Supplementary material iQbD: a TRL-indexed Quality-by-Design Paradigm for Medical Device Development

Thierry Bastogne

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I. Introduction

This document contains supplementary materials associated with an article: *iQbD: a TRL-indexed Quality-by-Design Paradigm for Medical Device Development* submitted to IEEE Transactions On Biomedical Engineering. This study proposes a new risk-based development paradigm and tests it on a study case presented below.

II. Prototype of Photobleaching Controller for Photodynamic Therapy

The study case is based on a photobleaching controller in photodynamic therapy. The laboratory prototype is described in Figure 1.

III. Central Composite Design of Experiment for Process Optimization

To find the optimal settings associated with the critical process parameters, a central composite design was applied to 27 mice. Nine conditions of experimentation were defined and each point was repeated three times. Such a design of experiments consists in adding two star points by factor (at a distance of α) to a factorial design [1], as illustrated in Figure 2.

IV. Failure Mode and Effect Analysis

A qualitative criticality assessment of process parameters was carried out by implementing a FMECA method. Tables 3, 4 and 5 show results of their hierarchical decomposition. Indeed some primary factors of risk can cause consequences which in turn become other secondary causes of malfunction and inefficacy. A color code was used to easily follow this decomposition. At the end of decomposition, severity, frequency and non-detectability of causes are evaluated according to scales given in Tables I. The resulting criticality ranking is finally presented in Table II. The most critical factor is the potential lack of accuracy for the positioning of the optical fiber. Particular attention was brought to fix this background variable during the experimental session. We only kept the factors with a relative criticality index greater to $C = 4\%$. Seven parameters are concerned but one of them related to the optical parameters cannot be controlled and its effect is taken into account in the error term of the ANOVA model. The six remaining factors are involved in the empirical criticality analysis based on a specific design of experiments whose experimental results are presented in the next section.

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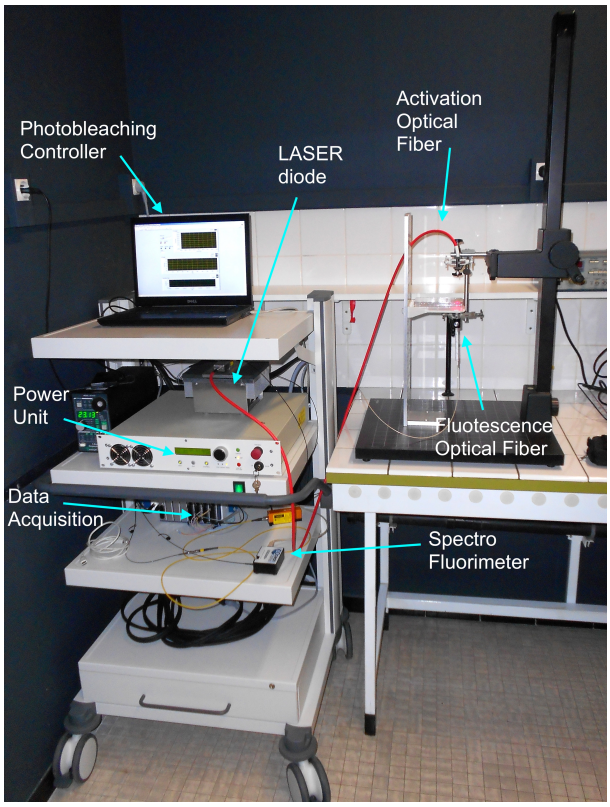

Fig. 1. Prototype of Photobleaching Controller for Photodynamic Therapy.

V. Results

A. Results of the Criticality Assessment

Ranking of the Criticality Assessment related to the FMECA study is presented in Table III.

B. Validation Results

In order to assess the reproducibility of the proposed method, the confirmatory study were performed with the optimal operating point. At the end of the treatments, the

Severity (S)	1 --> Low : no serious consequences
	2 --> Medium : minor consequences
	3 --> High : major consequences
	4 --> Very High : irreparable consequences
Frequency (F)	1 --> Low : rarely occurs
	2 --> Medium : occurs sometimes
	3 --> High : probably occurs
	4 --> Very High : almost certainly occurs
Non Detection (ND)	1 --> There exist very perceptible signs allowing users to avoid a failure
	2 --> Signs are not always perceptible by the user
	3 --> Signs cannot be easily measured
	4 --> No first sign of the event

TABLE I
TABLE OF THE FMECA SCORES FOR THE THREE CRITICALITY COMPOUNDS OF FMECA ANALYSIS: SEVERITY, FREQUENCY AND DETECTABILITY.

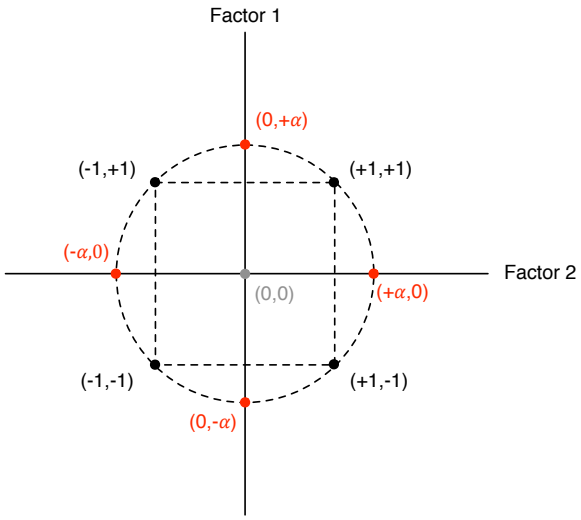

Fig. 2. Experimental points for a two factors central composite design of experiments, with the factorial points in black, the star points in red and the center point in grey ($\boldsymbol{\alpha = \sqrt[4]{2^2} = 1.414}$)

fluorescence index reached a mean of $\mu_{Pb_{end}} = 53.3\%$ ($\sigma_{Pb_{end}} = 2.3\%$). The mean total light dose applied for this modality was $\mu_D = 14.4$ mJ/cm^2 ($\sigma_D = 4.7$ mJ/cm^2). An equivalent continuous illumination was then performed 10 times in order to obtain the same light dose (approximately 90 seconds) and the mean fluorescence index reached was $\mu_{Pb_{end}} = 65.8\%$ ($\sigma_{Pb_{end}} = 5.1\%$).

REFERENCES

[1] LUNDSTEDT, T., SEIFERT, E., ABRAMO, L., THELIN, B., NYSTRÖM, Å., PETTERSEN, J., AND BERGMAN, R. Experimental design and optimization. *Chemometrics and Intelligent Laboratory Systems 42*, 1–2 (1998), 3 – 40.

Failure	Cause	Effect	Criticality Scores			
			S	F	ND	C
Non efficient control (bias ≠ 0 et variance > 0.1)	Wrong trajectory of photobleaching	Ineffective Treatment				
Wrong trajectory of photobleaching	Wrong use of the device	Inaccurate Control (biais ≠ 0 et var > 0.1)				
	Poor Maintenance					
	Unsuitable Environment					
	Internal technical problems					
	Uncontrolled variation of quantity of the administered photosensitizing agent					
	Uncontrolled variation of surface state of the skin					
Wrong use of the device	Wrong value of the drug-light interval	Wrong trajectories due to external factors				
	Bad orientation of the optical fiber					
	Too large distance between the optical fiber and the tumor					
	Wrong initial settings					
	Connection of the bundle		3	2	4	24
Poor Maintenance	Maintenance not made					
	Storage in wrong conditions of the photosensitizing agent or cells					
Inappropriate Environment	Environment light		3	1	1	3
	Environment disturbances		1	2	2	4
	Dust in connection		1	1	4	4
	Inappropriate degree of humidity		2	1	2	4
	Electrical grounding		3	1	1	3
	Inappropriate temperature		3	1	1	3
Internal Failures	Malfunction of optical connections		2	2	4	16
	Broken connections		4	1	4	16
	Damage on optical fiber		3	1	4	12
	Malfunction of the spectrometer					
	Non-functioning spectrometer					
	Malfunction of the LASER source					
	LASER source Non-functioning					
	Software failure		3	1	4	12

Fig. 3. Results of the Failure Mode and Effect Analysis (part 1)

Failure	Cause	Effect	Criticality Scores			
			S	F	ND	C
Uncontrolled variation of the administered dose of photosensitizing agent	Inappropriate dose		4	1	4	16
	Wrong physico-chemical characteristics		4	1	4	16
	Wrong photo-physical characteristics		4	1	4	16
Uncontrolled variations of features related to the element to be treated	Variation of accessibility		3	1	1	3
	Tumor heterogeneity		2	2	2	8
	Variation of tumor size		2	2	1	4
Wrong value of the drug light interval	Bad training	Wrong use of the device	3	1	3	9
	Lack of rigour		3	1	3	9
Wrong orientation of the optical fiber wrt tissue	Bad training		3	1	3	9
	Displacement after schock		3	1	4	12
	Tumor not readily accessible		3	2	1	6
	Lack of accuracy about the positioning device		3	3	4	36
Fiber-tumor distance outside the operating interval	Bad training		3	1	3	9
Wrong initial settings	Inappropriate spectral sensitivity					
	Wrong duty cycle of the light signal					
	Wrong treatment duration		3	2	4	24
	Inapproriate PDT end point		3	2	4	24
Unexecuted Maintenance	Maintenance team not available	Missed maintenance	1	3	2	6
	Omission		1	1	4	4
Inadequate storage of the photosensitizing agent or cells or animals	Inadequate degree of humidity		2	1	3	6
	Expiry date passed		3	2	2	12
Malfunction of the spectro-fluorimeter	Presence of vibrations or shocks	Internal failures	3	1	3	9
Non-functioning of the spectro-fluorimeter	Presence of vibrations or shocks		4	1	3	12
Malfunction of the LASER source	Malfunction of the cooling system					
Non-functioning of the LASER source	Non-functioning of the cooling system					
	Non-functioning of the power supply		4	1	2	8
	Non-functioning of the diode					

Fig. 4. Results of the Failure Mode and Effect Analysis (part 2)

Failure	Cause	Effect	Criticality Scores			
			S	F	ND	C
Inadequate spectral sensitivity	**Inadequate value for the signal integration period**	Wrong initial settings	3	2	4	24
	Inadequates values of the optical parameters		3	2	4	24
	Defective optical connector		3	1	3	9
	Indequate sensitivity of the CCD sensor.		4	1	4	16
Wrong value of the light duty cycle	**Inadequate value of the signal period**		3	2	4	24
	Inadequate value of the light intensity		3	2	4	24
Defective cooling system	Malfunction of the temperature control	Dysfonctionnement de la source laser				
	Malfunction of the Peltier effect		3	1	4	12
	Malfunction of the fan		3	1	4	12
Non-functioning of the cooling system	Non-functioning of the temperature control	Non-functioning of the light source				
	Non-functioning of the Peltier effect		4	1	4	16
	Non-functioning of the fan		4	1	4	16
Non-functioning of the diode	Presence of vibrations and schocks		4	1	4	16
Malfunction of the temperature control	Malfunction of the temperature sensor	Defective cooling system	4	1	3	12
	Malfunction of the controller		4	1	2	8
Non-functioning of the temperature control	Non-functioning of the temperature sensor	Non-functioning of the cooling system	4	1	2	8
	Non-functioning of the controller		4	1	2	8

Fig. 5. Results of the Failure Mode and Effect Analysis (part 3)

N°	Cause	C	%
1	Lack of accuracy for the positioning device	36	7,32
2	Connection bundle	24	4,88
3	Inadequate PDT Duration	24	4,88
4	Inadequate PDT trajectory endpoint	24	4,88
5	Inadequate Signal Period	24	4,88
6	Inadequate Intensity	24	4,88
7	Inadequate integration and sampling periods	24	4,88
8	Inadequate optical parameters	24	4,88
9	Malfunction of optical connectors	16	3,25
10	Non functioning of optical connectors	16	3,25
11	Inadequate dose of photosensitizing agent	16	3,25
12	Inadequate physico-chemical characteristics	16	3,25
13	Inadequate photophysical characteristics	16	3,25
14	Inadequate sensitivity of the CCD sensor	16	3,25
15	Malfunction of the Peltier effect	16	3,25
16	Malfunction of the fan	16	3,25
17	Vibration and shocks on the light source	16	3,25
18	Fiber deterioration	12	2,44
19	Software error	12	2,44
20	Displacement	12	2,44
21	Expiry date passed	12	2,44
22	Vibration and shocks on the spectrometer	12	2,44
23	Non functioning of the Peltier effect	12	2,44
24	Non functioning of the fan	12	2,44
25	Non functioning of the temperature sensor	12	2,44
26	Lack of training	9	1,83
27	Lack of rigour	9	1,83
31	Non functioning of optical connectors	9	1,83
32	Tumor heterogeneity	8	1,63
33	Non functioning of the diode power supply	8	1,63
34	Malfunction of the temperature controller	8	1,63
36	Non functioning of the temperature controller	8	1,63
37	Accessibility to the tumor	6	1,22
38	Unavailability of the maintenance team	6	1,22
39	Inadequate degree of humidity	6	1,22
40	Presence of interferences	4	0,81
41	Dust in connections	4	0,81
43	Variations of tumor size	4	0,81
44	Missed or forgotten maintenance	4	0,81
45	Inadequate light	3	0,61
46	Default of electrical grounding	3	0,61
47	Inadequate temperature	3	0,61

TABLE II
CRITICALITY RANKING OF RISK FACTORS AFTER FMECA

Plackett-Burman Design - Replicate 1								
N° Exp	Rand	U1	U2	U3	U4	U5	U6	Y
		s	%	s	A	s	Spectro.	
4	1	1800	25	30	15	3	Ext.	5984.80
5	2	900	50	30	10	3	Ext.	4965.60
2	3	900	50	60	15	1	Ext.	3536.30
6	4	1800	25	60	10	1	Ext.	4310.30
3	5	900	25	60	15	3	Int.	4801.20
8	6	900	25	30	10	1	Int.	1867.20
7	7	1800	50	30	15	1	Int.	2186.80
1	8	1800	50	60	10	3	Int.	4538.20
Plackett-Burman Design - Replicate 2								
N° Exp	Rand	U1	U2	U3	U4	U5	U6	Y
		s	%	s	A	s	Spectro.	
5	1	900	50	30	10	3	Ext.	3631.4
1	2	1800	50	60	10	3	Int.	4436.7
7	3	1800	50	30	15	1	Int.	4130.4
4	4	1800	25	30	15	3	Ext.	5560.3
3	5	900	25	60	15	3	Int.	5645.6
2	6	900	50	60	15	1	Ext.	4883.4
6	7	1800	25	60	10	1	Ext.	5796.3
8	8	900	25	30	10	1	Int.	7622.9
Plackett-Burman Design - Replicate 3								
N° Exp	Rand	Duree_PDT	End_Point_PDT	Periode_Signal	Intensité	Periode_Inte	Bundle	Y
		s	%	s	A	s	Spectro.	
1	1	1800	50	60	10	3	Int.	2798.8
4	2	1800	25	30	15	3	Ext.	6206.3
2	3	900	50	60	15	1	Ext.	2407.5
3	4	900	25	60	15	3	Int.	4548.1
8	5	900	25	30	10	1	Int.	4818
5	6	900	50	30	10	3	Ext.	3208.2
7	7	1800	50	30	15	1	Int.	3374.4
6	8	1800	25	60	10	1	Ext.	3219.3
Plackett-Burman Design - Replicate 4								
N° Exp	Rand	U1	U2	U3	U4	U5	U6	Y
		s	%	s	A	s	Spectro.	
2	1	900	50	60	15	1	Ext.	3187.9
3	2	900	25	60	15	3	Int.	5164.8
6	3	1800	25	60	10	1	Ext.	7164.2
1	4	1800	50	60	10	3	Int.	4603.7
5	5	900	50	30	10	3	Ext.	9923.5
8	6	900	25	30	10	1	Int.	4762.1
4	7	1800	25	30	15	3	Ext.	5279.1
7	8	1800	50	30	15	1	Int.	2749.8
Plackett-Burman Design - Replicate 5								
N° Exp	Rand	Duree_PDT	End_Point_PDT	Periode_Signal	Intensité	Periode_Inte	Bundle	Y
		s	%	s	A	s	Spectro.	
6	1	1800	25	60	10	1	Ext.	3463
4	2	1800	25	30	15	3	Ext.	5956
8	3	900	25	30	10	1	Int.	4130.8
5	4	900	50	30	10	3	Ext.	3471.4
1	5	1800	50	60	10	3	Int.	3614.2
2	6	900	50	60	15	1	Ext.	4779.3
3	7	900	25	60	15	3	Int.	4462.8
7	8	1800	50	30	15	1	Int.	3571.9

TABLE III

DESCRIPTION OF THE DESIGN OF EXPERIMENTS BASED ON A PLACKETT-BURMAN (HADAMARD) MATRIX. THE DESIGN WAS REPLICATED FIVE TIMES IN A RANDOMIZED ORDER OF THE EXPERIMENTAL CONDITIONS. EACH REPLICATE CORRESPONDS TO A DIFFERENT POSITION OF THE OPTICAL FIBER COLLECTING THE FLUORESCENCE SPECTRA ON THE TISSUE.

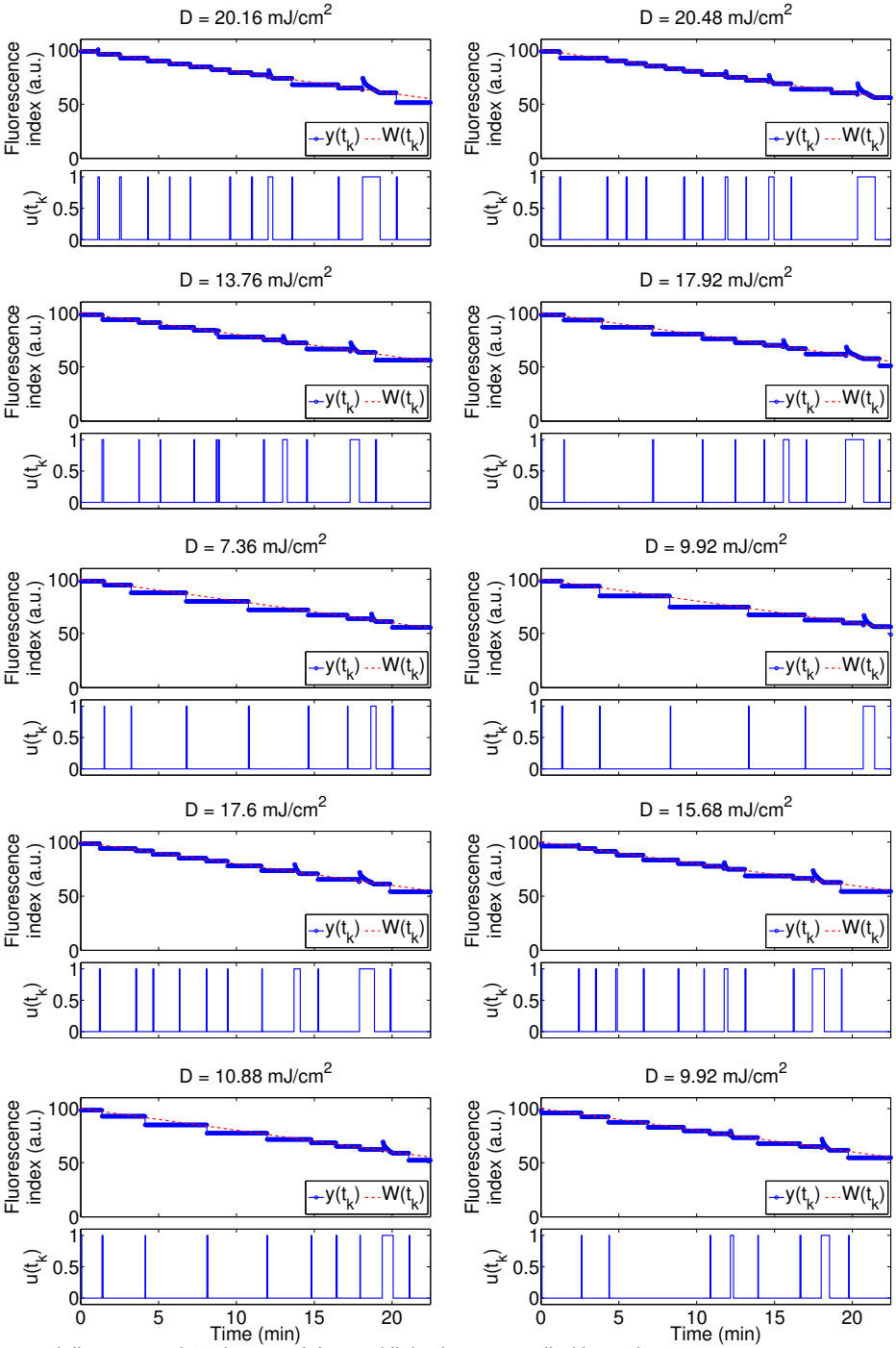

Fig. 6. Optimal treatment modality repeated 10 times and the total light dose D applied in each case