XXI IMEKO World Congress "Measurement in Research and Industry"
August 30 – September 4, 2015, Prague, Czech Republic

IMPLEMENTING FIRST STAGES OF QUALITY BY DESIGN APPROACH IN THE DEVELOPMENT OF AN ASSISTIVE ROBOTICS TECHNOLOGY

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Abstract – The Quality by Design (QbD) concept has been successfully used in the pharmaceutical industry since 2004. This work introduces the first steps for the implementation of QbD in the medical device field and incorporates metrological concerns to the quality approach, determining the Target Product Profile, Critical Quality Attributes and Critical Process Parameters for a robotic assistive technology development intended to help locomotion of elderly people.

Keywords: metrology, assistive technology, robotics, quality by design

1. INTRODUCTION

Considering the progressive increase in life expectancy and the consequent growth of the elderly population, an increased demand for assistive devices for mobility is estimated [1, 2], as also recognized by the World Health Organization, which recommended the member states to promote the availability, reliability and safety of assistive devices [3, 4]. Since the early 2000s, robotics has been strongly applied to the sector of medical devices, including assistive technologies [5]. The greater complexity of biomedical developments, in turn, also requires appropriate tools to guarantee its reliability [6, 7, 8].

In the pharmaceutical and biotechnology industry, since 2004, Quality by Design approach (QbD) has been applied to guarantee the quality of products [9]. This quality tool is associated with a better scientific understanding of critical processes and product quality by setting control strategies based on limits established during the development phase that contribute to the entire product life cycle, resulting in a process of flexible manufacturing and lean that allows its adaptation and continuous improvement [10, 11, 12]. However, metrological requirements do not appear in the QbD concept described in the literature [7].

The application of QbD in the pharmaceutical industry is carried out by a sequence of steps as indicated below [13]:

- Definition of the product profile target (TPP - Target Product Profile), composed of the quality characteristics of the product to ensure its safety and efficacy. This step consists of a tool for setting the strategic basis for the development of drug product being organized in clinical terms, including inter alia the pharmacology, indications and usage, which are associated with chemical aspects such as purity, stability, solubility, etc.

- Definition of the Critical Quality Attributes (CQA) consisting of the physical, chemical, biological and microbiological that need to be controlled to ensure the quality of the pharmaceutical product.

- Determination of the critical process parameters (CPP) whose variability limits need to be established to ensure a pharmaceutical product with the desired features.

- Determination of Design Space relating the input variables, process parameters and CQA is used to define the acceptance criteria of the variability of the process parameters. Thus, this step determines the optimized configuration of the CPPs by multivariate data analysis, and experimental design.

- Definition of Control Strategy, consisting of a quality control strategy based on the safety and efficacy of the product, enabling the continuous optimization of product characteristics.

Considering the importance of the devices with biomedical application reliability assurance in general, the application of the QbD approach in the development of products derived from this sector, such as biomedical technologies represents an important alternative for security and performance diagnosis, treatment, rehabilitation, etc. [7, 14].

This paper aims at adapting QbD, by determining its preliminary stages of TPP, CQA and CPP associated to the development of a robotic assistive device to help locomotion of the elderly, incorporating metrological aspects concerns to the quality approach. The studies also intend to contribute to the implementation of QbD approach to developing technologies with biomedical application.

2. METHODOLOGY

In order to determine the target product profile (TPP), which for the specific situation was considered as corresponding to the features of the most appropriate device

to the target population, we sought to identify the most relevant clinical aspects for the elderly population that should be met by technology assistive robotics in development. To this end a questionnaire was designed and applied to a multidisciplinary team of the Centre for Studies and Research on Ageing (CEPE) of the Secretariat of Health of the State of Rio de Janeiro, consisting of seventeen experts in medicine, physical therapy, occupational therapy, nursing, neuropsychology, nutrition, dental and social assistance. Most respondents that represented professional groups were those from the fields of medicine (23.53%), physiotherapy (17.65%) and occupational therapy (17.65%). With the results of the priority clinical groups were identified the groups of elderly patients to be benefited by the features of assistive device development and the most relevant clinical characteristics, associated with diseases highlighted by the expert respondents. Such clinical aspects were then grouped based on the functional deficits to which they relate.

Through statistical analysis, determining the functional deficits associated with clinical characteristics most often indicated by experts, also considering other aspects described in the literature, the clinical difficulties were identified and ordered to be prioritized and met by assistive technology. Based on these clinical priorities were outlined the features to be implemented in the developing device [5, 6], thus concluding the step of preparing the TPP.

Based on the information of this first stage in the literature and the use of risk analysis techniques, as recommended by the International Committee of Harmonization (ICH Q9), the Critical Quality Attributes (CQA) were specified, consisting of the characteristics technology which need to be controlled during the assembly process in order to guarantee its quality. Likewise, the critical process parameters were delineated, consisting of the parameters that have significant influence on the critical quality attributes of the device [9, 10].

Examples of evaluations to be considered in order to incorporate metrological aspects on the QbD methodology were analyzed. Thus, for the sensor components of the device, it is proposed to incorporate metrological characteristics with the aim of describing the behavior of the measuring systems.

3. RESULTS

In the present study we determined the initial stages of implementation of QbD approach to quality assurance a robotic assistive technology, by identifying the TPP associated with the configuration of the suitable features to the aging population; the determination of Critical Quality Attributes (CQA), consisting of the characteristics of technology that need to be controlled through the assembly process in order to guarantee its quality; and the Critical Process Parameters (CPP) that provide assurance of quality regarding the defined target device profile.

Through a questionnaire applied to a multidisciplinary group of experts from the Centre for Studies and Research on Ageing (CEPE), the most relevant clinical features were outlined, associated with disease groups highlighted by expert respondents and, based on this information were defined the functional deficits to be met by the features of assistive developing device were defined, as follows:

(1) Balance Disorder
(2) Mobility Impairment
(3) Visual Impairment
(4) Cognitive impairment
(5) Balance disorder associated with mobility impairment
(6) Balance disorder, mobility impairment and visual impairment
(7) Balance disorder, mobility, visual and cognitive impairments associated

Functional deficits with priority to be attended by technology were identified through the analysis of the Pareto diagram shown in Figure 1, in which the numbering was used (1) to (7) to identify functional deficits in the statistical study.

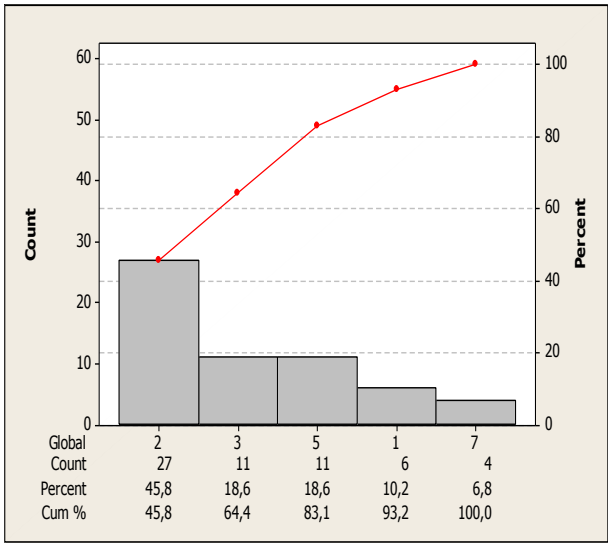

Fig. 1. Pareto diagram with the most common functional deficits in the patient groups to be benefited by assistive robotic device, based on the clinical characteristics indicated by the respondent multidisciplinary team.

As noted in Figure 1, the most relevant four clinical affections, in order of importance are:
- Mobility Impairment (code 2)
- Visual Impairment (code 3)
- Balance disorder associated with mobility impairment (code 5)
- Balance Disorder (code 1)

However, analyzing the data with more emphasis on the weights derived from the medical and physiotherapy area, the balance deficit starts to be set as the largest clinical priority to be benefited by technology.

The conclusion of the QbD step in determining the TPP was accomplished with the identification of priority features of assistive technology, involving the prevention of falls; assistance for mobility; and obstacle avoidance and positioning.

From TPP settings derived from the application of questionnaires and the data of literature regarding assistive robotic devices, as well as the application of risk analysis, the most critical characteristics of the technology (CQA) were defined (Table 1). These critical attributes to device quality assurance demand greater control of parameters

acceptance limits along its assembly. Table 1 presents the list of critical attributes identified and their classification according to their relevance in relation to assure the defined features of robotic assistive technology (TPP).

Table 1. Degree of relevance of critical attributes of quality (CQA) in relation to the features of the technology (TPP).

	TPP			
CQA	Fall Prevention	Mobility Aid	Obstacle Avoidance	Aesthetic Appearance
Design issues	High	Medium	Medium	High
Angle of the robot base measured by gyroscope	High	Medium	Medium	Low
Angular velocity	High	Medium	Low	Low
Emergency stop	High	High	High	Low
Force exerted by the user to start the robot-assisted mobility	High	High	Medium	Low
Force exerted by the user to push the device forward	High	Medium	Low	Low
Device speed adaptation to speed of patient	High	High	Low	Low
Performance of the device for going up and down step	High	High	Medium	Low
Obstacle detection	High	High	High	Low
Orientation to the goal	Low	Medium	High	Low
Listening and vibrating alarms.	Medium	High	Medium	Low
Global Positioning System	Low	Medium	High	Low
Device aesthetic focused on patient compliance	Low	Low	Low	High
Energy efficiency	High	High	High	Low
Maximum distance to reach the desired route	Low	Medium	High	Low
Route selection	Low	Medium	High	Low

Tables 2, 3, 4 and 5 present the critical process parameters (CPP) that make up the critical quality attributes (CQA) for each of the functionalities delineated for the device (TPP) are presented in Tables 2, 3, 4 and 5, respectively for the features of Fall Prevention, Mobility Aid, Obstacle Avoidance and Aesthetic Appearance.

One of the most important aspects in the field of assistive technology is the performance of the embodied measuring device operation. Thus, it becomes necessary to control the metrological characteristics of these components.

As shown in Figure 1, the measuring components of the device consist of the following elements:

1. MinIMU-9 v2 Gyro, Accelerometer, and Compass, constituted by a board that combines ST's L3GD20 3-axis gyroscope and LSM303DLHC 3-axis accelerometer and 3-axis magnetometer to form an inertial measurement unit (IMU). This element is used in processes associated with the functionalities of fall prevention, assisting locomotion and obstacle avoidance.
2. Rotary Optical Encoder (ENA1J-B28-L00100L), used in the features of fall prevention, assisting locomotion and obstacle avoidance.
3. High Performance Sonar Range Finder (LV-Max Sonar ®-EZ1), mainly used in the processes associated with the functionality of obstacle avoidance.
4. Global Positioning System (GPS).

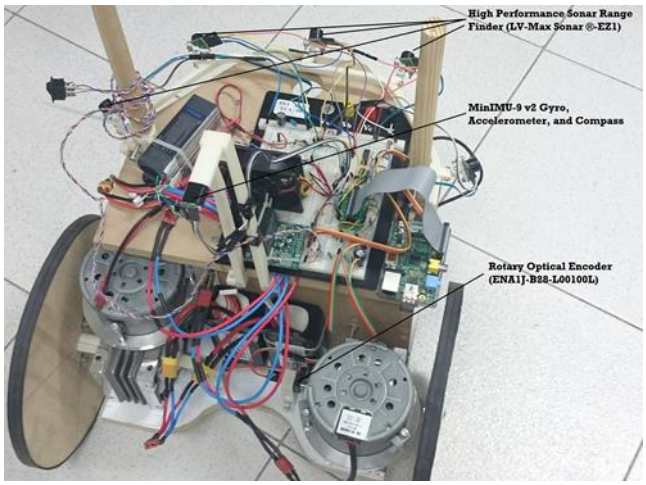

Fig. 1. Sensors embodied in the device prototype.

In order to introduce metrological criteria in the quality approach of QbD, it is proposed to incorporate the evaluation of metrological parameters of measuring components, with metrological traceability requirements, and include the estimative of measurement uncertainty associated to the evaluation of critical quality attributes identified and associated process parameters, contributing on the appropriate setting of the acceptance limits and configuration of the Design Space.

As a next step, by outlining the acceptance limits of the critical process parameters here identified, the Design Space, within which the operation meets the defined quality, can be configured.

Table 2. Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) associated to Fall Prevention.

TPP: Fall Prevention	
CQA	CPP
Design issues	Informational (message type)
	Adequacy for anthropometric aspects
	Chassis stiffness
	Device´s total mass
	Base form (wide)
	Basic shape (length)
	Ground clearance to base
	Wheel diameter
	Firmness and support of stability for hands
	The adequacy form and support material to hand to patient comfort
Angle of the robot base measured by gyroscope	Angle of climb
	Angle of descent
	Angle of lateral inclination
Angular velocity	Walking speed
	Speed stair ascent or descent
	Time of response to fall situation
Emergency stop.	Existence of an emergency stop mechanism

Table 3. Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) associated to Mobility Aid.

TPP: Mobility Aid.	
CQA	CPP
Force exerted by the user to start the robot-assisted mobility	Force during the navigation
	Strength at risk
Device speed adaptation to speed of patient.	Walking speed
	Speed stair ascent or descent
Performance of the device for going up and down step	Wheel diameter
	Arrangement of wheels in thier device base
	Tire Material
Force exerted by the user to push the device forward	Option of automatic or manual navigation modes

Table 4. Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) associated to Obstacle Avoidance.

TPP: Obstacle Avoidance	
CQA	CPP
Obstacle detection	Informational (message type). Sound or vibrating alarm
	Minimum detectable size of the obstacle based on the distance
	Number of sensors
	Field of View Sensor
	Sensors position
	Minimum distance of obstacle detection
Global positioning system (GPS)	GPS Resolution
	Minimum distance between the device and the obstacle-free space that allows the reformulation of the route
Route selection	

Table 5. Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) associated to Aesthetic Appearance.

TPP: Aesthetic Appearance	
CQA	CPP
Device aesthetic focused on patient compliance	Body aesthetic
	Chassis material
	Body Color
	Seat
	Storage compartments

4. CONCLUSIONS

In the present study we determined the initial stages of implementation of QbD approach to quality assurance of a robotic assistive technology, by identifying: the Target Product Profile (TPP), which was defined as corresponding to the most appropriate features to the needs of the patient groups to be benefited by the device; the Critical Quality Attributes (CQA), consisting of the properties that must be controlled within limits to ensure the desired quality, considering aspects of safety and performance; and the Critical Process Parameters (CPP), which demand control of variability limits in order to ensure the desired features of the technology.

In the second and third stages of the approach implementation (CQA and CPP), it is proposed the introduction of metrological aspects such as metrological traceability, measurement uncertainty estimative, among other metrological requirements, to be included in the framework of criteria of the QbD approach.

Preliminary results of QbD implementation contributed to the definition and optimization of the design strategy and development of an assistive robotic device.

This work also contributes to achieve the initial steps of the adaptation of QbD, a modern quality tool already successful and consolidated in the pharmaceutical and biotechnology industry, for implementation in the field of development of biomedical technologies.

ACKNOWLEDGMENTS

The authors thank the Center for Studies and Research on Ageing (CEPE) of the Secretariat of Health of the State of Rio de Janeiro and the Brazilian scientific funding agencies CAPES and FAPERJ.

REFERENCES

[1] X. Yu, “Approaches and Principles of Fall Detection for elderly and patient”, *10th International Conference on Institute for e-health Networking, Applications and Services*, pp. 1-2, Singapore, July 2008.

[2] O Almeida, M Zhang and J Liu, “Dynamic Fall Detection and Pace Measurement in Walking Sticks”, *Joint Workshop on High Confidence Medical Devices, Software, and Systems and Medical Device Plug-and-Play Interoperability*, 2007.

[3] United Nations Organization (UN), *Convention on the Rights of Persons with Disabilities*, United Nations, Geneva, 2006.

[4] World Health Organization (WHO), *Joint position paper on the provision of mobility devices in less-resourced settings: a step towards implementation of the Convention on the Rights of Persons with Disabilities (CRPD) related to personal mobility*, WHO, Geneva, 2011.

[5] O Almeida, M Zhang and J Liu, "Dynamic Fall Detection and Pace Measurement in Walking Sticks", *Joint Workshop on High Confidence Medical Devices, Software, and Systems and Medical Device Plug-and-Play Interoperability*, 2007.

[6] E. Costa Monteiro, "Biometrology: reliability of biomeasurements and ethical implications", "Biometrologia: confiabilidade nas biomedições e repercussões éticas", *Metrologia e Instrumentação*, vol. 6, pp. 6-12, 2007.

[7] E. Costa Monteiro and L. F. Leon. "Metrological Reliability of Medical Devices", *Journal of Physics*, Conference Series, Vol. 588, pp. 012032, 2015.

[8] D. Carlson, O. Oyesanmi and H. Coates, *Trends in medical technology and expected impact on public health* WHO, Geneva, 2010.

[9] A. S Rathore, "Roadmap for Implementation of Quality by Design (QbD) for Biotechnology Products", *Trends in Biotechnology*, Vol. 27, n° 9, pp. 546-553, 2009.

[10] N. Nadpara, R. V. Thumar, V. N. Kalola and P. B. Patel, "Quality by Design (QbD): a complete review". *International Journal of Pharmaceutical Sciences Review and Research*, Vol. 17, n° 4, pp. 20-28, 2012.

[11] International Committee for Harmonization., *ICH harmonized tripartite Guideline. Pharmaceutical Development Q8 (R2)*, August 2009.

[12] Federal Drugs Administration CDER, *Guidance for Industry. Q8 (R2) Pharmaceutical Development*, Food and Drug Administration, Rockville, 2009.

[13] B. Trivedi, "Quality by Design (QbD) in Pharmaceuticals", *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol. 4 Issue 1, 2012.

[14] I. Veljanovski, "Integrating Quality by Design (QbD) in Medical Device Manufacturing Concept, Benefits, and Challenges", *White Paper*, Stevens Institute of Technology, pp.1–9. 2010.