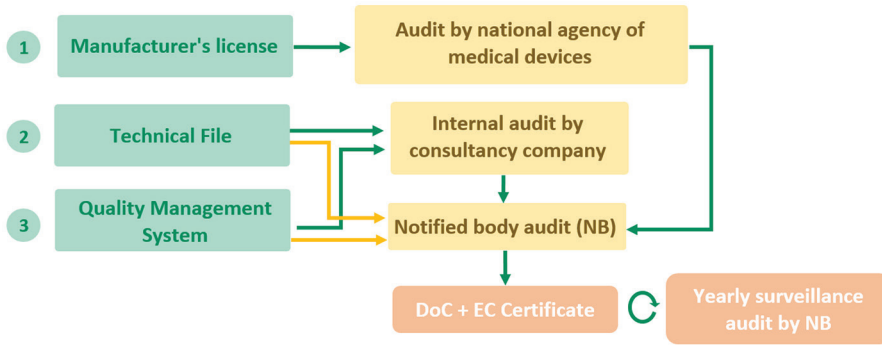

Figure 4.1 Main processes and steps for achieving the EC certificate.

4.1.3 The regulation processes

The regulation processes involved in the regulatory frame (for both the directive 93/42/EEC and the MDR 2017/745) are, in essence, very similar and are described hereafter. It must be noted that these processes affect the STAT-ON™ certification.

In order to achieve the EC Certificate and the Declaration of Conformity of the product, there are three main steps that any manufacturer has to follow:

- the manufacturer's license.
- the technical documentation.
- the quality management system.

The manufacturer's license is provided by the National Agency of Medicines and Medical Devices, after an audit that includes the procedures, the manufacturing process, and the people that are in charge of each process. This manufacturer's license is essential given that it enables the manufacturer to manufacture the medical device through an official agency and is also mandatory for the documentary audit to be done by the notified body.

The technical documentation and the quality management system are documents that gather all the necessary references for the preparatory internal audit permitting the audit done by the notified body. All these documents refer to the product and the company that manufactures and places the device in the market. A scheme of the processes and steps is shown in Figure 4.1.

The generation of all the mentioned documentation can take a long time (sometimes from 6 to 9 months), and the audit for the manufacturer's license done by the national agency of medical devices can take time as well (around

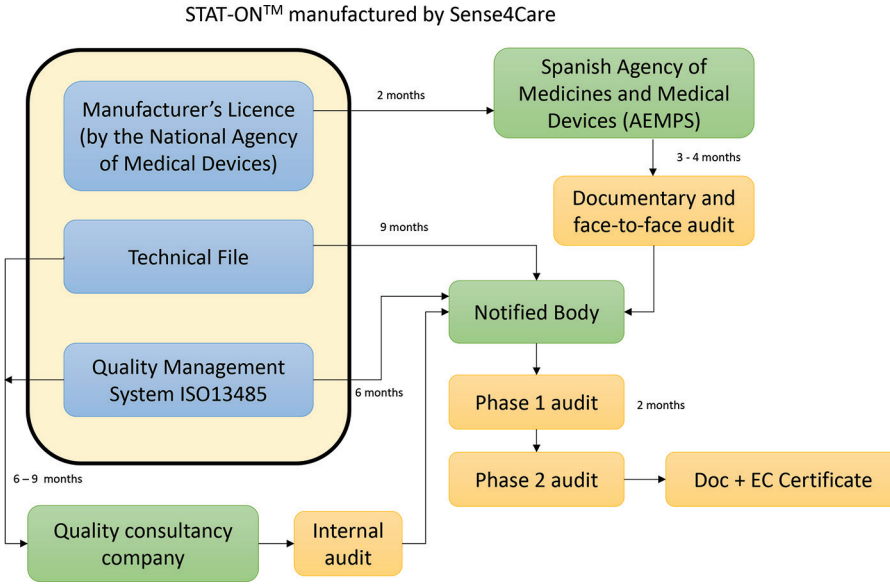

Figure 4.2 Whole detailed diagram process for achieving the EC Certificate.

two months since this is requested could be a good estimation). The audit to be done by the notified body can take extra time (one year is a good estimation, given that there are many documents to prepare). Finally, a review and a face-to-face audit process are required. These estimated times can be extended given the crowded scenario that notified bodies are facing. The European Commission has considered extending the adaptation of the medical devices from May 2024 to the year 2028 with conditions for manufacturers such as a rigorous commitment to adapt the medical device to the MDR.

In the case of the STAT-ON™, two days and a half were needed for the notified body audit. Before this process, a regulatory expert company also performed an internal audit of the manufacturer and the company that places the device in the market. It must be considered that the manufacturer can subcontract a specialized company in soldering, board production, and assembly procedures, which is the case of STAT-ON™. This company is also under strict rules and quality requirements. In this specific case, the company must comply with ISO13485 for manufacturing medical devices.

The complete process is depicted in Figure 4.2, where the presented timing is estimated. The time and delay strongly depend on the notified body's activity saturation and the manufacturer's ability to generate the complete requested documentation.

Figure 4.3 Manufacturer's license documentation.

Each one of the procedures is described in the next sections. In Section 2, it is summarized the manufacturer's license process. In Section 3, it is briefly described the content of the technical documentation, and in Section 4, the quality management system is presented.

4.2 The Manufacturer's License

The manufacturer's license is the necessary first step in the certification process that enables a manufacturer to place a medical device in the market. The manufacture's license is provided by each country's national agency of medicines and medical devices. In the case of Spain, it is driven by the Spanish Agency of Medicines and Medical Devices (AEMPS).

The complete list of the documentation to be prepared by the manufacturer company is in Figure 4.3, and some additional details are given in the following text. The requested documents are some of the documents that must be included in the quality management system (QMS) (see Section 4). Thus, when the QMS is performed, the manufacturer's license documents are implicit within the QMS.

The preliminary action to be performed is to request the national agency to start the manufacturer's license process, and it is necessary to elaborate and prepare a list of documents that are mainly related to the description of the manufacturer company: the description of the involved personnel, details about the contracts and agreements with subcontractors, information about the plants, the description of the procedures and controls in the company, details on the manufacturing processes, the complete organization and organigram of the company, etc.

The national agency (the AEMPS in the case of Spain) performs a documentary audit of these documents and also a face-to-face audit in the facilities of the manufacturer or in the facilities of the manufacturing process.

The manufacturer's license is valid for 5 years and must be renewed and audited once the expiration date arrives. Usually, the face-to-face audit takes no more than one day. It consists of an initial meeting, a visit to the subcontractor facilities (if any), a documentary review (related to the manufacturer and the subcontractor) of aspects related to the subcontractor, and the final reading and signing of the inspection report.

During the meeting, many points and aspects are checked and reviewed. Among them:

- Some specific aspects of the software (installation, validation protocol, etc.).
- Surveillance system, notification, and evaluation of adverse events.
- Work instructions in case of incidents and nonconformities treatment procedures.
- Procedures in case of a market product withdrawal.
- Company organigram and technical manager responsibilities.
- Manufacturing procedure, installation, and maintenance. Risk analysis management report.
- Design and control change procedure.
- Identification, traceability, and inspection state of the products procedure.
- Documents file system procedure (contract with subcontractors, fabrication order, product label model, providers follow-up, etc.)

An inspection is also performed on the subcontractor to check if they comply with ISO13485 (for manufacturing medical devices). However,

this inspection is not mandatory if the subcontractor owns the ISO 13485 certification.

If this inspection must be done, all the manufacturing processes are inspected and all the documents assigned to each manufacturing machinery are checked, as the ISO13485 indicates. The auditor can request additional documents from the subcontractor (packaging methods and instructions, calibration of the equipment, calibration plan, calibration certificates, machines' maintenance, etc.)

The estimated required timing is indicated in Figure 4.2; the generation of all the documents and the final audit can take from 8 to 12 months (6–9 months to generate the documents and 2–3 months to perform the audit process). If the procedure is successful, the certification, with a validity of five years, is provided to the company at the end of the audit. This certification is mandatory in the final audit performed by the notified body.

4.3 The Technical Documentation

The technical documentation is an important part of the regulatory process. In essence, it is a complete set of technical information about the medical device, comprising:

- The specification of its components: all the schemes, graphics, manuals, industrial design plans, codes, etc.
- The laboratory tests performed and succeeded, including their certification.

The technical documentation also includes the risk management file, the labeling, the required user manual of the device, and the clinical evaluation, including usability, endorsement by experts, and state-of-the-art. Finally, a commercial part for surveillance of the device after commercializing is also incorporated, along with the declaration of conformity and the final certification.

This block of documents is very extensive but provides all the details of the device aligned with the main technical standard IEC60601-1 for medical devices. The technical documentation structure can be divided into three main blocks: summary, detailed documentation, device modifications, and follow-up (see Figure 4.4).

4.3.1 Part A: The summary

Part A of the technical documentation contains the main information of the medical device, synthesized in a single document for a better and quicker

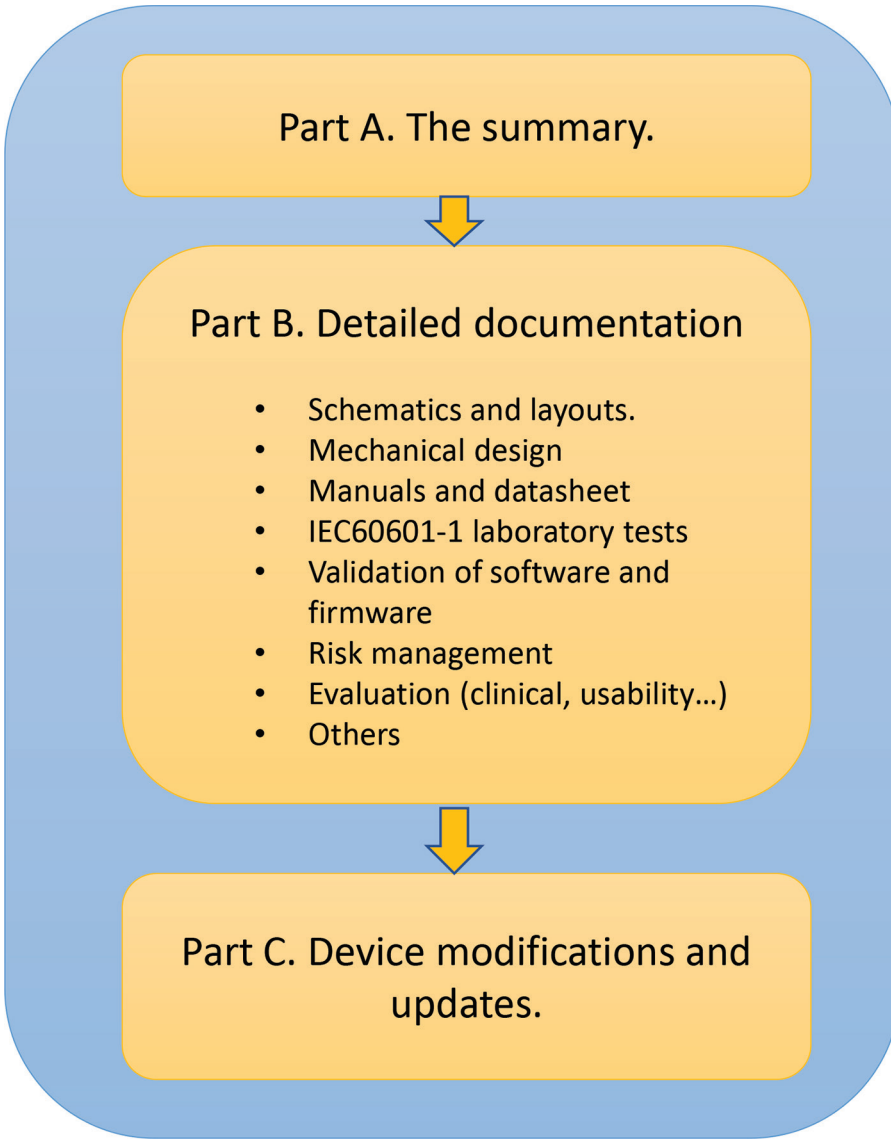

Figure 4.4 Structure of the technical documentation.

understanding (its classification, the purpose of use, contact information, the brief information of the manufacturing process and subcontractors, and how the company will deal with postmarketing surveillance).

This document is a guide for the auditors and is crucial for the manufacturer. The document is structured according to the detailed documentation

(part B) listed in Figure 4.4. Additionally, it must contain information about the manufacturer, a scope and device description, a product specification, and an analysis of similar devices on the market. The complete list of documents is in the next section when Part B is presented.

4.3.2 Part B: The detailed documentation

Part B of the technical documentation contains detailed information in the summary document. Part B is structured in different folders or subparts:

- Device description and specification, including variants and accessories with reference to previous versions of the device.
- Information supplied by the manufacturer (labeling, serial number, instructions of use and manuals, declaration of conformity, etc.)
- Design and manufacturing information. It must include:
  - The device design and specifications (technical description of the device and accessories, schematics and drawings, the necessary materials, calculations and critical design elements, the design and specification of the related software, and the finished device specifications, etc.).
  - Manufacturing details (manufacturing facilities, suppliers, processes and conditions, packaging and sterilization, traceability and batch records, etc.).
- General safety and performance requirements (checklist and list of applicable standards).
- Risk/benefit analysis and risk management (methodology, risk management summary of results, and final statement).
- Product verification and validation, with safety tests:
  - Safety of Electromedical Equipment – Tests performed and summary report as per EN 60601-1.
  - Electromagnetic Compatibility – Tests performed and summary report following EN 60601-1-2.
  - Biocompatibility of applied parts.
  - Functionality and efficacy tests.
  - Device lifetime. Stability/aging tests.

- Usability – tests performed and summary report following EN 62366.

- Clinical data. It must include a clinical evaluation report with conclusions concerning risk/benefit and a plan for postmarket clinical follow-up (PMCFU).
- Additional information must be provided in some specific cases:
  - Devices containing medicinal substances.
  - Devices or derivatives manufactured utilizing tissues or cells of human or animal origin.
  - Devices are composed of substances that are absorbed or locally dispersed in the human body.
  - Devices placed on the market are sterile or in a defined microbiological condition.
  - Devices with a measuring function.
  - Devices are to be connected to other devices in order to operate as intended.
- Final conclusion and Declaration of Conformity, with the EC Conformity Evaluation Procedure (done by the notified body).

The following section presents the concrete case of the STAT-ON™ medical device, and some related documents in its technical documentation are described.

4.3.2.1 STAT-ON™. The device description and specifications

This set of documents gathers the main description of the device, explaining the different parts and briefly describing how the system works. The mechanical and electrical diagrams accompany this documentation. The mechanical diagrams show the plans of the enclosure, the sealing strip, and the button membrane of the device. The electrical diagrams are composed of the schematics and layout of the electronic circuits. It is also necessary to include all the billing of the materials, their provider, and their cost.

The mechanical enclosure details have already been presented and discussed in Chapter 3, and the different figures included there show the enclosure design, its dimensions, the different parts, and the final aspect of the commercial device.

Furthermore, the document informs about the classification of the medical device, compliance with 93/42/EEC, and the category of the device.

The product pertains to the following devices' category: **04 Electromedical/mechanical.**

The product pertains to the following subcategories: **05 MD1301 Monitoring devices of nonvital physiological parameters.**

It also reported data about the notified body:

IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A. – NB 0051

Via Quintiliano, 43 20138 – Milano. Italy
Tel: +39 02 50731
Email: info@imq.it

The complete electrical diagrams are also part of the technical documentation. A complete description of the hardware electronics is contained in Section 3 of Chapter 3, where the final architecture and details of the redesign are conveniently detailed. Figure 4.5 shows, as an example, the schematics corresponding to the related Nordic nRF51822 processor circuitry.

4.3.2.2 STAT-ON™. The information supplied by the manufacturer

This document includes all the information provided by the manufacturer (Sense4Care SL, in this case) to the customer. This documentation must also include the labeling (per the regulation) and the user manual.

Fulfillment of labeling requirements

The content of product labeling (label unit, packaging labels, and instructions for the use) has been established per regulatory requirements of directive 93/42/EEC, Annex I.13 and with the requirements of the EN 15223-1:2016, EN 1041:2008 (it is necessary to remember that STAT-ON™ is a medical device under the directive 93/42/EEC, in adaptation process to the MDR 2017/745).

Product markings: Serial number label

Figure 4.6 shows the produced labeling for STAT-ON™, which contains the product lot number and some graphic symbols (following standard EN 15223-1). The serial number can have several combinations, but the lot and the serial number are mandatory. In the STAT-ON™ case, it comprises three-part codes: month and year of fabrication, lot number, and the serial number (SN). At its turn, the SN is composed of the fabrication date (zzzzz), the lot

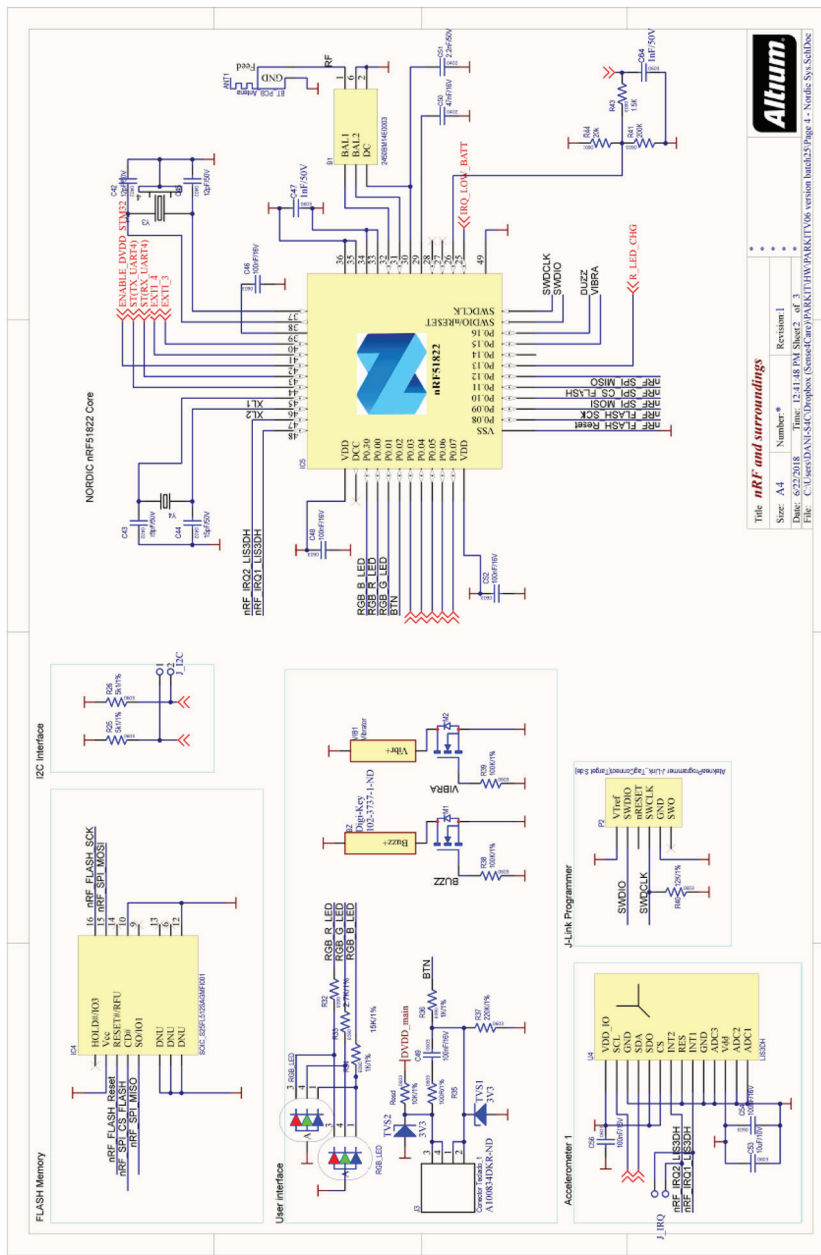

Figure 4.5 The schematics example corresponds to the nRF51822 processor.

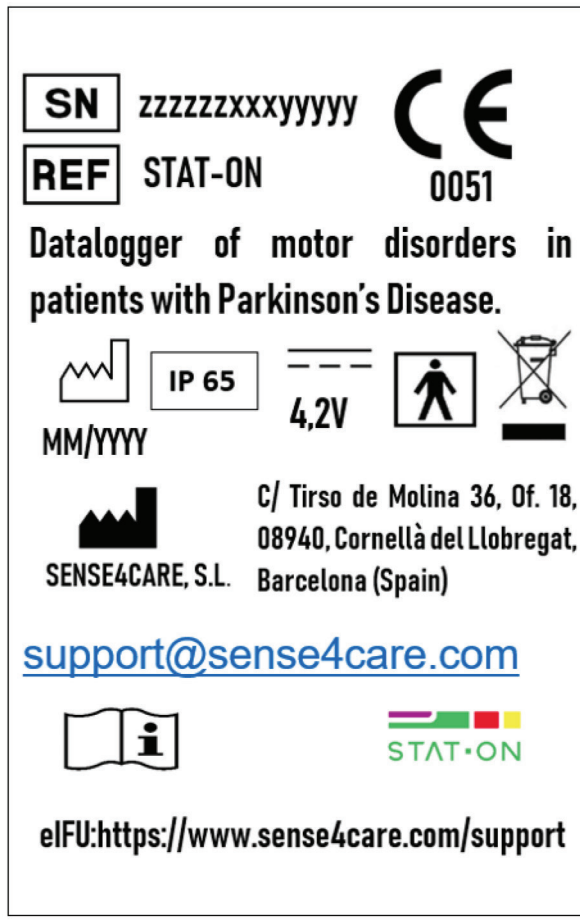

Figure 4.6 STAT-ON™ labeling

number (xxx), and the order number of the concrete device in the lot (yyyyy). Some more details are in Section 5.4 of Chapter 3.

Declaration of conformity

The declaration of conformity is an official document approved by the notified body, which is sent to the customer to confirm the compliance of the device with the set of rules and standards declared in the document. The document has to be dated, signed by the main responsible for the company, and accepted and validated by the notified body.

In concrete, this document establishes the following items:

- Description of the product family, indications, and intended use.

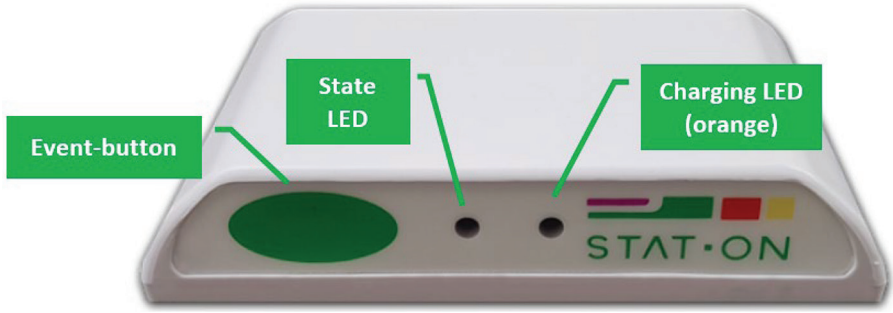

Figure 4.7 Sensor's interface.

- The drawings and specifications of the product and its components.
- Manufacturing requirements and procedures.
- Labeling and instructions for use.
- Design verification and validation, as well as chemical, biological, and functional testing, are performed according to applicable standards.
- Risk management report per EN ISO 14971.
- Clinical evaluation of the product following Annex X of directive 93/42/EEC and MEDDEV 2.7.1.
- The essential requirements checklist is in Annex I of directive 93/42/EEC.

Instructions for use

The user manual is a guide for the use of the sensor focused on the neurologist or the operator. It begins with a quick guide to installing the app and how to initialize the system, but it also explains the conditions of use, describes the parts of the system, the application, the outcomes of the sensor, and finally, it explains all the regulatory issues.

This document is extremely reviewed by the laboratories that certify the device. Thus, it is important that includes points such as the warnings, care and use instructions, indicating all the important information (who can use the device, its purpose, electrical isolation, contraindications, disposal instructions, and secondary or side effects, etc.).

The instructions for use document has to be readable, and a quick start is recommended.

In the STAT-ON™ case, the physical interface (Figure 4.7) is introduced, and the report is generated by the app when required, according to the registered and stored data (Figure 4.8 for details). In addition, a whole

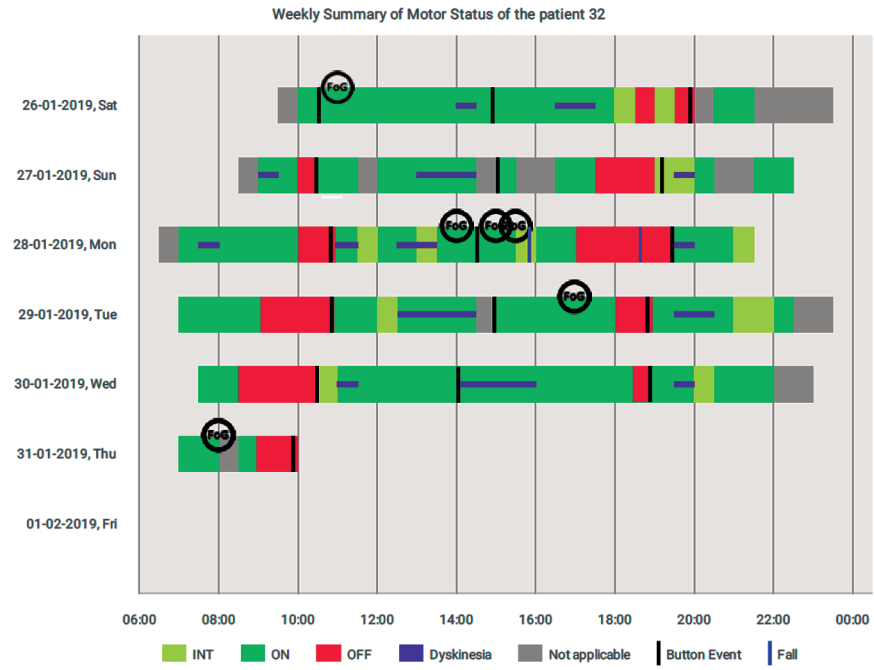

Figure 4.8 Weekly motor state report. The button pressed can indicate an intake of the medication.

section is included to explain the report to help professionals interpret it correctly.

A statement about data protection is also included, stating that in compliance with the general data protection regulation (GDPR), the company Sense4Care S.L. guarantees that collected data is uniquely stored within the device and that only the user is responsible for the use of these data.

In its present form, STAT-ON™ cannot share the collected data with a third party without the user's consent. Therefore, sense4Care S.L. will only access data under the express consent of the user and the owner of the STAT-ON™ device. Furthermore, shared data to Sense4Care S.L. will always be pseudo-anonymized and kept under the strictest security and confidentiality measures.

The technical documentation must include the complete list of the STAT-ON™ technical specifications and the ordered list of all the related standards and regulations affecting the device. This information was already included in Tables 3.7 and 3.8 of chapter 3.

4.3.2.3 STAT-ON™. Design and manufacturing information

This section of the technical documentation specifies the set of the necessary material to manufacture the STAT-ON™ device. Again, some electrical schematics and diagrams are included in this document as an annex. Moreover, specifications and regulatory tests must also be included.

The documentation includes the datasheets of the used devices. The datasheet of the used battery is particularly important in accordance with the IEC622133. The corresponding test report IEC62133-2 must also be included since this report guarantees the safety conditions of the battery and its use.

Another important document is the bill of the material, which is divided into two documents, the internal bill of material of the circuit, and the bill of material of the device.

Next, the production and final verification essays procedure must be attached, where the procedure is described, which the manufacturer must strictly follow. Finally, the batch file comprises the manufacturer procedures documents, including design and change controls, program elaboration, construction, replication, and installation procedures. Moreover, the fabrication orders, registers, and storage registers are also included.

The entitled "*Manufacturing and Verification & Final Tests*" document contains all the aforementioned information. It also contains all the manufacturing processes, including the following steps:

1. Fabrication order requested by the manufacturer.
2. Purchase of material.
3. Manufacturing order (subcontractor).
4. Phases of manufacturing (the SMD mounting and the assembly of the electronic elements in the enclosure of the equipment).
5. Review by the Responsible Technician (manufacturer).
6. Registration in the warehouse (subcontractor).
7. Shipment to the customer (subcontractor).
8. If it is in the subcontractor's warehouse for more than 1 month, it is sent to Sense4Care and stored in a locked cabinet at the Sense4Care offices.
9. Shipping to the customer (Sense4Care).

It is necessary to describe the inspection process. During the manufacturing process, the production personnel inspects the performed work (all the

specific checks and inspections to be carried out are specified in the work instructions).

At the end of the operations of a job, the completion of the work performed and its verification will be recorded in the production records of the manufacturing order in process. In addition, in cases of incidents or defects, the losses caused are indicated in the same record.

Manufacturing records allow to the establishment of the quantities manufactured. The final inspections of the products are intended to determine if the product is suitable for marketing. To do this, a check is made with the model's specifications indicated in the manufacturing order.

In the event of noncompliant results of the inspections/checks, the entire manufacturing order will be rejected and will be treated according to the established nonconformity treatment procedure.

After reviewing and verifying the closure of the manufacturing order by the production manager and checking all the manufacturing and control records (batch file), in the event of favorable results, the technical manager releases the batch of products authorizing their placement, being available to commercial/sales. Otherwise, the technical manager retains the product, treated as a nonconforming product.

All records relating to manufacturing and release are filed together in the batch file to maintain the traceability of manufactured and distributed products.

The traceability and batch records are important and will be included in the quality system folder when the manufacturing process is executed every time. These files will control the number of units, purchase orders, and the number of nonconformities and will provide important information to the technical responsible for taking future decisions in the manufacturing process.

4.3.2.4 STAT-ON™. General safety and performance requirements

A systematic review of the fulfillment of the general safety and performance requirements/essential requirements set out in annex I of Directive 93/42/EEC must be provided in the technical documentation. The checklist indicates the applicability of each requirement, applied technical standards, and a pointer to the relevant sections of the technical documentation that support fulfillment.

A list of applicable/applied standards with the publication year is provided in the technical documentation. In addition, the list indicates whether or not the standards are harmonized with Directive 93/42/EEC.

Table 4.1 Risk management list for STAT-ON™.

Life-cycle phase	Risk management activity to be performed
Design	Identification of hazards and preliminary evaluation Risk control measures – selection and implementation Control measures – verification Preliminary Risks Management Report.
Transfer to production	Revision of the applicability and correct implementation of all the control measures that imply materials control, suppliers, subcontractors and/or process controls. Any unexpected risk or modified control measure will be documented and entered into the risk control records.
Routine production	Any abnormal tendency regarding the product safety characteristics will be analyzed to determine whether a corrective/preventive action is to be taken. The impact of the corrective/preventive measures taken to maintain or to increase product safety will be analyzed and entered into the risk management records.
Commercialization/ postproduction	Any customer complaint that originates changes/ corrections to the product will be analyzed to determine its impact on the existing risk evaluations. Feedback from the market will be monitored to determine whether it is convenient to implement corrective/preventive action.
End of useful life/ end of validity period	A device lifetime of 10 years (shelf-life) is scheduled for this product. However, product manufacturing samples will be kept in order to be able to confirm their functionality, even at the end of the specified device lifetime. Upon discontinuing product commercialization, this risks management plan will be closed, and all the documentation in the risks management file will be kept for a minimum of 10 years.

4.3.2.5 STAT-ON™. Risk management

Risk management is performed in each product life-cycle phase, following the requirements and activities set out in EN ISO 14971[3]. Generally, the life cycle defined for the product (for the case of STAT-ON™) is as indicated in Table 4.1.

The documentation that must be generated for the product and kept in the risk management file includes the definition of the risk management plan, the report of the initial risk management (with the risk assessment in the design phase and transfer to production), and the reports of the Product Review (including the continuous assessment of risks and including

information feedback from the different stages of production and marketing routine/postproduction).

The methodology used for risk management activities is as indicated in the general procedure of "risk management," stated in EN ISO 14971, and includes the following items apply to all products:

- Establish the risk management policy and qualification of the team engaged in risk management.
- Definition of a scale of probability of occurrence of hazards and a range of levels of severity of the consequences if the hazard occurs.
- It establishes a general framework for risk acceptability criteria based on the combination of likelihood and severity levels.

For a given medical product, the following characteristics must be specified:

- Intended use and the features related to safety.
- Identification of hazards under normal and fault conditions based on the experience and the applicable regulations.
- Risk assessment (estimation of probability) associated with each hazard to determine initial acceptability.
- In the case of unacceptable risks, the analysis of possible causes or sources of hazards and the options available for controlling and/or mitigating the risk.
- Selection and implementation of the available options for controlling and/or mitigating the risk.
- Re-evaluation, after the implementation of risk control options and/or mitigation, to determine if there are residual risks.

The risk management report must include the following:

- The list of hazards is considered under both normal and fault conditions.
- Possible consequences for patients, users, and third parties and the possible causes.
- Estimating the initial risk (before control/mitigation), defining the implemented control measures/mitigation.
- Final risk estimates (after control/mitigation), including the determination of the acceptability of the final risk.

- Review the possible generation of new risks following implementing control measures/mitigation.

All the conclusions drawn regarding the effectiveness of the adopted measures and risk/benefit balance are set out in the final declaration of the report signed by the team responsible for risk management. As indicated in the EN ISO 14971, the following list of documentation is required:

- Risk management plan.
- Record of personnel qualification.
- Qualitative and quantitative characteristics.
- Dangers identification – risks preliminary estimate.
- Control methods/risk mitigation.
- Residual risk evaluation.
- Warnings to include in the label and instructions for use (IFU).
- Usability protocol.
- Validation of usability.
- Usability study report.

4.3.2.6 STAT-ON™. Product verification

In this part of the technical documentation, a set of documents must be included, according to directive EC 60601-1 [4], with the different published corrigendum and amendments, and the directives EN 300330V2.1.1 and EN 300328V2.1 [5, 6]: the obtained certificates, the performed laboratory tests, and others such as the transport test certificates. It must also include the clinical evaluation report, signed by experts, and the software validation, which is a set test performed on the app under the EN62304 regulation [7].

Software validation

The software validation part must include a series of documents that aims to test the firmware and the software associated with the medical device under EN62304. The tests carried out and validated by the manufacturer are also tested and validated by the notified body. This validation is carried out in order to provide documented evidence of the confirmation that the software app product gives correct and reliable functionality as per the legal and user's established requirements.

The identification of the person responsible for the performance of the validation process must be done and kept in the validation archive, along with the following documentation:

- Software validation plan records (validating personnel, source of the programs, flow diagrams, intended use, etc.)
- The related publications and reference standards and the applicable legislation and rules.

Since the STAT-ON™ product has two associated parts of the software (the Firmware and the user app), it is necessary to generate two separate software validation processes.

Clinical evaluation

The clinical evaluation report is a mandatory part of the product verification in the technical documentation of the medical device product. For the case of STAT-ON™, the followed methodology is according to directive 93/42/EEC (Annexes I.6a, II.3.1 and II.3.2. (c)) [8]. Furthermore, it must be considered that the evaluation of the clinical data is performed per Annex X, Section 1.1.1 of directive 93/42/EEC taking into account the guidelines set out in the guide "EU Medical Devices Documents" (MEDDEV 2.7.1 (rev. 4 of June 2016)).

The main objectives of the clinical evaluation are the following:

- Establish that the device requirements on safety (applied standards, etc.) are properly analyzed and that all the hazards, information on risk mitigation, and other clinically relevant information were identified and included in the information supplied by the manufacturer.
- Establish that the balance clinical benefit/risk ratio is positive when the system is used according to the established indications and purposes.
    - Any risks identified in the risk analysis are minimized and acceptable.
    - The intended purpose of the STAT-ON™ is supported by clinical evidence.
    - Warnings of residual risks included in the IFU are supported by sufficient clinical evidence.
    - Establish that the clinical benefits of the STAT-ON™ device are suitable within the widely accepted, given the current state-of-the-art, the intended use of the product, and the established clinical indications.
- Establish that undesirable side effects are acceptable.

- Establish provisions for proactive updating of the clinical evaluation to reflect changes in state-of-the-art through the application of postmarket surveillance (PMS) and postmarket clinical follow-up (PMCFU).

Considering the experience gained by the manufacturer along the redesign and development cycle of STAT-ON™, as well as relevant information from other similar products, the following actions have been taken in order to gather relevant information:

1. Searches of reference literature to establish the scientific basis widely established and technical needs that must be covered.
2. Search and review of the background and clinical experience, both published and unpublished, including comparison with similar or equivalent products already on the market.
3. Specific search of published relevant scientific literature and clinical research results focused on analyzing the possible benefits, safety, and injuries made by STAT-ON™.

In the case of STAT-ON™, strategies 1) and 2) have been used to establish the aspects and characteristics of the product for which the manufacturer believes that there is already sufficient scientific, technical and/or clinical data.

Strategy 3) has been used to study the clinical data related to the most relevant information to establish whether there is sufficient data concerning clinical safety and performance to ensure compliance with applicable regulatory requirements.

4.3.3 Part C: Updates/device modifications

This last part of the technical documentation is composed of documents that must be updated every year or 2 years depending on the requirement of the document in particular. This part is composed of the following:

- Change orders
- Technical documentation on postmarket surveillance
  - Postmarket surveillance plan (PMS plan)
  - PMS reports
  - Periodic safety update reports
  - Postmarket surveillance reports

The changes orders affect the STAT-ON™ device, for example, updates on the software app or modifications of the user manual, quality system, mechanical changes, or even electrical changes.

All these changes must be reported in the technical documentation and the quality system.

The technical documentation on postmarket surveillance must include information about sales, nonconformities, productions, planned actions, administrative information, and customers.

These PMS documents are filled out yearly or every 2 years with the information provided by the sales team and quality department. The objective is to establish a control on the number of sales for the management review and set the company plans for next year.

4.4 Quality Management System

This section describes the quality management system (QMS) of the company, which is based on the standard EN ISO 13485: 2016 [9]. The QMS is crucial for a company since it manages the quality of all processes and the products commercialized. Furthermore, the QMS documents the structure, procedures, responsibilities, and processes needed for effective quality management.

The QMS aims to manage all the processes that take part in the production and commercialization of a medical device, passing from the manufacturing of the device and the purchase of components to the sales control, customer satisfaction surveillance, human resources of the company, problems arisen, audits, company facilities, company structure, etc.

The major benefits of the QMS include the following:

- Enhancement of customer satisfaction by meeting their needs and requirements.
- Providing the right direction to achieve the company's objectives, goals, and mission.
- Maintaining and controlling documents and records.
- Helping in business expansion and growth.
- Identifying risks and generating opportunities to mitigate them.
- Improving the product and the process quality.
- Reducing cost and increasing productivity.

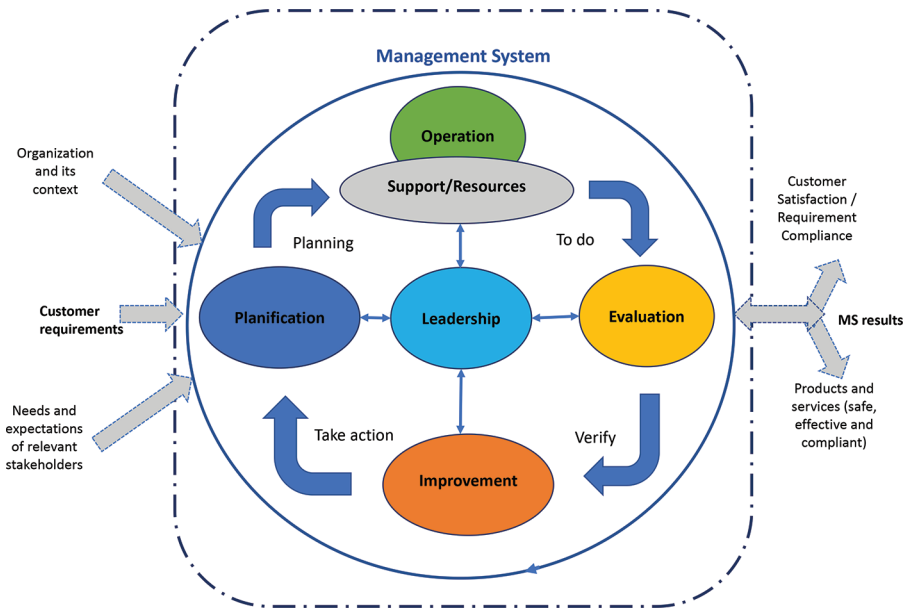

Figure 4.9 PDCA approach to the QMS.

- Engaging employees to achieve functional objectives and the organization's goals.
- Identifying and reducing process variations.
- Detecting and preventing defects or mistakes.
- Facilitating and identifying training needs of workers and staff.

Figure 4.9 shows a PDCA (plan-do-check-act) approach to the relationship between the main actors, processes, and expected outputs and results in the QMS of the company.

From a practical point of view, the most important document of the QMS is the quality manual, a real summary of the whole QMS. In this document, it is possible to find all the information about the company, the team, the facilities, the location, the aim and business of the company, the context in which it was created, the competitors, the scope and scope, and the relation with customers.

The QMS is established to implement the quality policy, to make the achievement of the quality objectives easy, and to ensure compliance with applicable regulatory requirements and with customer requirements. The QMS includes the policies, processes, and procedures to which reference is

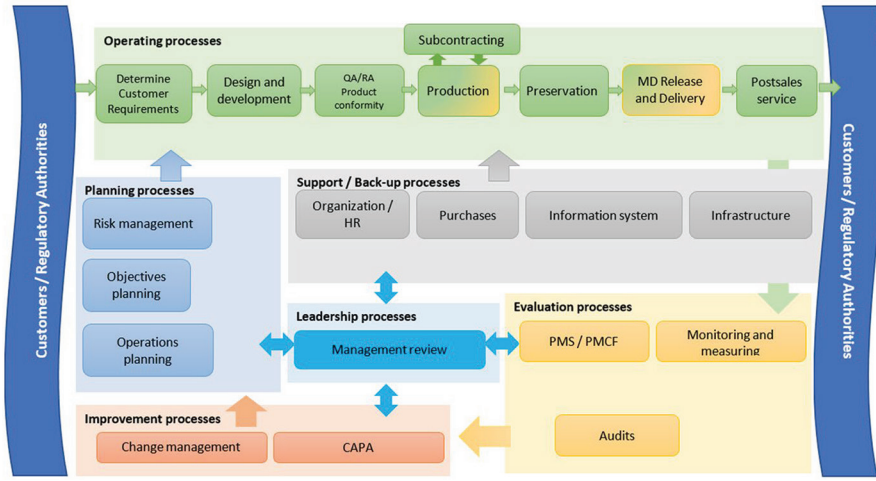

Figure 4.10 Involved processes in quality system.

made, the organizational structure of the company, and the precise responsibilities for the implementation of the activities to achieve the objectives set based on a focused approach in the process risk management document procedure.

The quality manual and the associated documentation establishes how to apply and maintain the QMS. Likewise, it identifies the criteria and methods required to guarantee the effective operation and control of the system. It identifies the measurements, monitoring, analysis, information, and actions necessary to achieve the planned results, conserve the system's effectiveness and improve it continuously.

Figure 4.10 shows the main processes necessary to implement the quality system for the manufacturing and supply of medical devices. The different interrelationships are also indicated.

As it is indicated, there exist an important set of processes related to the operative parts: determination of the customer requirements, the design, and development of the product, the production and manufacturing process, the conformity of the product with the regulation, the specific release and delivery process of the medical device, the postsales service, etc.

These processes must be planned (planification of the involved operations, how the risks are managed, and the objectives must be planned, etc.). There is a specific part for the evaluation of the processes with concrete measuring and monitoring processes, together with the required audits to be prepared periodically.

Additional processes for support are required: organization, purchases, information systems, and the necessary infrastructure. The processes for the improvement of the processes are also a very important part.

The quality system requires a very well-organized and structured set of documents. This is an important part of the work to be done and includes the following list:

Quality manual

It is a description of the quality system of the company. It contains references to the used documented procedures, the description of the QS processes, their interaction, and the critical reviews of the documentation structure.

Quality politics

It contains the mission statement of the organization as well as its intentions in relation to quality, risk management, and compliance with regulatory requirements.

Process map

It contains a diagram indicating the different relevant processes of the organization, the sequence, and their interaction.

Procedures

Describe the activities carried out in the framework of the QS to meet the requirements established in accordance with the reference regulations. Here, are also included the work instructions, the control guidelines / analytical methods, the manufacturing guidelines...

Quality records

They keep the results obtained along the quality process and show that the activities are carried out according to the applicable regulations and comply with applicable regulatory requirements.

Plans

They establish the necessary planning and programming to establish the time schedule to carry out the required actions to maintain compliance of the QS (audit plan, calibration plan, training plan, etc.).

Quality objectives

It contains the declaration of the concrete quantitative aspirations of the organization derived from the quality policy and related to quality processes, risk management, and compliance with regulatory requirements.

File of health product (medical device file)

It is necessary to maintain a file for each type of health product or family of medical devices, containing all the generated documents that are necessary to demonstrate compliance with the applicable regulatory requirements.

Process risk management file

This file contains all the reports and tests related to process risk management

Regulatory submissions

The file contains the documentation related to the regulatory presentations, such as the manufacturer license (to be presented to the AEMPS in Spain, the Register & Listing (to be submitted to the FDA in United States, etc.

Communications notified bodies

The file contains the documentation related to the notified bodies involved in the conformity assessment of the product (applications, certificates, audit reports, etc.).

Batch file/manufacturing records

These verified and approved record sets provide traceability of each product or many products. They also identify the quantities of manufactured and released products for commercialization.

External documentation

This is a set of reference documents. For example, the international technical standards and the legal requirements applicable to the products (regulation, standards/guides, contracts, agreements, etc.)

The different types of documents integrated into the structure of the QMS are described in the procedure structure and minimum contents of the quality system documents.

In the case of products manufactured by the company, the technical documentation of the product, according to the procedure preparation and control of technical product documentation, must be included (technical documentation already described in the above text).

In the case of imported/distributed products, the documentation will include the certificates, product documentation, and regulatory records according to the procedure file of imported/distributed health products.

It is important to note that:

- Maintaining registers/records of data is mandatory to provide evidence of the effective operation of the QS compliance with regulatory requirements and product and service conformity with the established customer and regulatory requirements. The registration forms must be included as annexes in the procedures that explain their use.
- The identification, storage, recovery, protection, retention time, and final disposition of the records are defined in the procedure of records control.
- The records can be both in paper and electronic format. Backup copies of the records are made in computer support. Records containing personal or confidential health data are duly protected per the applicable regulatory requirements.
- The records of the quality system shall be kept on file during the minimum period established in the QMS. This period will be longer than the product's useful life and at least 10 years (15 years in the case of implantable products) after the last product has been manufactured.

The documents listed above must be generated according to the corresponding procedures and instructions described in the QMS. In the case of a medical device, like the STAT-ON™ device, 60 items can be found, giving an idea of the work to be done and its complexity. Additionally, many of them include instructions and registers to be filled in regularly.

Since the complete list of the involved processes should be excessive, along with the rest of this section, a summary of the most representative processes will be presented according to the scheme of Figure 4.10.

- **Quality manual folder**

This is the most important part of the QMS, where the quality manual is included, and the structure of the company is described. It also includes: the list of documents, the involved processes and their relationship, the responsible for each of them, the quality policy, and the designation by the board of management of the different charges and roles, etc. Figure 4.11 shows the typical structure of a company manufacturing medical devices.

- **Description and procedure management**

In this procedure, the main objective is to establish the necessary information for the planning, management, and monitoring of the processes used by the company to carry out its activities in the frame of the QMS.

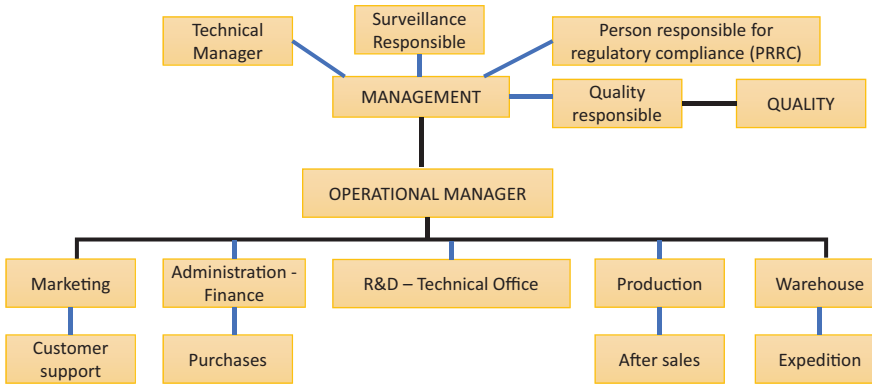

Figure 4.11 Company's structure as described in the quality manual.

- **Manage outsourced processes**

In the case of Sense4Care (the company manufacturing STAT-ON™) a great part of the production is subcontracted. The management outsourced processes are very important since it describes the relevant processes of the company that are outsourced or subcontracted as established in the process map (operating processes part). The processes establish their control and maintenance to confirm their continuous suitability for the company. It also includes the treatment of interactions with crucial suppliers/suppliers (suppliers that provide materials or services that may have a critical and direct impact on the conformity of the final marketed product).

Those involved in the control of the process and the owner of the process will maintain the control of the process monitoring, alerting about the quality by opening a corrective/preventive action, in case of observing an anomalous trend.

- **Process risk management**

The management of risks is a crucial aspect of the QS, and it is implemented as part of the QMS. The risks associated with the procedures can affect the activities of the company, coming from any internal or external source. They can also come from outsourced processes. Additionally, all the applied changes in current practices may also have an impact, generating a risk.

For this reason, managing risks is not an activity limited to certain people or areas of the company, and it is generally applicable in all areas.

This procedure, as part of the planning processes, establishes a methodology by which all types of risks must be proactively detected and managed to try to minimize their impact and the actual or potential damage they may cause according to EN ISO 31000.

- **Software quality validation**

Embedded software or necessarily related applications are important parts of the actual medical devices. Therefore, the procedure's main objective for the software validation is to establish the methodology used for the validation before initial use and the subsequent periodic revalidation of the software through the preparation and execution of master validation plans.

This procedure applies to all computer applications (software) used in the quality management system and in the product being the software app and the internal firmware of the microcontroller in the case of STAT-ON™.

- **PS file – preparation and control of technical documentation**

The medical device file, also called technical file under the MDD or technical documentation under the MDR, must follow some structure, rules, and control of the documents. The structure is described in Section 3 of this document. This procedure determines the methodology and systematics for preparing the medical devices' technical documentation (the technical documentation – TD). In the case of STAT-ON™, this file is important and according to the specification given in the technical documentation above.

- **Documentary file-Fab**

This procedure is an important piece of the Operating processes since it defines the system that allows tracing the materials used in the manufacturing process of the marketed products, both internally and by our subcontractors, as well as the destination of all the medical devices manufactured by the company and the period of conservation of the records associated with these said activities.

In order to maintain the company's activity within the quality standards and according to the regulations, it is fundamental to organize the review and planification objectives. The following processes must be implemented with this objective:

- **QMS planning** (yearly definition of improvements)
- **QMS review** (definition of the necessary information for the periodic review of the quality system)
- **Risk management product (**development of the risk management policy adopted by management to guarantee the supply of medical devices that are safe, effective, and fit for their purpose, keeping the potential risks associated with their use acceptable in relation to the benefit for the patient and compatible with a high level of safety and protection of health, considering the general current knowledge)

- **Design and change control (**all medical devices could be affected by some changes, in the app, in the hardware, or even in the QMS. It is important to notify and follow a set of rules such as the procedures to identify the problem, the modification performed, and the gravity of the modification, and notify the NB if this is relevant for the MD)
- **Internal audits (**determination of the conformity or nonconformity of the quality management system with the planned and documented provisions, with the requirements preestablished by the company and the applicable regulations. Analysis of the effectiveness of the quality system. Satisfaction of the regulatory requirements of surveillance and prevention of nonconformities)

STAT-ON™ is a medical device Class IIa with the EC mark. The QMS of the manufacturing company (Sense4Care) must implement and follow a set of processes to comply with the applicable regulation and legislation. The most important processes are:

- **Determination and monitoring of requirements (**established strategy for regulatory compliance and regulatory requirements applicable to products). It includes:
  - **t**he steps to be taken to determine and periodically review the applicable regulatory and normative requirements.
  - description of the steps to follow to check the regulatory requirements applicable to the product in the countries and jurisdictions where it will be placed on the market and how to proceed with the conformity assessment.
  - description of the steps to follow for the registration of new products (in Europe, in Spain, etc.)
- **Qualification and classification of products (**establish a method to determine if a product falls within the scope of the regulation applicable to medical devices. If this is the case, establish a method of determining the risk classification of the product according to the applicable regulation. It also defines a method to determine the category and subcategory of the product, and a method to determine the naming code applicable to the product, etc.).
- **Product registrations – EUDAMED** (EUDAMED is the main database of the European Union concerning medical devices. The procedure defines the nomenclature of the product and the process of product registrations in EUDAMED).

- **Clinical evaluation and postmarketing clinical follow-up (PMCF)** (establishment of the procedure for systematic searching, appraisal, and analysis of relevant clinical data, including the review of the postmarket surveillance (PMS) clinical experience and the postmarket clinical follow-up (PMCF) of medical devices, by planning, conducting and documenting a clinical evaluation according to the requirements established in Article 61 and Annex XIV of regulation (EU) 2017/745).
- **Conformity assessment (**it documents how to proceed with the Conformity Evaluation of the devices with intervention of a notified body, specifically in the stages of precommercialization and postmarket).
- **Software (SW) manufacturing and installation** (definition of the actions taken to carry out the construction, copies, installation and maintenance of the final version of a medical device (medical software). Establishes the mechanisms used in the production of a computer program that runs on a Smartphone or tablets).
- **Distribution of medical devices** (defines the protocol for the medical device distribution: contracts, agreements, requirements for each country, etc.)
- **Identification – UDI** (establishes the process of treatment for the UDI for Europe. The UDI is the unique device identifier for the medical devices registered in Europe).

As STAT-ON™ is a medical device mainly sold in Europe, and for this reason, it is necessary to define a set of processes to define and ensure the quality of the postmarketing and the relationship with the customers:

- **After-sales service and technical assistance** (establishes an after-sales service that ensures the customers the correct installation and maintenance of the products sold).
- **Customer feedback (postmarket surveillance)** (definition of a proactive and systematic postmarket surveillance system that includes: analysis of production information of the product, product tracking, early detection of observed adverse events, detection of opportunities for product and safety improvement, etc.)
- **Compliance with regulatory requirements** (establishment of compliance with the product's applicable market requirements, including those established by customers and those established by regulations).

- **Customer satisfaction** (establishment of the process for obtaining and using information related to the client's perception, regarding compliance with the established requirements. Each manufacturer must decide which is the correct customer contact channel).
- **Claims treatment** (definition of the mechanism to treat any claim done by the customer. The main goal is to ensure that all claims received are dealt with in a diligent and expeditious manner and ensure that claims are analyzed to determine if an incident must be reported to the competent authorities. The following types of claims are contemplated: product operation and features, product safety, reliability and duration of the product, identification and/or appearance of the product, packaging, labeling defects, etc.)
- **Regulatory audits and inspections** (within the yearly performed audit, it is necessary to establish the QMS for receiving regulatory audits/inspections from notified bodies and/or sanitary/competent authorities).
- **Treatment of noncompliant product** (establishment of the methodology to try to solve appearing problems and nonconformities with the product. The company must ensure the identification and control of any material, component, process, or product/service that does not comply with the applicable requirements and prevent its unintentional use or delivery. Finally, it is determined the registers that must be kept to indicate the nature of the nonconformities found and the actions are taken to correct them).

In order to ensure success in the implementation of the company's QMS, it is very important to have the active involvement of the staff and diverse personnel. Therefore, among others, the following processes must be implemented:

- **Human resources and competence** (definition of the competences of each one of the managers and staff of the company. Establishment of the responsibilities and authorities associated with the different jobs. It is also established how the necessary competency for people performing work that may affect product quality is defined and reviewed).
- **Staff training and education** (definition of how staff training needs are identified, how training actions are planned, and the information to be recorded for the training actions that are carried out).

4.5 Conclusions

The regulatory process of a medical device is a complete and complex process that involves several players. The immensity of the file structure and the rigorous surveillance performed by authorities make this process very expensive, time-consuming, and exhausting. On the other hand, this process's rigorousness is the reason why medical devices are safe for patients, reliable for medical healthcare professionals, ensuring that no cheap, easy, or dangerous device could affect the integrity of any patient.

As shown in the present chapter, there are three main important parts in a regulatory process: the manufacturer's license, the technical documentation, and the quality management system. Different authorities audit all these parts and the final outcome is a single certificate called EC certificate. The complete process can take a long time (around two years, according to the personal authors' experience), highly depending on the saturation of the regulatory system and the available notified bodies.

Currently, Europe is living in a period of several changes with the introduction of the new MDR, which is valid from May 2021, the Brexit process that obligates the manufacturers to achieve a new certificate called UKCA, and the global crisis scenario given by several factors are affecting the plans of the companies. Furthermore, this whole situation is saturating the notified bodies' activity, enlarging the time for auditing, and being dangerous for the roadmaps of companies to meet the time requirements of customers and project deadlines.

Apart from the required time, the related costs might vary depending on the laboratory tests a medical device requires. After this, the quality manager and technical manager are responsible for keeping the system notifying the notified bodies and authorities when necessary. The QMS is audited yearly and requires a systematic expense that is difficult to keep.

STAT-ON™ was certified in June 2019, and so far, successive yearly surveillance audits have been done. The QMS has already been adapted to the MDR; now, the technical documentation must be adapted to the requirements of the European Commission in the coming future. It must also be considered that the EC certificate achieved by Sense4Care expires five years after the date it was achieved, as well as the manufacturer's license. The main advantage is that since the technical documentation is audited every year, only a few changes will be required for the renewal.

The chapter presented details on the process to be followed in Europe. Similar steps must be done in territories such as Japan or United States with

the PMDA and FDA, respectively. The process practically begins from the beginning, although the QMS and technical documentation are similar. The TGA in Australia is another certificate, but as European Union and Australia have some agreements, the process is easier. Other territories are of interest, but the company must establish a trade-off between the expenses of the team in the regulatory process and the benefits achieved in each territory, making it a challenge for the company to reach new territories.

Sense4Care roadmap is to completely adapt the sensor to the new MDR, achieving as well the UKCA, the TGA, and jumping to the United States and Japanese territories by achieving FDA and PMDA certificates, respectively.

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