Multi-parameter fuzzy design space for QbD approach applied in the development of biomedical devices

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Abstract. Since 2004, on the recommendation of the Food and Drug Administration (FDA), the concept of Quality by Design (QbD) has been widely applied by the pharmaceutical industry in drug development. The paradigm for quality assurance has been changed from inspections tests to focusing on increasing control within manufacturing processes. Recently, the methodology of QbD has gained space in the area of development of transducers for biomedical application. In order to advance on the adoption of this approach to the characteristics and needs of this new field, a methodology of representation of a multi-parameter Design Space with fuzzy inference was developed.

1. Introduction
The development of new sensors/transducers applied to the biomedical area must follow high standards of reliability, searching for high sensitivity, accuracy and precision; low-cost of fabrication and operation; low complexity; portability; as well as safety/innocuousness; in order to present efficacy in the treatment of patients, without generating adverse effects [1-2]. Based on these precepts, PUC-Rio's Biometrology Laboratory (LaBioMet) carries out research for the development of sensors and transducers based on properties such as the Giant Magnetoimpedance (GMI) effect. In this line of research, a system for localization of non-ferromagnetic metallic objects inside the human body, using GMI magnetometers, is currently in its advanced stages of development. This device is designed to help medical staff by providing an innocuous and more accurate foreign body location technique for effective surgical removal since all the currently available alternatives (radiography, computed tomography, and radioscopy) use ionizing radiation and lead to long and often unsuccessful procedures. [3-10]. The principle of operation of the developed system consists of using a solenoid as a time-varying primary magnetic field generator, which causes the occurrence of eddy currents in metallic bodies. These currents consequently produce a time-varying secondary magnetic flux density that can be measured by high sensitivity magnetometers in gradiometric (differential) configuration.

Since 2004, a new approach to quality assurance of products and processes has been used by the pharmaceutical industry. This new approach known as Quality by Design (QbD) is formed by a series of steps aimed at ensuring the quality of products manufactured more efficiently, both in operating costs and in their final quality [12-13]. According to the International Conference on Harmonization...
(ICH), QbD is defined by the identification of product-related factors, such as the Target Product Profile (TPP), Critical Quality Attribute (CQA) and Critical Process Parameters (CPP) and the relationship between them (Design Space and Control Strategy).

In a simplified way, QbD seeks to establish the dependence that the critical attributes of the product (CQA) present with the critical process parameters (CPP) of the product. The understanding of these relationships is obtained by means of the Design Space (DS) that establishes the way in which two or more parameters interact to represent a CQA specification better. In this way, operation bands are defined optimizing the operation of the CPPs and guaranteeing the final quality, safety, and efficacy of the product (TPP) [14-18].

Aiming at guaranteeing the quality of prototypes under development in LaBioMet, studies for the adaptation and implementation of the methodology proposed in QbD in the process of developing biomedical technologies were performed [19-21]. However, in this case, emerges the challenge of establishing a method that would allow the development of a Design Space formed by the significant number of parameters comprised in this new application, with multiple CQA and CPPs (represented by different units and ranges of operation).

This work describes the adaptations performed on the methodology based on fuzzy inference system [20, 21], with the objective of implementing a multi-parameter QbD approach to outline the Design Space for the development of the biomedical device for non-ferromagnetic metallic foreign bodies localization using low-cost GMI sensors.

2. Methods

The implementation of the QbD methodology required a series of discussions, conducted by the involved researchers, to identify all possible Critical Quality Attributes and Process Parameters (CPP and CQA) directly associated with the Target Product Profile (TPP) of the developing system for metallic foreign bodies localization. As a result, 21 CPPs and 8 CQAs representing the critical aspects of quality assurance for the localization system were identified.

The risk analysis between CPPs and CQAs, as characterized, as a preliminary step, for outlining the Design Space (DS) image representative of the relation between all critical indexes. Basically, it was established the degrees of influence that each CPP had on the CQA (high, medium or low); and the parameters classified with high impact were selected for consideration in the Design Space configuration.

After this first screening, all possible cases of CQA related to a given CPP were identified. The procedure was repeated for the other CPPs, resulting in the complete group of parameters.

For a particular CPP (e.g., CPP1) operating band’s determination, a fuzzy inference (FI) were performed between this CPP in respect to and each CQA with a high degree of influence with it. Each FI generates a two-dimensional graph representing the bands that optimize the given CPP under analysis.

Concerning CPP1, 5 CQAs had a high degree of influence, resulting in a fuzzy inference with five different CPP bands (each one according to all the previously CQAs identified as high related). In this particular case, the CPP1 according to the CQA4, CQA6, CQA7 and CQA8 were the same, and the only case different appear for the CPP1 according to the CQA5. As a result, it was possible to obtain a two-dimensional graph (of the best bands of operation) that represent the CPPs (for CQA4, CQA6, CQA7, and CQA8) in one axis and the CPP1 with respect to the CQA5 in the other. The intersection between the result of CPP in each axis of this two-dimensional graph enabled the description of the band of operation in which the CPP guaranteed the appropriate quality of the device.

The same methodology was applied to calculate the band of operation of the CPP2 in this work.

When there are more than two operating bands of a given CPP (when analyzed in respect to all significant CQAs), the visualization of the graph becomes restrict to a one-dimensional, where one axis (horizontal axis) represents the best's operation's band to the CPP in question, and the other axis (vertical axis) represents the degree of conformity the operating values.
3. Results

In this work, a full implementation of QbD approach was conducted for calculating the best bands of operation of the CPP\textsubscript{1} and CPP\textsubscript{2}.

The Critical Quality Attributes, Process Parameters (CPP\textsubscript{s} and CQA\textsubscript{s}) directly associated with the Target Product Profile (TPP\textsubscript{s}) identified by the researchers of the present project (developing system for metallic foreign bodies localization) were obtained through a brainstorm, and the result is presented in Table 1. As a consequence of this effort, it was possible to conduct a study of a risk analysis between all CPP\textsubscript{s} and CQA\textsubscript{s}, as shown in Table 2.

Table 1 – The relevant TPP, CQA and CPP identified for the metallic foreign bodies localization’s system.

| Code | Target Product Profile (TPP) | Critical Quality Attributes (CQA) | Code | Critical Process Parameter (CPP) |
|------|-----------------------------|----------------------------------|------|----------------------------------|
| TPP\textsubscript{1} | Location of metallic foreign body (non-magnetic) | CQA\textsubscript{1} Spatial resolution | CPP\textsubscript{1} Frequency of the primary field |
| TPP\textsubscript{2} | High accuracy | CQA\textsubscript{2} Operation at ambient temperature | CPP\textsubscript{2} Current intensity |
| TPP\textsubscript{3} | Low measurement uncertainty | CQA\textsubscript{3} Transducer sensitivity | CPP\textsubscript{3} Current intensity (circuit) |
| TPP\textsubscript{4} | Environmental sustainability | CQA\textsubscript{4} SIGNAL TO NOISE RATIO | CPP\textsubscript{4} Circuit’s supply voltage |
| TPP\textsubscript{5} | Safety (harmlessness) | CQA\textsubscript{5} Secondary magnetic flux | CPP\textsubscript{5} Sensor sensitivity |
| TPP\textsubscript{6} | Low complexity manufacturing | CQA\textsubscript{6} Resolution time | CPP\textsubscript{6} Solenoid’s dimensions |
| TPP\textsubscript{7} | Low manufacturing cost | CQA\textsubscript{7} Circuit characteristics | CPP\textsubscript{7} GMI supply voltage |
| TPP\textsubscript{8} | Low operating cost | CQA\textsubscript{8} Set up | CPP\textsubscript{8} Oscillator supply voltage |
| TPP\textsubscript{9} | Reduced complexity of operation | CQA\textsubscript{9} Sensor characteristics | CPP\textsubscript{9} Sensor characteristics |
| TPP\textsubscript{10} | Portability | CQA\textsubscript{10} AC in GMI sensor | CPP\textsubscript{10} AC frequency of the current in the sensor |
| CPP\textsubscript{11} | Low complexity (calibration included) | CQA\textsubscript{11} Homogeneity of the sensor | CPP\textsubscript{12} Sensor size |
| TPP\textsubscript{12} | Low cost of maintenance (calibration included) | CQA\textsubscript{12} Gradiometric configuration | CPP\textsubscript{13} Homogeneity of the sensor |
| | | | CPP\textsubscript{14} Voltage Stability |
| | | | CPP\textsubscript{15} Signal amplification |
| | | | CPP\textsubscript{16} Relative position between the sensors and solenoid |

Table 2 – Risk Analysis of all the parameters CPP and CAQ.

| Code (CPP) | Code (CQA) |
|------------|------------|
| CPP\textsubscript{1} | L L L L L H M L L L L H L L L L L L |
| CPP\textsubscript{2} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{3} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{4} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{5} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{6} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{7} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{8} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{9} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{10} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{11} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{12} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{13} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{14} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{15} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{16} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{17} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{18} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{19} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{20} | L L L L L L L L L L L L L L L L |
| CPP\textsubscript{21} | L L L L L L L L L L L L L L L L |

The Design Space maps for all the associations between CPP\textsubscript{1} according to all high influenced CQA\textsubscript{s} was built. The same was performed to the CPP\textsubscript{2}.
Figure 1a presents DS relative to CPP₁, which is the critical process parameter that corresponds to the frequency of a primary magnetic flux density, used to induce eddy currents in the foreign object. The induced currents generate a secondary magnetic flux density that can be detected by the sensing component of the system.

Figure 1 – Design Space maps obtained for the whole set of associations of the CPP₁ (frequency of the primary magnetic flux density) in respect to all CQA₅ with high influence. In (a), the map of the Design Space obtained for the CPP₁ and, in (b), the results of its frequency range that optimizes the device’s operation.

The map of Design Space for CPP₂ (figure 1a) allows identifying the range of the frequency of the solenoid’s excitation current that ensures the appropriate quality of the localization system (figure 1b).

In this case, the operating band between 7 kHz and 11 kHz was well evaluated but the best operating band obtained was between 7 kHz and 9 kHz.

Figure 2a presents DS relative to CPP₂, which is the critical process parameter that corresponds to the current intensity of a primary magnetic generator, used to induce eddy currents in the foreign object. The bands of operating of this Process Parameter are best observed in the figure 2b.

Figure 2 – Design Space maps obtained for the whole set of associations of the CPP₂ (Current Intensity) in respect to all CQA₅ with high influence. In (a), the map of the Design Space obtained for the CPP₂ and, in (b), the results of its current range that optimizes the device’s operation.

For the CPP₂, the map of Design Space (figure 2a) allows identifying the range of intensity of the solenoid’s excitation current that ensures the appropriate quality of the localization system (figure 2b). It’s possible to observe that the best operation band is approximately from 1.6 mA to 2.0 mA.
4. Conclusion

This work presents an evolved adaptation of the Quality by Design (QbD), already used in the pharmaceutical industry, for the quality assurance of biomedical technologies. The existence of a large number of parameters characterizing these applications has been considered in the fuzzy inference to configure a resulting representation of the multi-parameter Design Space.

Unlike what occurs in the pharmaceutical industry, the $CPP_s$ for the QbD applied to the development of sensors/transducers has no dependence whatsoever. In this scenery, the analysis of the Design Space becomes restricted to the inference fuzzy of all the bands of operation of a given $CPP$ regarding all the $CQA_s$ with high relevance.

The developed approach was applied to the complete critical process parameter corresponding to the frequency of the primary magnetic flux density generated by the locating device, and the intensity of the current applied to the primary magnetic field generator (solenoid). The analysis allowed identifying the appropriate range of frequency between 7 kHz and 11 kHz (figure 1b), and the range of current intensity between 1.6 mA to 2.0 mA (figure 2b), for the performance of the transducer (considering all the other relevant requirements of the non-magnetic metallic foreign body localization system). Nevertheless, it is possible to restrict the operating bands of the $CPP_1$ to a better zone (7 kHz to 9 kHz). Since the present study performed a full analysis of $CPP_1$ and $CPP_2$ associations with the whole set of $CQA_s$, and our previous study, in [21], evaluated the same critical parameters considering their interaction with just two quality attributes, a slight difference was observed in the best-operating bands obtained. This aspect stresses the importance of the complete analysis of the QbD application.

The presented advancements on the implementation of the QbD approach in the development of health technologies can contribute as a step forward in ensuring reliable diagnosis and treatments.

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