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A complexity analysis model for management of Good Manufacturing Practice and ISO 9000-2001 compliancy simultaneous projects. *Case study in the pharmaceutical industry*

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ABSTRACT

Quality improvement is definitively one of the major leading forces nowadays. In the manufacturing industry, the globalisation trend forces companies to modify their processes in order to comply to specific quality regulations. In pharmaceutical industry, the FDA Good Manufacturing Practices (GMPs) represent a landmark in defining the *Quality Product,* which is a complex multifaceted concept ("In conformity with identity, purity, physical shape and stability requirements" Code of Federal Regulations, 2000). Even if the FDA regulation has been defined for U.S. market, lots of European companies are starting to implement GMPs compliancy projects.
The European UNI EN ISO 9000-2001 regulation concentrates anyway on *Quality Assurance*, which is defined as a mean to make stakeholders confident about compliancy to their requirements. ISO 9000-2001 and GMPs regulations are neither in antithesis nor in alternative, but are complementary; pharmaceutical companies are now persuaded that *Quality Assurance* is a strategic objective as well as *Quality Product,* to be pursued by process optimisation and by production planning and control.
Any modification in the process structure of an industrial plant in order to meet the requirement of a quality regulation requires a deep commitment and big expenditures; when the aim is the complete compliancy to two main regulations such as US GMPs and EU ISO 9000-2001 the project management is definitively critical.
This paper aims to develop a project evaluation and management model for a program of plant adaptation to meet simultaneously both GMPs and ISO 9000-2001 standards; such model is based on a complexity analysis procedure for process modification and updating, and it is focused on the exploitation of the potential synergies among the adaptation project activities.
The proposed model is divided in three main phases: firstly, quality requirements are disaggregated according to relevant operative areas, in order to outline adaptation activities characteristics. Then, the second phase aims to estimate the impact on each operative area performance of the relative adaptation activities; for this purpose, activities complexity is evaluated using specific indicators and weighted through cost elements. Finally, the model concludes with gap analysis procedure which is used to plan a coordinated and optimised simultaneous adaptation project management.
The model has been tested in a pharmaceutical company that was already GMPs compliance since '90 and during 2000 was adapting its production process for a GMPs review and for the first ISO external audit. We applied our proposal to both the adaptation projects and we succeeded in obtaining important confirmation about achievable benefits in terms of reducing costs and activities balancing.

INTRODUCTION

Quality is nowadays a decisive factor for the survival of companies; during time, the high competitive environment in which modern industries live, has designed a business model in which voluntary quality regulations, on top of the laws, define what can be traded and what not.
The Quality Factor should not concern a company function any more, but must be incapsulated in the company mission; it should not represent an extra stage at the end of the production flow, but must be integrated with Strategy Function, Planning, Marketing, Research and Development, Human Resource Management, especially in those companies which deal with international markets; this because quality issues concern each aspect of company management.

Pharmaceutical industry is deeply affected by quality matters; the concept of *Quality Product* assumes a broader meaning with respect to the traditional definition: since the '70, the American regulation known as *Good Manufacturing Practice* (GMP) states the requirements for the product to be traded in the United States; with the market globalisation trend, this regulation has become of critical importance for all of those companies over a certain size. Actually, the GMPs are considered the most authoritative regulations in the pharmaceutical field.
On the other side, the implementation of the GMP regulation is complex and onerous; the Department of Health reviews are frequent, and GMP compliancy is mandatory to deal with United States market. For this reason the *UNI EN ISO 9000 regulation* was initially underestimated by the pharmaceutical industry, because of the fear of incompatibility of the simultaneous application of the procedures of both regulations.
Anyway, competitive environment forces to consider even economical and managerial efficiency issues, which are exposed in the European regulation. Nowadays pharmaceutical companies are now persuaded that *Quality Assurance* is a strategic objective as well as *Quality Product,* to be pursued by process optimisation and by production planning and control.
Any modification in the process structure of an industrial plant in order to meet the requirement of a quality regulation requires a deep commitment and big expenditures; when the aim is the complete compliancy to two main regulations such as US GMPs and EU ISO 9000-2001 the project management is definitively critical; companies need to gain the compliancy to both regulation avoiding troubles with complex project management issues: often the simultaneous implementation GMPs and UNI EN ISO 9000 regulation has lead to dramatic waste in resource and time.
This paper aims to develop a project evaluation and management model for a program of plant adaptation to meet simultaneously both GMPs and ISO 9000-2001 standards; such model is based on a complexity analysis procedure for process modification and updating, and it is focused on the exploitation of the potential synergies among the adaptation project activities. The proposed model is divided in three main phases:

PHASE I

In the first phase the aim is to situate the GMPs and ISO 9000-2001 adaptation projects in a general logic framework. To this extent a matrix representation of the problem has been used; for each regulation, a matrix relates *business functions* with *complexity factors*, which are intended to be the criticity sources for the company.
Reasonably, the complexity factors can be easily deduced examining a significant number of the reports written by the inspectors at the end of each audit procedure. In our case, the International Society for Pharmaceutical Engineering and the Italian Corporation Certichim had provided a complete report of those GMPs and Quality System requirements that have more been neglected during the years 1995-98. Unfortunately, the complexity factors found out with this procedure lack of homogeneity and hence the direct confrontation of the two matrix is impossible; for this reason it is necessary to identify some common topics to which each complexity factor will be brought back. The above mentioned matrices are therefore transformed in *business functions / control areas* matrices (BF/CA matrices), an unique representation which is simultaneously suitable for both GMPs and ISO regulation. More in depth, for each control area an activity list is generated, examining the check lists and the regulation text, and for each business function a responsible is found, examining the organization chart. Now the two matrices will differ only in the list of activities per each control area, being different the requirements and the check lists for the two GMPs and ISO regulation, while the business functions will be the same because they refer to the organization. The elements of the matrices are binary values and simply indicates if there is correspondence between the activity and the function or not.

In this way we can visualize the impact of each adaptation activity on the control areas.
Moreover, in order to evaluate the complexity factors in the control areas, two *complexity vectors* Gc and Ic have been identified, respectively for the GMPs and ISO regulation: the generic element gc_i (ic_i) represent the percentage of neglected requirements in the GMP (ISO) compliancy project inside the *i*-th control area, as it is shown in Exhibit 1. An illustrative example of the BF/CA matrices is shown below in Exhibit 2.

Exhibit 1

Control Areas	Gc	Ic
Operational (OP)	0.49	0.04
Facility (FAC)	0.09	0.08
Material/component (M/C)	0.03	0.19
Equipment (EQ)	0.09	0.05
Design control (DC)	0.03	0.02
Finished product control (FPC)	0.14	0.04
General controls (CG)	0.14	0.59

Exhibit 2

		Control Areas						
		OP	FAC	M/C	EQ	DC	FPC	CG
Business Functions	Management (GMG)							
	Production (PRO)							
	Safety (SAF)							
	Quality Assurance (QA)							
	Quality Control (QC)							
	Technical Service / Engineering (TSE)							
	Technical management (TMG)							
	Information Technology (IT)							
	Logistic (LOG)							
	Management Control (MGC)							
	Purchasing (PUR)							
	Consultino (CON)							

Analysing these two vectors it is possible to notice that each regulation has a specific control area which is critical: the GMPs concentrates on production hence *Operational* area is critical; while the ISO focuses on generic organizational factors hence *General Controls* area results critical. These vectors will be used as weights in phase II.

PHASE II:
Now we have to attribute to each activity a value which quantifies the company effort needed to reach the compliancy level as far as that activity is concerned. These values are obviously dependant on the current compliancy level of the entire company; they indicates the gap between the current situation and the regulation standards, and can be evaluated starting from the answers to the questions showed below:

1. Are the regulation requirements *substantially* fulfilled and do the needed improvements concern only minor aspects (document formats, etc.) ?
2. Does the company need to implement few improvement of little importance ?
3. Does the company need to implement few improvement of considerable importance ?
4. Does the company need to implement lots of improvement of considerable importance ?
5. Does the company need to implement lots of improvement of major importance ?

As a result we can modify the elements in the BF/CA matrices substituting the 1-values with the indexes just calculated. In this way we obtain two new matrices, Ga for the GMPs and Ia for the

ISO 9000-2001 regulations, which illustrates the required effort of the company in each compliancy project. At this point, through the multiplication of matrix Ga and vector Gc and the multiplication of matrix Ia and vector Ic we obtain a final value which indicates the *complexity* and *required effort* respectively for the GMPs and ISO 9000-2001 regulations compliancy activities to be carried out by each responsible, that means in each business function. We will call these two vectors Eg and Ei.

PHASE III:

Now the procedure puts in evidence the existence of analogies in the two regulation requirements, which will have a great influence the compliancy projects simultaneous implementation. These analogies will result in a sort of overlapping among the respective activities in the Gc and Ga matrices, and our aim is therefore now to define an *overlapping ratio*. The overlapping ratio of activities A and B indicates the quota of activity B which has been already performed once activity A has been completed. Obviously, the exploitation of the overlapping benefits is heavily dependant on the sequence by which the activities are carried out. At last, it is possible to merge the data from phase II – that means, *complexity* and *effort* required by each business function per each regulation compliancy project – and from phase III – that means, optimisation chances to be exploited through overlapping maximisation – to find synergies and opportunities of a simultaneous project management. The model has been tested in a pharmaceutical company that was already GMPs compliance since 1990 and during 2000 was adapting its production process for a GMPs review and for the first ISO external audit. We applied our proposal to both the adaptation projects and we succeeded in obtaining important confirmation about achievable benefits in terms of reducing costs and activities balancing.

CONSIDERATIONS ON CASE ANALYSIS RESULTS

By the way of an example, in Exhibit 3 below are shown the Eg and Ei vectors obtained from the model application in the case analysis.

Exhibit 3

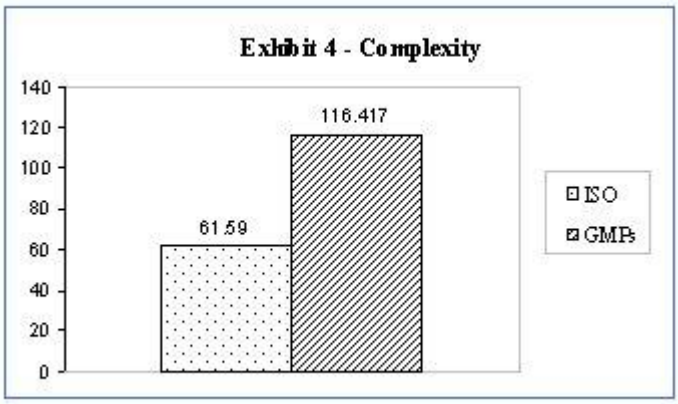
Ei Vector – ISO

GMG	Quality policy	1.30
	Approvation	3.25
PRO	Design	0
	Control	4.70
QA	Quality documentation	8.95
	Quality recordings	2.98
	Audit	2.60
	Training	0.65
QC	Control	3.08
	Recordings / documentation	2.08
TSE	Maintenance	2.09
	Calibration	2.09
	Design	1.95
TMG	Audit	6.73
IT	Control	1.95
LOG	Inventory management	2.98
	Distribution management	3.08
PUR	Control	3.98
	Audit	3.25
R&D	Design	0
CON	Documentation	1.3
	Training	2.6

Eg Vector - GMPs

GMG	Quality policy	0.28
	Approvation	0.63
PRO	Design	1.09
	Control	14.92
SAF	Planning	0.807
QA	Quality documentation	15.79
	Quality recordings	15.2
	Audit	0.56
	Training	0.28
QC	Control	9.62
	Recordings / documentation	9.06
TSE	Maintenance	2.48
	Calibration	3.14
	Design	6.48
TMG	Audit	8.29
IT	Control	4.39
	Calibration	4.39
LOG	Inventory management	2.79
	Distribution management	3.97
MGC	Quality costs accounting	0.56
PUR	Audit	1.45
CON	Validation document	5.83
	Training	0.56
	Design	3.83

From the comparison of the two vectors it is immediately possible to single out a higher complexity for the GMPs compliancy project in the case analysis, shown in Exhibit 4.



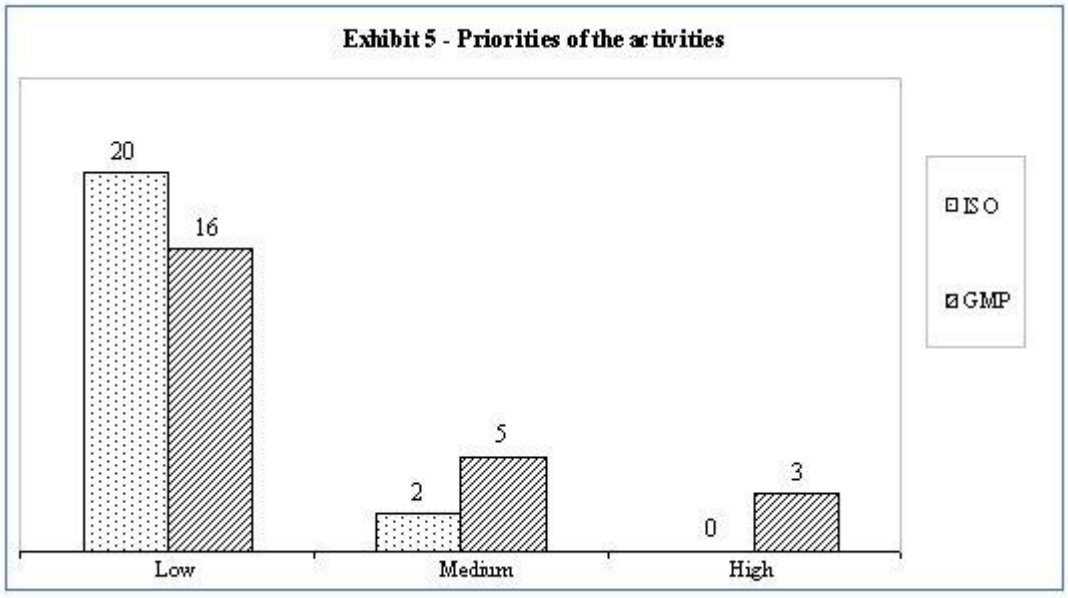
Vector E structure permits to compare the two projects even as far as the impact on the control areas is concerned, through the sum of the values of the activities in each control area group: the result is written below:

- Production Area: is deeply involved by the GMPs project because of the significant weight of the control activities;
- Quality Assurance Area: the two projects show a similar impact on this area, though GMPs project value is higher. This due to the higher commitment required in the documentation and reporting activity, which represent an increase in the project management complication;
- Quality Control Area: even in this area the two project values are comparable, though the gap is higher. The distance is proportional to the differences in the requirements of the two regulations;
- Technical Services/Engineering Area: the design activities in the GMPs project influences a higher complexity for the US regulation;
- Information technology: the GMPs project deeply influences this area because of the validation activities of the automatic control system;
- Logistic Area: in this area the ISO compliancy project has a higher impact and the cause is still brought bask to documentation criticity;
- Purchasing Area: even in this area the ISO project has a higher impact, due to the order management requirements, that in the GMPs are not so strict.
- Consultant Area: the impact of GMPs project in this area is higher because a GMPs consultant is more expensive with respect to an ISO9000-2001 consultant because of his deeper knowledge and preparation in technical and engineering matters.

In order to put in evidence the critical aspects of both projects it is possible to classify the values in three ranges; these classes will be used in the project planning phase to determine the priorities of the adaptation activities:

- Low priority [0,5]
- Medium priority [6,10]
- High priority [11,15]

An interesting result is depicted below in Exhibit 5: it is shown the distribution of all the activities of both projects divided per priority class.



The greater part of the ISO 9000-2001 project activity priorities are located at a lower level, that is the activities to be performed in order to reach the compliancy concern minor aspects for the company analysed in this case, while the GMPs project requires medium and high priority activities.

Specifically, the project for the compliancy to the US regulation requires certain activities with specific characteristics (Quality Documentation, Controls..) which are not present at all in the ISO project. Often the same activity is present in both project, but the complexity in the GMPs project is higher due to higher importance given to the production and the control aspects in the American regulation.