Quality by Design approach in the development of a magnetic transducer for biomedical measurements: preliminary results on Design Space configuration

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Abstract. The concept of Quality by Design (QbD) has been widely used by the pharmaceutical industry since 2004, changing the focus on inspections to embrace greater control in the manufacturing process. This new approach contributed to lower production costs and higher quality of medicines. This work discusses the first steps towards the implementation of a QbD approach aimed at ensuring the quality of a biomedical device under development. This device will be applied as a non-magnetic metallic foreign body localization system for surgical removal guidance. It should be highlighted that a new approach was used to define the Design Space, based on fuzzy logic rather than the typical statistical techniques.

1. Introduction

Removal of foreign bodies is a common challenge in the medical practice. The widely available localization procedures are radiography, computed tomography and radioscopy [1, 2]. However, such techniques do not give sufficient information and are inefficient to localize small objects. In addition, they can cause excessive exposure of the patient and surgical staff to ionizing radiation [1]. An even greater challenge is posed by foreign bodies consisting of firearms projectiles, since they are usually made of materials that do not possess a remnant magnetic field [3]. In this case, the induction of eddy currents in the metallic object by a primary alternating magnetic field source generates a secondary magnetic field that can be measured by high sensitivity magnetic sensors [3-5].

The Laboratory of Biometrology (LaBioMet) at PUC-Rio conducts research in the area of non-invasive clinical diagnosis [1-3, 5-9], and is currently developing a biomedical device aimed at locating non-magnetic metallic foreign bodies and guiding their surgical removal. This device is based on a high sensitivity magnetic transducer, since the secondary magnetic fields are extremely weak [3, 5]. The device design is being guided by some major aspects relevant for biomedical technology developments, such as: high sensitivity, low cost of fabrication and operation, low complexity, safety, portability, among others [10, 11].

Quality by Design (QbD) is a tool that has been successfully and widely used by the pharmaceutical and biotechnology industry since 2004, when the Food and Drug Administration (FDA) recommended a new method for quality assurance [12]. According to the International...
Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [13], the QbD implementation requires identification of a set of information associated with the development of the product, including:

- **Target Product Profile (TPP)** - characteristics that guarantee the quality of a product and ensure its safety and efficiency. It constitutes a set of attributes that indicates the purpose of the product, on which are established development strategies. The pharmaceutical industry associates TPP with aspects such as pharmacology, indications and method of use; and relating to chemical properties, as solubility and stability.

- **Critical Quality Attributes (CQA)** – physical, chemical or biological properties, which must operate within a certain range or distribution so as to ensure a pre-defined product quality.

- **Critical Process Parameters (CPP)** - process parameters whose variability has an impact on any critical quality attribute and, therefore, should be monitored or controlled to ensure the desired quality.

- **Design Space** - multidimensional space assigning a combination of the material’s attributes and/or parameters of the process to ensure quality. It is the best set of parameters, determined statistically, which enables the accommodation of any change in the CPPs.

- **Control Strategy** - a planned set of controls, derived from current product and process understanding that ensure performance and product quality.

The QbD concept improves the scientific understanding of the entire production chain of a given product, and consequently brings light to the critical attributes for the quality of the product [14-20]. In that way, it enables the development of a set of control strategies based on articulation bands and operating limits [19]. Thus, the emphasis is no longer in control inspections because, as mentioned in the ICH Q8 guidance, “quality cannot be tested into products; it should be built-in or should be by design” [12, 13]. As a consequence, lower production costs and increasing quality are among the expected benefits. Recent studies are pointing out new solutions as alternative to statistical techniques conventionally used in the QbD concept by means of computing methods for pharmaceutical industry [19].

Steps toward another line of application of QbD have been addressed by recent works, that discuss the possibility of adapting the QbD approach in order to apply it in the development of biomedical technologies [11, 13, 20, 21].

In this work, QbD is adapted in order to be applied in the development of a health technology for non-magnetic metallic foreign bodies localization, by means of a high sensitivity and low cost magnetic sensor, based on giant magnetoimpedance (GMI). Aiming at implementing this quality tool for the biomedical device under development, their specific parameters of TPP, CQA and CPP were identified. Moreover, it should be noticed that the present work proposes a new approach to configure the Design Space, based on a fuzzy inference system (FIS) framework, rather than the conventional statistical approaches.

2. **Methods**

Aiming at meeting the metrological priorities, considering the biomedical application of the measuring device under development [10, 11], the Target Product Profile (TPP) of QbD, associated to the functionalities of the technology, was defined. Based on the TPP and on risk analysis techniques, the Critical Quality Attributes (CQA) were specified, consisting of the technology characteristics which need to be controlled during the assembly process, in order to guarantee its quality. Likewise, the Critical Process Parameters (CPP) were outlined, consisting of the parameters that have significant influence on the critical quality attributes of the device. These three earliest stages of QbD were determined with the support of a brainstorming activity performed by a multidisciplinary team.

In order to outline the next step, which is the definition of the Design Space, the input ranges of the CPPs were defined. These ranges were established aiming at ensure suitable operational values for all CQAs.

On the contrary of the huge databases available in the pharmaceutical industry, there is a lack of such databases for biomedical technologies, precluding the use of the statistical methods
conventionally employed in that sector. Consequently, the adaptation of the conventional QbD method was necessary. Therefore, the Design Space configuration was formulated by a new approach based on a fuzzy inference system, enabling the analysis of complex systems without the need for sophisticated statistical models. Such inference is based on the interaction of linguistic variables and membership functions, which may be defined by experts brainstorm.

Aiming at exemplifying the process for Design Space configuration, the developed algorithm was applied to characterize the relationship of a set of two CPPs and two CQAs. The estimated optimal operating ranges for the two selected CPPs (amplitude of the AC electric current passing through the solenoid that generates the primary magnetic flux density, CPP\(_{B2}\); and its frequency, CPP\(_{A2}\)) with respect to two CQAs (transducer sensitivity, CQA\(_3\); and secondary magnetic flux density, CQA\(_7\)). The linguistic variables adopted represent the level of suitability of each process parameter value (Unsuitable, Acceptable and Ideal) to the adequacy of each defined CQA to the desired quality of the device’s TPPs. Furthermore, fuzzy membership functions were employed to represent how much each operating value refers to the linguistic variables. The fuzzy inference for the two CQAs generated two maps of operating ranges. In this way, the Design Space can be obtained by intersecting the best performance area for the two CQA maps.

3. Results

The Target Product Profile (TPP) was defined according to the health technology features that meet the associated surgical demands of foreign body detection and localization. The next step consisted in determining the Critical Quality Attributes (CQA) corresponding to the critical technology features that need to be evaluated throughout the device development and manufacturing process. With the CQA data, risk analysis, as well as brainstorming, the Critical Process Parameters (CPP) related with each CQA were determined. Table 1 presents the resulting features associated with these three early stages of QbD (TPP, CQA and CPP) applied to the developing biomedical system under development.

Based on TPP, CQA and CPP indicators (Table 1), a risk analysis between each TPP and CQA, as well as between each CQA and CPP, indicated the degree of relevance between each other (classified as High, Medium and Low).

As stated in the previous section, the Design Space configuration was adapted for biomedical technology applications by incorporating a fuzzy system. For assessing the device performance according to Design Space, it is proposed the adoption, among the QbD requirements, of metrological traceability of the measurement results of the defined CPP parameters, including its adequacy to a specified target measurement uncertainty.

In order to illustrate this adaptation, two critical attributes associated to the technology, the transducer sensitivity (CQA\(_3\)) and the secondary magnetic flux density (CQA\(_7\)), were studied in relation to two critical parameters, the frequency of the primary magnetic flux density (CPP\(_{A2}\)) and the current intensity (CPP\(_{B2}\)) passing through the solenoid that generates this primary magnetic source. The definition of CPP ranges of values for process parameters were obtained by means of theoretical models, simulations or experimental results. For instance, the relation of the secondary magnetic flux density (CQA\(_7\)) with the frequency of the primary magnetic field (CPP\(_{A2}\)) can be established in such way that the magnetic flux density increases with the frequency until about 100 kHz, when it saturates around a maximum value [2]. Thus, the range between 0 and 100 Hz presents lower performance for CQA\(_7\), while the acceptable range between 100 Hz and 10 kHz evolves into a better classification, and frequencies above 10 kHz can be considered ideal, being predominantly of higher performance, as shown in figure 1b.

The optimal ranges for the values of frequency of the primary magnetic flux density (CPP\(_{A2}\)) and the current intensity passing through the solenoid (CPP\(_{B2}\)), considering the two critical attributes of “transducer sensitivity” and “secondary magnetic flux density”, CQA\(_3\) and CQA\(_7\) respectively, are represented in figures 1a and 1b. Although for CQA\(_7\) a wide area of the surface plot corresponds to ideal performance, for CQA\(_3\), higher performance is obtained only within a limited range of CPP values.
Table 1. TPP, CQA and CPP indicators for the system under development, for non-magnetic metallic foreign bodies localization in humans.

| Code | Target Product Profile (TPP) | Code | Critical Quality Attributes (CQA) | Code | Critical Process Parameters (CPP) |
|------|-----------------------------|------|----------------------------------|------|----------------------------------|
| A    | High sensitivity magnetic transducer | 1    | Spatial Resolution | A2   | Frequency of the primary field |
| B    | Location of foreign body (non-magnetic) | 2    | Operation at ambient temperature | B2   | Current intensity |
| C    | High accuracy | 3    | Transducer sensitivity | C2   | Current intensity (circuit) |
| D    | Low measurement uncertainty | 4    | Gradiometric configuration | D2   | Circuit’s supply voltage |
| E    | Foreign body location at different distances | 5    | Signal to noise ratio | E2   | Solenoid dimensions |
| F    | Environmental sustainability | 6    | Primary magnetic flux | F2   | GMI supply voltage |
| G    | Safety | 7    | Secondary magnetic flux | G2   | Oscillator supply voltage |
| H    | Low complexity manufacturing | 8    | Resolution time | H2   | Supply Voltage (Conditioner) |
| I    | Low manufacturing cost | 9    | Circuit characteristics (size) | J2   | AC frequency of the current in the sensor |
| J    | Harmlessness | 10   | Circuit characteristics (components) | L2   | Sensor size |
| L    | Low operating cost | 11   | Sample characteristics sensor | M2   | Homogeneity of the sensor |
| M    | Reduced complexity of operation | 12   | Signal processing | N2   | Voltage Stability |
| N    | Portability | 13   | Signal processing | O2   | Signal amplification |
| O    | Low maintenance complexity | 14   | Signal processing | P2   | Relative position between the sensors and solenoid |
| P    | Low cost of maintenance (calibration included) | 15   | Signal processing | Q2   | Circuit noise |

The Design Space obtained by combining both CQA requirements, as shown in figures 2a and 2b, indicates that the highest performance is obtained for frequencies between 7 and 9 kHz for the primary magnetic field, with an AC current passing through the solenoid between 0.6 and 1.8 mA.

![Figure 1](image1.png)

**Figure 1.** Surface plot of the FIS of CPP$_{A2}$ and CPP$_{B2}$ in respect of (a) CQA$_3$ and (b) CQA$_7$. 
By analyzing the zoomed surface plot of the Design Space (figure 2b), the possibility of applying frequencies between 3 and 9 kHz is evidenced, provided that the maximum allowed current intensity is reduced as frequency decreases.

4. Conclusion
In the present work, the modern quality tool, Quality by Design (QbD), that has been applied since 2004 in the pharmaceutical and biotechnology industries is adapted for application in the development of a biomedical technology aimed at non-magnetic metallic foreign body localization.

The basic stages of the QbD methodology were adapted in order to define the health technology features that meet the associated surgical demands of foreign body detection and localization, including the Target Product Profile (TPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP). Considering that the lack of databases for biomedical technologies precludes the use of the statistical methods conventionally employed by QbD in the pharmaceutical industry, the Design Space configuration becomes a challenge to be overcome. Therefore, a recently proposed QbD-fuzzy system was adapted to the biomedical localization system in order to designate the range of CPP values associated with the highest performance of the device under development [21]. It is proposed the adoption of the requirement of metrological traceability and adequacy to a target uncertainty in the CPP values assessment. These aspects are not taken into consideration in the classical approach of QbD. In order to illustrate the possible information obtained by outlining the Design Space, two critical attributes associated to the technology (CQA3 and CQA7) were studied in relation to two CPPs (CPPA2 and CPPB2). As a result, the optimal ranges for the values of frequency of the primary magnetic flux density and the current intensity passing through the solenoid that generates this primary magnetic field, considering the two critical attributes of “transducer sensitivity” and “secondary magnetic flux density”, CQA3 and CQA7, respectively, were represented by a Design Space area. The obtained results indicate that the best possible performance combining both CQA requirements are obtained for frequencies between 7 and 9 kHz and AC current intensities between 0.6 and 1.8 mA. According to the Design Space configuration, it is also possible to apply frequencies between 3 and 7 kHz, as long as the maximum allowed current intensity is reduced as the frequency decreases.

The obtained Design Space configuration, for the selected CQAs and CPPs associated to the non-magnetic metallic foreign body localization system, points out the potential contribution of QbD for the scientific understanding of the processes and, consequently, for ensuring proper and safe performance of biomedical technologies under development.
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