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SYSTEM APPROACH TO THE MODELLING OF THE PROCESS OF FORMULA MODIFICATION OF PHARMACEUTICAL PRODUCTS

SUSTAVSKI PRISTUP MODELIRANJU PROCESA PROMJENE RECEPTURE FARMACEUTSKOG PROIZVODA

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Abs t r a c t

This paper presents the dynamic model of formula modification created using the system approach and methodology of system dynamics. The development of the qualitative (general) model is divided in two parts. The first part describes the process of formula modification as a system by defining its purpose and vievvpoints. It describes the subjects participating in the observed process according to the stages of methodology of system dynamics. It also gives the verbal and structural description of the process. The second part presents the system flowchart and mathematical and computer model of the system using POVVERSIM software svmbols. The quantitative (concrete) system model was developed according to the relevant information gathered by interviewing the employees involved in the observed process and one of many possible simulation scenarios was created. The final part emphasizes the effects achieved by the development of the qualitative and quantitative model of the system and points to the possibility of practical use of the developed simulation model in the management of the process of formula modification of a pharmaceutical product by introducing concrete data about a real system.

Sažetak

U ovom radu prikazan je dinamički model sustava procesa promjene recepture, pri čijoj izradi je korišten sustavski pristup i metodologija sustavske dinamike. Razvoj kvalitativnog(općeg) modela sustava podijeljen je u dva dijela. U prvom dijelu, opisom svrhe, te iznošenjem motrišta razmatranja, prikazan je proces promjene recepture kao sustav. Prema fazama metodologije sustavske dinamike opisani su subjekti koji sudjeluju u promatranom procesu, te verbalni i stukturni opis procesa. Koristeći simboliku simulacijskog paketa POVVERSIM, u drugom dijelu rada prikazan je dijagram toka i matematičko računarski model promatranog sustava. Kvantitativni(konkretni) model sustava razvijen je prema intuitivnim podacima dobivenim intervjuiranjem kompetentnih osoba koje sudjeluju u realizaciji promatranog procesa, te je prema tome proveden jedan od njegovih mogućih simulacijskih scenarija. U zaključnom dijelu rada istaknuti su efekti dobiveni razvojem kvalitatitvnog i kvantitativnog modela sustava i ukazano je na mogućnost praktične primjene razvijenog simulacijskog modela u upravljanju procesom promjene recepture farmaceutskog proizvoda, uvođenjem konkretnih podataka o realnom sustavu

l.INTRODUCTION

The control of modifications as a procedure is present in pharmaceutical industry in order to document and control the management of ali modifications that could have influence on the final pharamceutical quality of the product.

On the basis of article 26, item 7 of the Act on Drugs and Medical Products the Regulation on Good Manufacturing Practice was passed, prescribing ali the principles and guidelines of good manufacturing practice /I/.

Good manufacturing practice implies a part of the system of quality assurance that ensures consistent and permament production of drugs and medical products vvhich are manufactured and controlled in compliance with the existent quality standards /2/.

Article 20, item 2 /2/ should be emphasized as it includes legally prescribed need for a comprehensive system of quality assurance that includes good manufacturing practice and quality control.

In the phase of the production of a pharamaceutical product, the control of modifications refers to the followving changes vvithin the observed company:

- change of the manufacturer/supplier
- change of the type of immediate packaging
- modification of formula and manufacturing procedure
- change of quality requirements.

This paper presents the model of formula modification created using the system approach and methodology of system dvnamics. The development of the model is divided in two parts. The first part describes the process of formula modification as a system. The second part presents the dvnamic model of the system

and its simulation scenario. The quantitive model was developed according to the relevant information gathered by interviewing the employees involved in the observed process. The closing part lists the advantages of system dynamics approach to the problem and and gives guidelines for further research.

2. THE PROCESS OF FORMULA MODIFICATION AS A SYSTEM

The f irst section of this chapter describes the purpose of this process and defines the viewpoint of the process analysis. In order to show as well as possible the process of formula modification itself, each subject is briefly described and its hierarchy diagram is shown. Material and informational flovvs of the observed process are described vvith the verbal model.

2.1. The purpose of the process and the viewpoint of its analysis

The process of product formula modification is a controlled and documented managmement of the proposed formula modification so that at every moment it could be established who proposed the modification and why, vvhether the modification was accepted or rejected and why and to which extent the implementation of the modification was successful. Such a definition of the observed process determines the purpose of its existence. Non-adherence of the defined process vvould have negative influence on the finaly quality of the pharamaceutical product and on the business success of the pharmaceutical company.

In order to improve and accelerate the above-mentioned process the viewpoint will be the observation of the process of formula modifiaction vvith regards to its duration. The observation of the process of formula modification is recorded in document E006. Since E006 with negative opinion does not take too much time in the process and is only filed away, its omission will not disrupt the flow of the process. By follovving the circulation of E006 we will get insight into possible congestions of the active subjects in the process. In accordance vvith the vievvpoint, only the flovv of documents vvith positive opinion on proposed modifications will be observed.

2.2. Subjects in the process of product formula modification

This section briefly describes the role of each subject in the process of formula modification. The described subjects are teams of people responsible for a certain activity in the process.

Department of Quality Assurance encourages and coordinates performance of activities and implementataion of standards that contribute to overall product quality. Quality policy is described in the introductory part as well as the control of changes as a segment of the work of Quality Assurance.

Department of Research and Development develops new formulas on the basis of the accepted proposal of modification. It offers and analyzes possible solutions of the problem on the basis of the obtained information on shortcomings of the existent formula.

Department of Quality Control controls the quality of products. It defines quality parameters of the product within the observed process and develops new methods of analyses. One of the tasks is the analysis of repeatability and accuracy of analvtical methods.

Department of Stability Testing follovvs alterations of product quality by repeating the analytical procedure at different time intervals and in different storage conditions.

Registration Department deals with registrations and renewal of registrations of drugs. After receiving the affirmative ansvver from Department of Quality Assurance it prepares documenation for registration of the product and sends it to state institutes and to the Ministry of Health of the Republic of Croatia.

2.3. Features of the process of formula modification as a system

The application of system analysis makes it possible to view the process of formula modification in pharmaceutical industry as an integral system that:

- has certain functions
- has a structure
- is a place where organizational, economical, technical and technological and other processes take place
- has relationships vvith the environment
- uses certain resources
- has a time dimension

Certainly there are other features that enable a complete comprehension of such a model.

The next section presents the verbal description of the system.

2.3.1 Svstem description

The process of formula modification starts with submitting a proposal in the form of document E006 where ali the neccessary acitivities are noted and vvhich is an input into the described system. It is an independent random variable. Document E006 is sent to Quality Assurance (QA), thus increasing its vvorkload - after the change of speed of input flovv the state of documents in QA is increased. Quality Assurance evaluates the feasibility of the proposed modification and approves or disapproves it. Their decision is recorded in E006 and sent to R&D. This means that there is a certain delay needed for QA to make their judgment, record it in E006 and send it to R&D. The state of documents in QA that increased regarding the speed of input flovv causes the increase of the speed of document output. It results in the slovved increase of document states and the speed of document output. This way the E006 output speed from QA gradually comes close to E006 QA input speed. E006

output speed from QA is monitored through the state of documents in QA corresponding to an exponential delay /3/ of the first order. Regarding the fact that there are three consecutive exponential delays of the first order, the E006 output speed from QA will be defined as an exponential delay of the third order /3/.

R&D receives E006 and makes decision on further continuation of the process. If R&D agrees with the modification, that is recorded in E006 and sent to Quality Control (QC), which makes positive influence on its workload. As with QA, the document state in R&D is increased regarding the speed of input flow and that also causes the increase in the speed of output flow from R&D to QC. E006 speed to QC is defined as an exponential delay of the third order. After QC finishes its activities, E006 is sent to Stability Control (SC). The speed of that flow is also defined as an exponential delay of the third order. SC returns E006 to R&D, R&D to QA and QA to Registrations (REG). Following the process flow, the workload of any subject positively influences the workload of the next one and is decreasing the workload of the previous one. This can be represented with negative feedback loop. It is possible to see the circles of feedback activity between two subjects which are shown on the structural diagram in the next chapter. System output is a documentation made by REG on the basis of received E006.

2.3.2 System hierarchy diagram

We will first define the basic characteristics of the system in order to make a system hierarchy diagram. The basic characteristics are /6/:

1) elements (E) - functional parts of the system
2) structure (R) - relations within the system
3) function (F) - the purpose and role of the system

Departments that take part in the described process are the elements of the system and its structure is made of the flows and data of the E006 paper.

The function or the purpose of the system /6/ is described in the beginning of the chapter.

Figure 2.1. shows the hierarchy diagram of the product formula modification system, according to the previously stated rules.

Table 2.1. explains the symbols used in the hierarchy diagram.

Table 2.1. The meaning of the symbols used in the hierarchy jdiagram

Svmbol	Meaning
S	Product formula modification system
E,	Quality Assurance (QA)
PS_9	Research & Development (R&D)
"r	Development
$E,^2$	Stability Control (SC)
E,	Quality Control (QC)
E_4	Registrations (REG)

The dynamic model of the system will be shown in the next chapter.

3. DYNAMIC MODEL OF SYSTEM

The methodology of system dynamics is briefly described in this chapter. It is followved by the structural model of the system. The system flowchart made with Powersim Studio Express 2003 software is shown in the end.

3.1. Methodology of system dynamics

System dynamics is a methodology of research, modeling, simulation and optimization of complex dynamic systems /5/. The purpose of system dynamics is to create a logical simulation model of some real dynamic system, so that this model could predict the future behavior of the system and provide a numerical and graphical represenatation of that behavior /6/. System dvnamics expresses future behavior through the values of system parameters in discrete time series /6/.

System dynamics methodology consists of six phases *IS/:*

1) problem definition
2) making dvnamic hypotheses for the cause of the problem
3) computer simulation

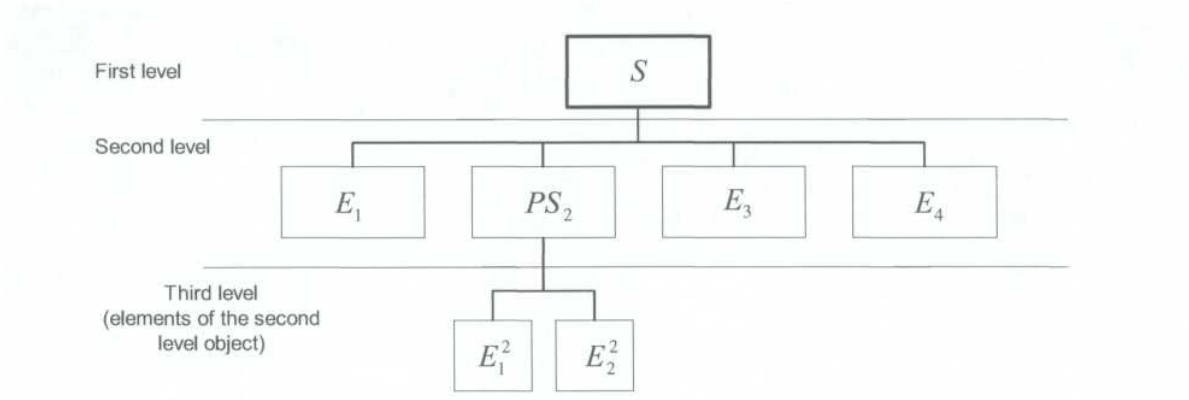

Figure 2.1. Hierarchy diagram of the product formula modification system

4) comparative testing of the model and the real system
5) testing of beneficial alternative policies
6) solution implementation

Problem definition (verbal description of the svstem) is given in the previous chapter /6/.

The structural svstem model is shovvn in the next section.

3.2. Structural system model

The structural svstem model shown in figure 3.1. is built according to the verbal description. It describes causal relationships betvveen the elements.

Every element sends document E006 to the next element in the structure, thus increasing (+) its workload and decreasing (-) its own vvorkload. Figure 3.1. shows the negative feedback loops ((-)FBL_n).

3.3. System flowchart with POWERSIM symbols

This section describes the Powersim software, its flowchart symbols and the flowchart of the observed system.

3.3.1. Powersim Studio Express 2003

Powersim Studio Express 2003 (service release 3) software was used to make the flovvchart of our system. It is a product of Powersim Softvvare AS companv. We have used the fully functional 60 days trial version downloaded from their Internet site www.powersim.com.

These are the common steps when vvorking with Powersim Studio:
1) creating new simulation project
2) creating the measurement units

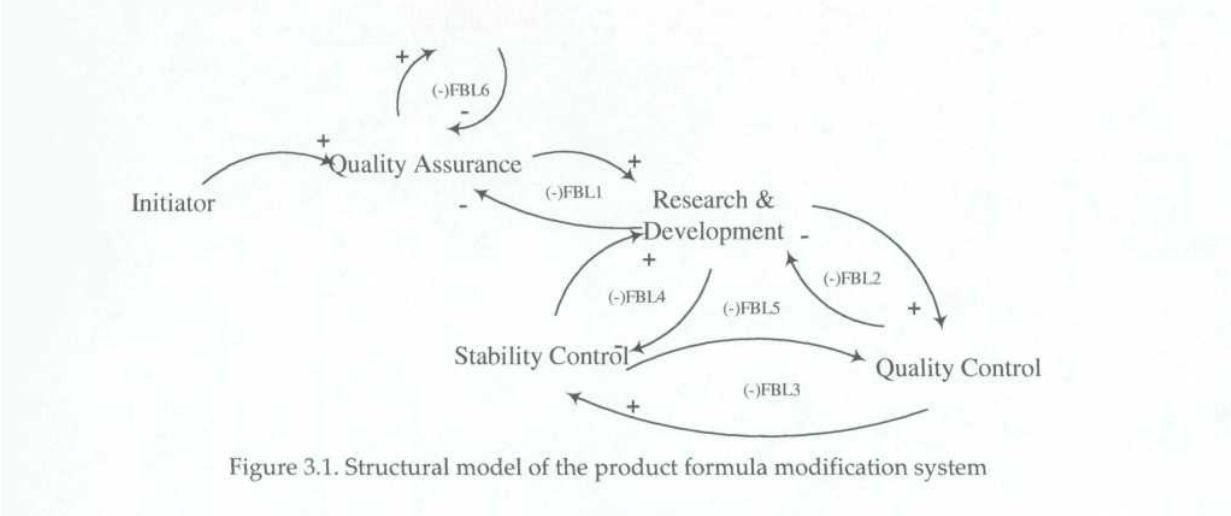

Figure 3.1. Structural model of the product formula modification system

Registrations

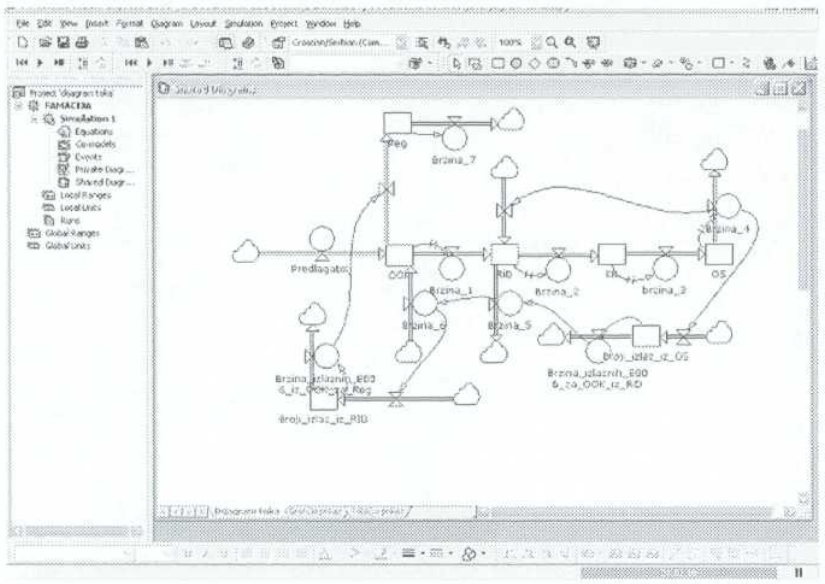

Figure 3.2. Powersim Studio Express 2003 initial screen

3) creating variables, relations and flows
4) defining variables and flows
5) simulation setting
6) creating input/output data
7) adding navigational capabilities and documentation
8) creating/storing referential data
9) presentation setting

Figure 3.2. shows the initial screen of the application:

POWERSIM is a strong software tool for the interactive construction of the computer simulation models of complex dvnamic svstems by applving the methodologv of svstem dvnamics and it may be used for educational and industrial purposes.

3.3.2. Powersim symbols

Powersim Studio Express 2003 has 23 symbols available for flovvchart design. Some of those symbols are shown in table 3.1.:

3.3.3. Flowchart of the formula modification system

This section shows the previously described flovvchart. This flowchart gives a finer representation of the model and provides a simpler and more reliable transition to definition of model equations /3/ and computer model. Figure 3.3. shows the flowchart.

Table 3.2. contains description of ali the functions shown in the flowchart.

Table 3.1. Some of the Povversim flowchart symbols

Symbol name	Symbol	Symbol description
Level		Value that accumulates with time
Speed of change		Flow of manageable level input/output
Flow		Measurable value flow
Flow with delay		Measurable value flow *with delay*
Flow source/destination		Flow source/destination outside of the system
Constant		Constant factor of the model
Working variable		Description of algebraic information

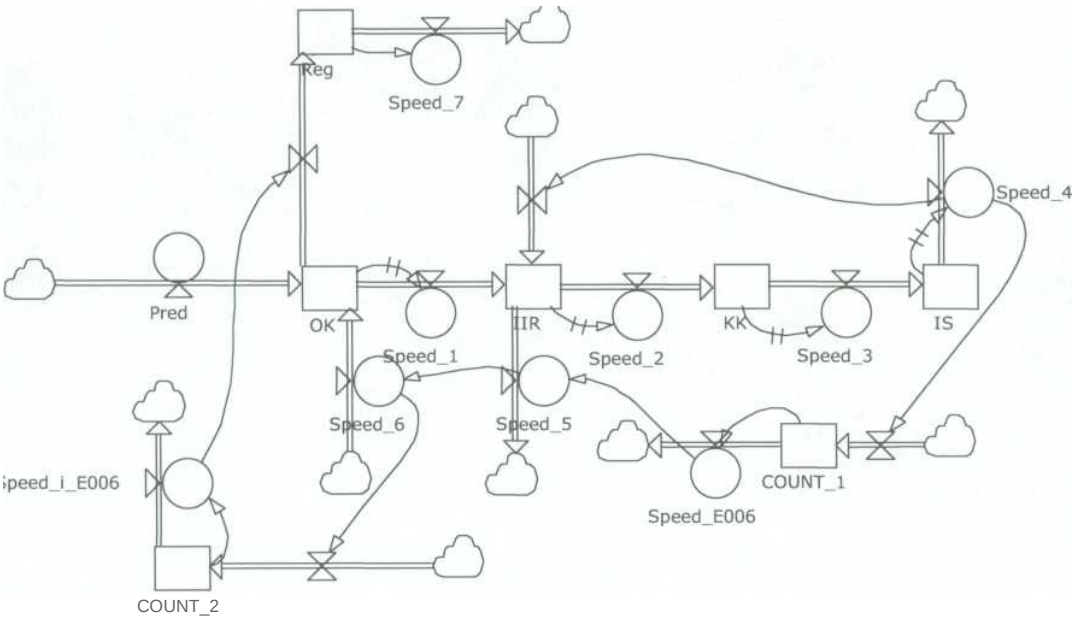

Figure 3.3. Formula modification system flovvchart

Table 3.1.Meaning of the flovvchart functions

Function name	Description
Pred	Average number of formula modification proposals
QA	Document state at Quality Assurance
Speed_1	Document speed between QA and R&D
R&D	Document state at R&D
Speed_2	Document speed between R&D and QC
QC	Document state at Quality Control
Speed_3	Document speed betvveen QC and SC
SC	Document state at Stability Control
Speed_4	Document speed betvveen SC and R&D
COUNTJ	Document state betvveen SC and R&D
Speed_E006	Output documents speed betvveen R&D and QA
Speed_5	Document speed betvveen QA and R&D
Speed_6	E006 document speed betvveen QA and REG
COUNT 2	Document state betvveen QA and REG
Speed_i_E006	Output documents speed betvveen QA and REG
Reg	Document state in REG
Speed_7	Documentation speed betvveen REG and State Ministry

3.4. Mathematical and computer model

Using object-oriented POVVERSIM software for creating system flowchart, a mathematical-computer model is also created. Every single symbol corresponds to an exact equation describing the dynamics of the system. This mathematical/computer model represents the state changes according to the flowchart shown above.

init COUNT_1 = 0 (1)

flow COUNT_1 = +dt*Speed_4 -dt*Speed_E006 (2)

This block of equations describes the change of the state of documents between Stability Control and Quality Assurance. Equation (1) defines the initial value of the state. Equation (2) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$\frac{d(COUNT\_1 - COUNT\_1_0)}{d} = Speed\_4 - Speed\_E006$$

The next block of equations describes the change of the state of documents betvveen Quality Assurance and Registration.

init COUNT_2 = 0 (3)

flow COUNT_2 = -dt*Speed_i_E006 +dt*Speed_6 (4)

Equation (3) defines the initial value of the state. Equation (4) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$\frac{d(COUNT\_2 - COUNT\_2_0)}{d} = Speed\_6 - Speed\_i\_E006$$

The next block of equations describes the state of documents in Quality Control.

init QC = 0 (5)

flow QC = -dt*Speed_3 +dt*Speed_2 (6)

Equation (5) defines the initial value of the state. Equation (6) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$\frac{d(Q - Q_0)}{d} = Speed\_2 - Speed\_3$$

The next block of equations describes the state of documents in Quality Assurance.

init QA = 0 (7)

flow QA = -dt*Speed_i_E006 +dt*Speed_6 -dt*Speed_ (8)

1+dt*Pred

Equation (7) defines the initial value of the state. Equation (8) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$d(S\ S\ o) = Speed\_6 - Speed\_1 + pred - Speed\_/\_ £006$$

The next block of equations describes the state of documents in Stability Control.

init SC = 0 (9)

flow SC = -dt*Speed_4 +dt*Speed_3 (10)

Equation (9) defines the initial value of the state. Equation (10) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$\frac{d(\mathbb{S}' - \mathbb{S}'_0)}{d} = Speed\_3 - Speed\_4$$

The next block of equations describes the state of documents in Registrations.

init Reg = 0 (11)

flow Reg - +dt*Speed_i_E006 -dt*Speed_7 (12)

Equation (11) defines the initial value of the state. Equation (12) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$\frac{d(REG - REG_0)}{d} = Speed\_i\_E006 - Speed\_7$$

The next block of equations describes the state of documents in Research & Development.

init RD = 0 (13)

flow RD - -dt*Speed_5 +dt*Speed_4 +dt*Speed_l (14) - dt*Speed_2

Equation (13) defines the initial value of the state. Equation (14) describes input/output flows causing that state to change. The mathematical model representing this block is:

$$d(B\ -B_0)/ti = Speed\ 1\text{-}Speed\_2 + Speed\ 4\text{-}Speed\ 5$$

Now we will give equations which describe the speed that influence the state of documents. Equation

factors were formed on the basis of the experience of the people taking part in the process.

aux Speed_l = DELAYMTR(QA, 3,3) (15)

aux Speed_2 = DELAYMTR(RD, 6,3) (16)

aux Speed_3 = DELAYMTR(QC, 3,3) (17)

aux Speed_4 = DELAYMTR(SC, 3,3) (18)

aux Speed_6 = Speed_5 (19)

aux Speed_7 = Reg **(20)**

aux Speed_ _E006 = COUNT_1 (21)

aux Pred = RANDOM(0+0.5) (22)

aux Speed_5 = Speed_i_E006 (23)

aux Speed_i_E006 = COUNT_1 (24)

Equation (15) represents the speed of the documents coming from Quality Assurance to Research & Development designed as an exponential delay of material flow of third order. The same is with equations (16), (17) and (18). Equation (19) defines the speed of documents going to Registrations. Equation (20) describes the output flows from Registrations. Equation (21) defines the output flows from Research & Development to Quality Assurance. Equation (22) defines an independent stochastic variable describing the average number of formula modification proposals. Equation (23) describes the speed of documents going from Research & Development to Quality Assurance. The output flows from Quality Assurance to Registrations are described with equation (24).

3.5. Simulation scenario according to the system model

Simulation is based on the intuitive insights of the authors gained during the interviews with people taking part in the process. Figure 3.4. shows the average number of modificiation proposals per time unit (3 days).

When defining the simulation scenario the time unit of 3 days within a 10-year simulation period was

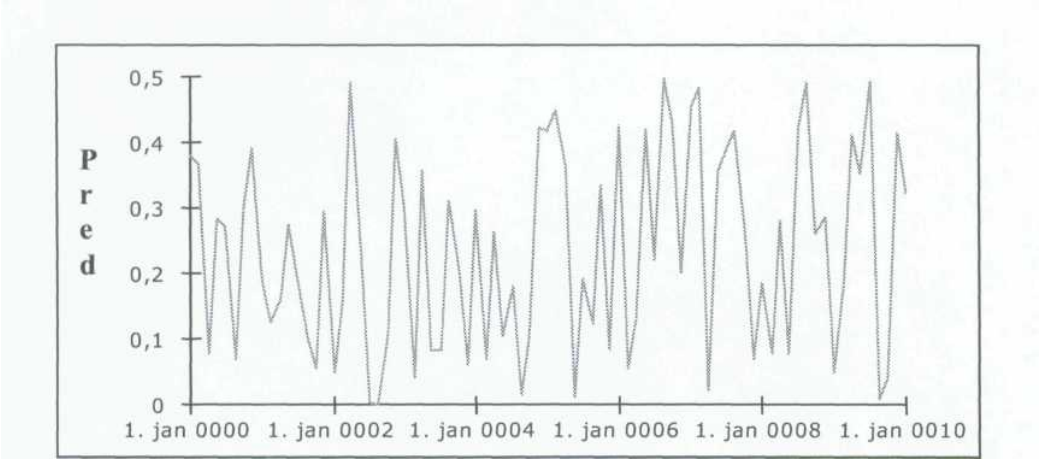

Figure 3.4. Average number of modificiation proposals per time unit

assumed intuitively, on the basis of the interviews with competent individuals who take part in the system.

During one year there are 1 to 5 demands for the *formula modification and they are stochastically* distributed over three-day time intervals.

Random variable Pred with values from 0 to 0.5 is shovvn on Y-axis. Values represent the average number of formula modification proposals. X-axis is a simulation time frame of 10 years, from Jan 1st 2000 (shown as 1. jan 0000) to Jan 1st 2010 (shown as 1. jan 0010).

In table 3.3. numerical values of the load of each element in the system for formula modification are represented. Quoted data have been established intuitivelv, on the basis of interviews of participants in the process, and the weight factor of load from 0 to 1.5 is the result of the chosen simulation scenario.

Figure 3.5. shows the workload on ali the elements of the formula modification system (on the basis of data in table 3.3.).

Graphs QA and R&D show significant variations of workload which pose a great strain on R&D. There are also variations between QA and QC and SC, but they are less significant.

In view of ali this the conclusion can be made that the system of the process of formula modification of a pharmaceutical product has serious drawbacks and its optimization is indispensable.

4. CONCLUSION

System approach to the modeling of the process of formula modification used in this work has confirmed its basic advantages in the analysis of complex problems: the integral observation of the process as a system from a determined viewpoint on the developed system model, systematic analysis of ali the relevant elements of processes and their cause-and-effect connections, heuristic research approach founded on systematic scientific methods, creativity of a researcher and modern information technologv.

After defining the process of formula modification as a system, by using the method of system dvnamics the structural model was developed which identified cause-and-effect connections between the elements of the system.

The structural diagram has served as the basis for the construction of flow charts in symbols of simulation package POWERSIM and for the development of the computer simulation model.

The developed simulation model has enabled the dynamic analysis of the system with the aim of discovering its weaknesses (delay of the material and information flows) and of creating possibilities for the prediction of future behaviors of the formula modification system (significant deviation of the behavior of the relevant variables of the system in the future caused by delay).

Table 3.3. VVorkload on each element of the system

Time	QA	R&D	QC	SC	REG
1. Jan 0000	0,00	0,00	0,00	0,00	0,00
1. Jan 0002	0,42	0,02	0,00	0,00	0,00
1. Jan 0004	0,49	0,31	0,00	0.00	0.00
1. Jan 0006	0,21	0.97	0.05	0.00	0.00
1. Jan 0008	0,05	1.46	0.30	0,03	0,00
1. Jan 0010	0,10	1,09	0.92	0.22	0.00

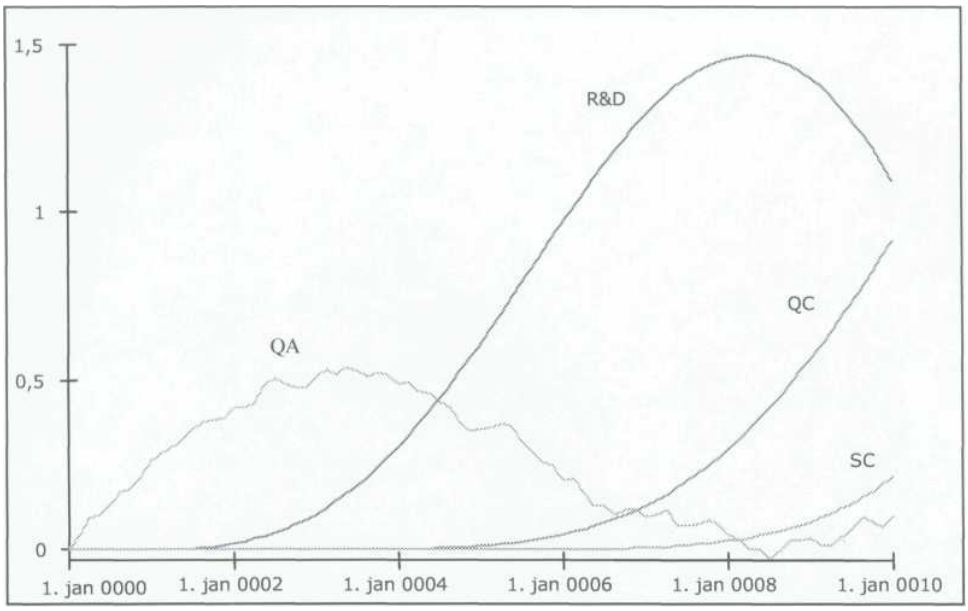

Figure 3.5. The workload on the elements of the formula modification system

The application of the developed simulation model to the real system implies the construction of the quantitative simulation model based on details of the work of the real system, which would enable quality experimental research of possibilities for the improvement of the formula modification process management, without endangering the real system.

Literature:

III Act on Drugs and Medicines, Narodne novine, 124/97.
121 Regulation on Good Manufacturing Practice, Narodne novine, 71/99. *131* Čerić, V.: Simulacijsko modeliranje, Školska knjiga, Zagreb, 1993.
/4/ Forrester J. W.: *Principles of Systems,* Massachusetts Institute of Technologv Press Cambridge, Massachusetts and London, England, Second Preliminarv Edition, 1980. *lb I* Munitić, A.: Kompjuterska simulacija uz pomoć sistemske dinamike, Ivo Lola Ribar, RO Računari Lola omladinska tvornica, Split, 1989. *16/* Radošević, D.: Osnove teorije sustava, Nakladni zavod matice Hrvatske, Zagreb, 2001. *171* Richardson, G. P, Pugh A. L. III: *Introduction To System Dynamics Modelling ivith Dynamo,* The MIT Press, Cambridge, Massachusetts, and London, England, 1981. /8/
http://www.albany.edu/cpr/sds *191*
http://www.powersim.com /IO/
http://sysdyn.clexchange.org/gsp98/papers/D-4614.pdf