

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

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

Thierry Bastogne

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

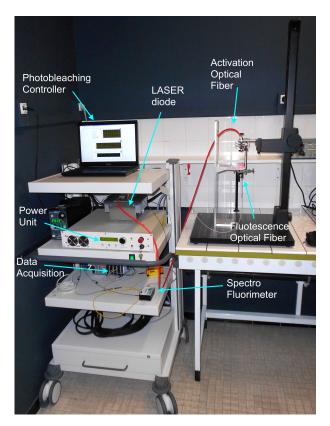


Fig. 1. Prototype of Photobleaching Controller for Photodynamic Therapy.

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.

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

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	1> Low : no serious consequences			
0 11 (0)	2> Medium : minor consequences			
Severity (S)	3> High : major consequences			
	4> Very High : irreparable consequences			
	1> Low : rarely occurs			
F(F)	2> Medium : occurs sometimes			
Frequency (F)	3> High : probably occurs			
	4> Very High : almost certainly occurs			
	1> There exist very perceptible signs allowing users to avoid a failure			
Non Detection (ND)	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.

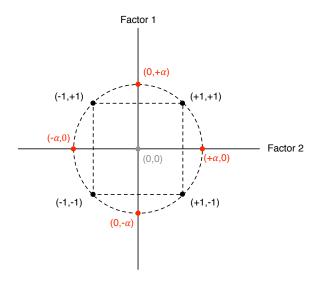


Fig. 2. Experimental points for a two factors central composite design of experiments, with the factorial points in black, the star points in red and the center point in grey ($\alpha=\sqrt[4]{2^2}=1.414$)

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 $\mu_D=14.4~{\rm mJ/cm^2}$ ($\sigma_D=4.7~{\rm mJ/cm^2}$). 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		
	- Incu			F	ND	С
Non efficient control (bias ≠ 0 et variance > 0.1)	Wrong trajectory of photobleaching	Ineffective Treatment				
	Wrong use of the device					
	Poor Maintenance					
	Unsuitable Environment					
Wrong trajectory of photobleaching	Internal technical problems	Inaccurate Control (biais ≠ 0 et var > 0.1)				
priotobleaching	Uncontrolled variation of quantity of the administered photosensitizing agent	0 et val > 0.1)				
	Uncontrolled variation of surface state of the skin					
	Wrong value of the drug-light interval					
	Bad orientation of the optical fiber					
Wrong use of the device	Too large distance between the optical fiber and the tumor					
	Wrong initial settings					
	Connection of the bundle			2	4	24
	Maintenance not made					
Poor Maintenance	Storage in wrong conditions of the photosensitizing agent or cells					
	Environment light		3	1	1	3
	Environment disturbances		1	2	2	4
Inanaranriata Environment	Dust in connection	Wrong trajectories due to	1	1	4	4
Inappropriate Environment	Inappropriate degree of humidity	external factors	2	1	2	4
	Electrical grounding		3	1	1	3
	Inappropriate temperature		3	1	1	3
	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					
Internal Failures	Non-functioning spectrometer					
Internal Failures	Non-functioning spectrometer					
Internal Failures	Malfunction of the LASER source					
Internal Failures						

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

Failure	Cause	Effect		Criticality Scores			
			S	F	ND	С	
	Inappropriate dose		4	1	4	16	
Uncontrolled variation of the administered dose of	Wrong physico-chemical characteristics		4	1	4	16	
photosensitizing agent	Wrong photo-physical characteristics		4	1	4	16	
Uncontrolled variations of	Variation of accessibility		3	1	1	3	
features related to the element to be treated	Tumor heterogeneity		2	2	2	8	
	Variation of tumor size		2	2	1	4	
Wrong value of the drug light	Bad training		3	1	3	9	
interval	Lack of rigour		3	1	3	9	
	Bad training		3	1	3	9	
	Displacement after schock		3	1	4	12	
Wrong orientation of the optical fiber wrt tissue	Tumor not readily accessible		3	2	1	6	
iibei wit tissue	Lack of accuracy about the positioning device	Wrong use of the device	3	3	4	36	
Fiber-tumor distance outside the operating interval	Bad training			1	3	9	
	Inappropriate spectral sensitivity						
Wrong initial settings	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		1	3	2	6	
Offexecuted Maintenance	Omission	Missed maintenance	1	1	4	4	
Inadequate storage of the photosensitizing agent or cells or	Inadequate degree of humidity	Misseu maintenance	2	1	3	6	
animals	Expiry date passed		3	2	2	12	
Malfunction of the spectro- fluorimeter	Presence of vibrations or shocks		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 cooling system	Internal failures					
Non-functioning of the LASER source	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	С	
	Inadequate value for the signal integration period		3	2	4	24	
Inadequate spectral sensitivity	Inadequates values of the optical parameters		3	2	4	24	
	Defective optical connector	Wrong initial settings	3	1	3	9	
	Indequate sensitivity of the CCD sensor.	wrong milai sectings	4	1	4	16	
Wrong value of the light duty	Inadequate value of the signal period		3	2	4	24	
cycle	Inadequate value of the light intensity		3	2	4	24	
	Malfunction of the temperature control	Dysfonctionnement de la source laser					
Defective cooling system	Malfunction of the Peltier effect			1	4	12	
	Malfunction of the fan		3	1	4	12	
	Non-functioning of the temperature control						
Non-functioning of the cooling system	Non-functioning of the Peltier effect	Non-functioning of the light source	4	1	4	16	
	Non-functioning of the fan	ing.i.e source	4	1	4	16	
Non-functioning of the diode	Presence of vibrations and schocks]		1	4	16	
Malfunction of the temperature	Malfunction of the temperature sensor	Defective cooling system		1	3	12	
CONTROL	Malfunction of the controller			1	2	8	
Non-functioning of the temperature control	Non-functioning of the temperature sensor	Non-functioning of the cooling system		1	2	8	
temperature control	Non-functioning of the controller			1	2	8	

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

N°	Cause	С	%
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

	Plac	kett-Burman D	esign - Replica	ite 1				
N° Exp	Rand	U1	U2	U3	U4	U5	U6	
	Kuitu							Υ
		1000	%	S 20	A 1.5	S	Spectro.	5004.00
5	1 2	1800 900	25 50	30	15 10	3	Ext. Ext.	5984.80 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
	Plac	kett-Burman D	esign - Replica	ate 2				
N° Exp	Rand	U1	U2	U3	U4	U5	U6	Υ
		S	%	S	Α	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 7	900 1800	50 25	60	15 10	1	Ext.	4883.4
<u>6</u> 8	8	900	25	30	10	1	Ext. Int.	5796.3 7622.9
8			Design - Replica		10	1	1111.	7022.9
_			End Point P	Periode_		Periode_	I	
N° Exp	Rand	Duree_PDT	DT	Signal	Intensité	Inte	Bundle	Υ
		S	%	s	Α	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				60	10	1	Ext.	3219.3
Plackett-Burman Design - Replicate 4								
	8 Plac	1800 kett-Burman D	25 Design - Replica		-			
N° Exp		kett-Burman D U1	Design - Replica	ute 4	U4	U5	U6	Υ
•	Plac Rand	kett-Burman D U1	Design - Replica U2 %	U3	А	S	Spectro.	
2	Plac Rand	U1 s 900	U2 % 50	U3 s 60	A 15	s 1	Spectro. Ext.	3187.9
2 3	Rand 1 2	U1 s 900 900	vesign - Replica vec	s 60 60	A 15 15	s 1 3	Spectro. Ext. Int.	3187.9 5164.8
2 3 6	Rand 1 2 3	U1 \$ 900 900 1800	## Comparison of Comparison ## Comparison of Comparison	s 60 60 60	A 15 15 10	s 1 3	Spectro. Ext. Int. Ext.	3187.9 5164.8 7164.2
2 3 6 1	Plac Rand 1 2 3 4	### Company of the co	## Comparison of Comparison ## Comparison of Comparison	s 60 60 60	A 15 15 10 10	s 1 3 1	Spectro. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7
2 3 6 1 5	Place Rand 1 2 3 4 5	s 900 900 1800 1800 900	### Company of the co	s 60 60 60 30	A 15 15 10 10 10	s 1 3 1 3 3	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext.	3187.9 5164.8 7164.2 4603.7 9923.5
2 3 6 1 5	Place Rand 1 2 3 4 5 6	s 900 900 1800 1800 900 900	## Page 12 ## Pa	s 60 60 60 30 30 30	A 15 15 10 10 10	s 1 3 1 3 3 1	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1
2 3 6 1 5 8	Place Rand 1 2 3 4 5 6 7	s 900 900 1800 1800 900 900 1800	wesign - Replica W2 % 50 25 25 50 50 25 25	s 60 60 60 30 30 30	A 15 15 10 10 10 10 10	\$ 1 3 1 3 3 1 3 3 1 3 3	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1
2 3 6 1 5	Place Rand 1 2 3 4 5 6 7 8	### No. 1800 1	### Replica ### U2 % 50 25 25 50 50 25 25 50 50 50 50 50 50 50 5	s 60 60 60 30 30 30 30 30	A 15 15 10 10 10	s 1 3 1 3 3 1	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1
2 3 6 1 5 8	Place Rand 1 2 3 4 5 6 7 8	### No. 1800 1	### PROPRIET ### P	ste 4 U3 \$ 60 60 60 60 30 30 30 30 tte 5 Periode_	A 15 15 10 10 10 10 10	s 1 3 1 3 3 1 3 1 Periode_	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8
2 3 6 1 5 8 4	Place Rand 1 2 3 4 5 6 7 8 Place	### STATE STATE	## Page 18	s 60 60 60 30 30 30 ste 5 Periode_Signal	A 15 15 10 10 10 10 15 15	\$ 1 3 1 3 1 3 1 9 Periode_Inte	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Bundle	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1
2 3 6 1 5 8 4 7	Place Rand 1 2 3 4 5 6 7 8 Place Rand	### STAND PROPERTY ### STAND ### STA	### Page 18	s 60 60 60 30 30 30 30 ste 5 Periode_Signal S	A 15 15 10 10 10 10 15 15 15 A	s 1 3 1 3 3 1 3 1 Periode_	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Switch Bundle Spectro.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8
2 3 6 1 5 8 4	Place Rand 1 2 3 4 5 6 7 8 Place	### STATE STATE	## Page 18	s 60 60 60 30 30 30 30 ste 5 Periode_Signal 5 60	A 15 15 10 10 10 10 15 15	\$ 1 3 1 3 3 1 3 1 Periode_ Inte	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Bundle	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8
2 3 6 1 5 8 4 7	Place Rand 1 2 3 4 5 6 7 8 Place Rand	### STAND PROPERTY	## Page 12	s 60 60 60 30 30 30 ste 5 Periode_Signal \$ 60 30 30 30 \$ 30 \$ 30 \$ 30 \$ 30 \$ 30	A 15 15 10 10 10 10 15 15 15 15 A 110	\$ 1 3 1 3 3 1 3 3 1 1 Periode_ Inte	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Section Ext. Ext. Ext. Ext. Ext. Ext. Ext. Ext.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y
2 3 6 1 5 8 4 7 N° Exp	Place Rand 1 2 3 4 5 6 7 8 Place Rand	\$ 900 900 1800 9800 9800 1800 9800 9800 98	## Page 12	s 60 60 60 30 30 ste 5 Periode_Signal \$ 60 30 30 30 30 30 30 30 30 30 30 30 30 30	A 15 15 10 10 10 10 15 15 15 15 15 15 15 15 15 15 11 11 11	s 1 3 1 3 1 3 1 3 1 Periode_ Inte s 1 3 1	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Sundle Spectro. Ext. Ext.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y
2 3 6 1 5 8 4 7 N° Exp	Place Rand 1 2 3 4 5 6 7 8 Place Rand	U1 S 900 900 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 900 1800 1800 1800 1800 1800 1800 1800 900 18	### Company of the image of the	s 60 60 60 30 30 30 ste 5 Periode_Signal \$ 60 30 30 30 \$ 30 \$ 30 \$ 30 \$ 30 \$ 30	A 15 10 10 10 10 10 15 15 15 15 15 15 11 Intensité A 10 15 10	\$ 1 3 1 3 3 1 1 3 1 1 Periode_ Inte	Spectro. Ext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Sext. Int. Ext. Int. Ext. Int. Ext. Int. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y 3463 5956 4130.8
2 3 6 1 5 8 4 7 N° Exp	Place Rand 1 2 3 4 5 6 7 8 Place Rand	U1 S 900 900 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 1800 900 900 900 900 900 900 900 900	## Point Poi	ste 4 U3 \$ 60 60 60 60 30 30 30 30 ste 5 Periode_Signal \$ 60 30 30 30	A 15 10 10 10 10 10 15 15 15 15 15 11 10 10 10 10 10 10 10 10 10 10 10 10	s 1 3 1 3 1 3 1 3 1 1 3 1 Periode_ Inte s 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3	Spectro. Ext. Int. Ext. Ext. Int. Ext. Ext. Ext. Ext.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y 3463 5956 4130.8 3471.4
2 3 6 1 5 8 4 7 N° Exp	Rand 1 2 3 4 5 6 7 8 Place Rand 1 2 3 4 5 5 6 7 8 9 1 4 5 6 7 8 7 8 9 1 6 7 8 7 8 7 8 8 9 1 6 7 8 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 7 8 8 9 1 6 8 8 8 9 1 6 8 8 8 9 1 6 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	S 900 900 1800 1800 900 1800 900 1800 900 1800 1800 1800 1800 1800 1800 1800 1800 900 1800 900 180	## Page 12 ## Pa	ste 4 U3 \$ 60 60 60 30 30 30 30 ste 5 Periode_Signal \$ 60 30 30 60 60 60 60	A 15 10 10 10 10 10 15 15 15 15 15 11 10 10 11 15 15 15 15	s 1 3 1 3 1 3 1 3 1 1 3 1 1 8 Periode_ Inte s 1 3 1 3 3 3 3 1	Spectro. Ext. Int.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y 3463 5956 4130.8 3471.4 3614.2
2 3 6 1 5 8 4 7 N° Exp	Rand 1 2 3 4 5 6 7 8 Place Rand 1 2 3 4 5 6 7 8 6 7 8 9 1 2 3 4 5 6 6 7 8 6 6 7 8 6 7 8 7 8 8 8 8 8 9 8 8 9 8 8 8 8 8 8 8 8	S 900 900 1800 900 1800 900 1800 900 1800 900 1800 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900 900 1800 900	### Replica ### U2 %	ste 4 U3 S 60 60 60 60 30 30 30 30 ste 5 Periode_Signal S 60 30 30 30 60 60	A 15 10 10 10 10 10 15 15 15 15 11 10 10 10 11 10 15 15 15	s 1 3 1 3 1 3 1 Periode_ Inte s 1 3 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1 1 3 1	Spectro. Ext. Int. Ext. Ext. Int. Ext. Ext. Ext. Int. Ext.	3187.9 5164.8 7164.2 4603.7 9923.5 4762.1 5279.1 2749.8 Y 3463 5956 4130.8 3471.4 3614.2 4779.3

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.

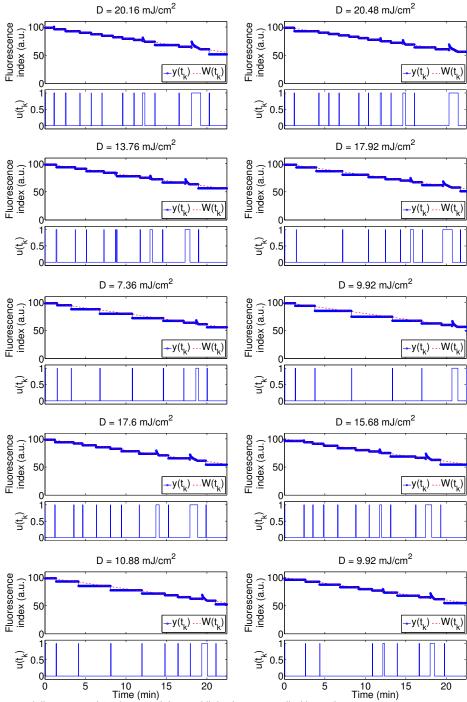


Fig. 6. Optimal treatment modality repeated 10 times and the total light dose D applied in each case