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SIMULATION OF THE DRUG DEVELOPMENT PROCESS: A CASE STUDY FROM THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

This paper uses a case study from the pharmaceutical industry to show how simulation modeling can be applied to understanding large, highly-complex processes such as drug development. I conclude that simulation provides an enhanced resource planning capability compared with that provided by traditional spreadsheet analysis. This capability difference stems from the ability of a simulation to better reflect the variation which defines such complicated processes. The conditions which facilitate exploitation of this advantage include: capturing process information at the correct level of abstraction; successfully incorporating this information into a simulation model; and allowing easy user access to critical parameters via an intuitive interface.

1 INTRODUCTION

The process of developing a new drug compound is lengthy, costly, risky, and extraordinarily complex. On average, of 5,000 new compounds tested in a lab, only five actually make it to clinical trials, and only one of those will be approved for clinical use. Elapsed time can be 12 to 15 years. Hence, the average cost of a new medicine is about $500 million (*The Wall Street Journal*, 2000).

Pharmaceutical companies must offset these high fixed costs by taking advantage of drug patents obtained while drugs are still in development. However, the life of these patents is limited, and the amount of revenue a new drug will yield depends on how quickly it is brought to market. Given this incentive, a pharmaceutical company has tremendous motivation to decrease cycle time by effectively using resources and by improving process efficiencies. Each day of cycle time reduction yields an additional $1 million in additional revenue (Breckinridge, 1998).

The task of effectively employing resources to reduce cycle time demands a tool which captures the tremendous variability of the drug development process and the complex interactions of these sources of variation. The answer to almost any question concerning this process--whether it be how long an activity takes, what resources are required, or what activity sequence is followed--is invariably "it depends." Characteristics such as the rate and timing of arriving projects, the rates of attrition in various development stages, the number and timing of clinical trials per project, and the resource requirements for a project all contain substantial variability. This variability is not effectively captured by spreadsheet analysis, which often only reflects average values of highly-variable parameters. A manager needs a more robust resource planning capability to deal with the complexity of the process.

The pharmaceutical company analyzed in this study takes new compounds from its research laboratories and develops these compounds for eventual launch in the market. This process begins with synthesizing the raw drug substance on a larger scale, followed by animal testing, human testing, and obtaining regulatory approval for clinical use. They have aggressive corporate goals for decreasing the cycle time for this development process and also for increasing the annual throughput of new drugs. This company is also involved in several process redesign efforts which will affect the sequencing of clinical trials, the success rates of new compounds, the volume of new compounds entering the process, and the touch time required at several key activities.

The company was not comfortable that its current re-engineering projects and static resource planning tools would allow it to meet it's goals. Among its concerns were:

- How will variability affect the effectiveness of my process reengineering projects?
- What unforeseen effects will changing one part of the process have on resources across the process?
- To which re-engineering efforts should we apply our limited resources in order to best support our goals?
- What staffing levels will we need to meet our cycle time reduction goals?

- What staffing levels will we need to meet our throughput goals?
- What will my staffing and processes need to look like in order to meet both of these goals simultaneously?

Andersen Consulting's Capability Modeling and Simulation group developed a resource planning capability to help the company determine their desired resource levels, while prototyping and proving key aspects of their on-going change efforts. This tool allows the user to experiment with certain key parameters--resource levels, arrival rates, attrition rates, activity sequencing, activity times--in order to define an effective plan for meeting its cycle time and throughput goals.

2 APPROACH

2.1 Data Collection

Andersen Consulting utilized process mapping workshops to develop an understanding of the drug development process. These workshops captured process information at the level of detail needed to model resource constrained behavior. These workshops focused on recording process information at the activity level. Each activity had inputs, outputs, business rules, resource information, and activity times. Figure 1 shows an example of such an activity.

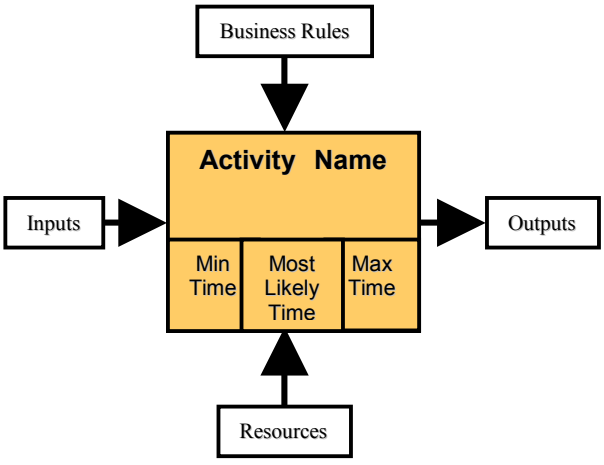


Figure 1: Sample Activity

Capturing the needed level of activity specificity required for this lengthy, complex process constituted a substantial effort--over 2,000 activities were mapped. The process was divided into the following five sub-processes in order to enable a timely completion of data collection: Preclinical Development; Clinical Operations; Regulatory Submissions; Product Development; and Decision Making. In each sub-process, the process maps were refined until the company felt comfortable with their level of detail and with the assumptions around the activities. The company also specified what variables they were particularly interested in experimenting around and what kinds of outputs they would find useful.

2.2 Model Development

These static models formed the basis for developing a discrete event simulation model of the company's drug development process in Arena®. This model was built in three stages, as shown in Figure 2 below.

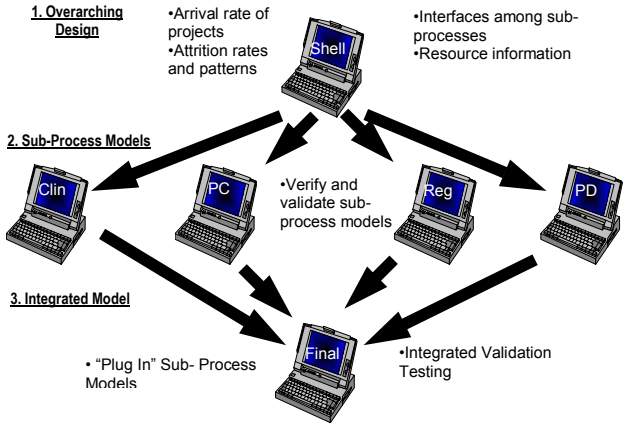


Figure 2: Development Process

The first stage leveraged the overarching logical framework of the decisions process mapping, which spanned the entire drug development process. This model contained all the arrival data, attrition data, resource information, interfaces to the other four sub-processes, final animation and output views. This model formed a shell of the final simulation, with black box delay times in place of the code for the Preclinical, Clinical, Product Development and Regulatory sub-processes. Specifying these critical modeling details early in the development process flushed out many potential problems while the model was still small and easy to manipulate. It also established a solid basis for the remaining development steps.

The second stage consisted of building and validating each of the remaining four sub-process models independently, using the shell model as a development test bed. This approach allowed four separate developers to work freely while remaining within the framework of the larger model structure.

The third stage entailed substituting each sub-process model in the shell model to form the integrated simulation capability. This staged development approach allowed Andersen Consulting to compile and run this 2000-activity model with only one error, virtually eliminating the final debugging phase of the development process. All the potential bugs had already been found and corrected in the smaller, more nimble models.

2.3 Model Inputs

The key to the utility of the drug development simulation model is its ease of use in manipulating input data. This capability is enabled by an extensive use of variables in place of constants during model development. By contrast, "hardcoding" constants into the model requires a user to find and open all relevant simulation modules in order to manipulate input data. This approach is not desirable in any model, and especially not in a large model.

Thus, all variables are available to be accessed via a more intuitive interface, such as the Graphical User Interface (GUI) built with Visual Basic for Applications (VBA) shown below in Figure 3.

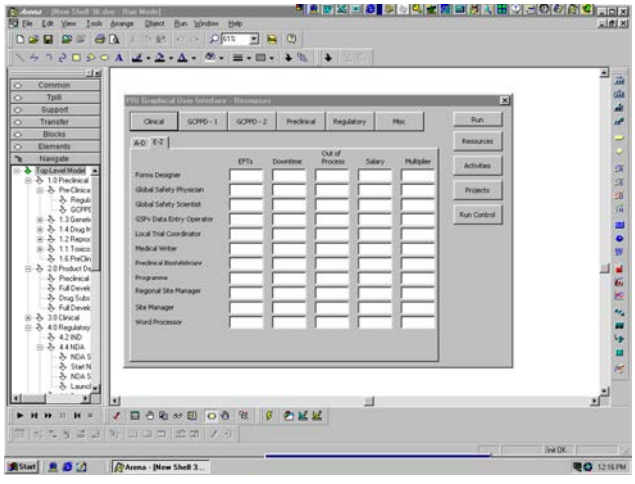


Figure 3: Graphical User Interface

Through such an advanced interface, a user can make many changes to model parameters, including:

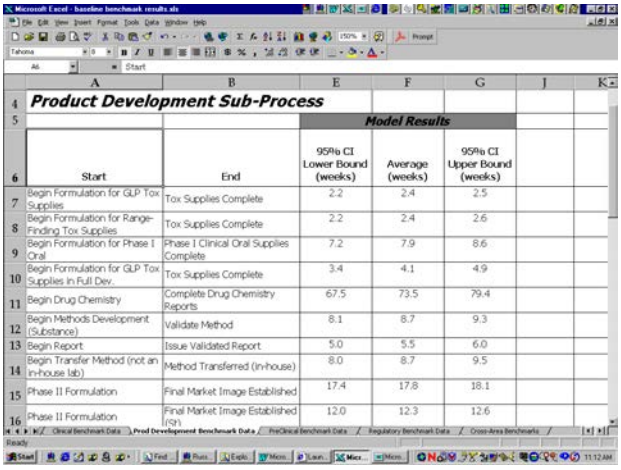
- The Equivalent Full Time (EFT) quantity for each resource role
- The fraction of the time each resource role is not participating in the modeled process (downtime)
- The fraction of the time each resource is scheduled to be unavailable (due to vacation, required training, etc.)
- The salary and multiplier for each resource role
- The arrival distribution
- The probability of attrition at each stage of development
- The parameters for selecting the number of clinical trials to have per compound and per development phase
- The sequencing of the start dates for clinical trials
- Activity durations
- Branching logic at key decision points.

2.4 Model Outputs

Upon completion of the simulation, the model's output statistics are processed by a Microsoft® Excel workbook. These outputs include the following:

- Test conditions
- Resource utilization by resource role
- Throughput
- Cycle time
- Work In Process (WIP)

Figure 4 shows an example of the cycle time output.



Product Development Sub-Process

		Model Results		
Start	End	95% CI Lower Bound (weeks)	Average (weeks)	95% CI Upper Bound (weeks)
Begin Formulation for GLP Tox Supplies	Tox Supplies Complete	2.2	2.4	2.5
Begin Formulation for Range-Finding Tox Supplies	Tox Supplies Complete	2.2	2.4	2.6
Begin Formulation for Phase I Oral	Phase I Clinical Oral Supplies Complete	7.2	7.9	8.6
Begin Formulation for GLP Tox Supplies in Full Dev.	Tox Supplies Complete	3.4	4.1	4.9
Begin Drug Chemistry	Complete Drug Chemistry Reports	67.5	73.5	79.4
Begin Methods Development (Substance)	Validate Method	8.1	8.7	9.3
Begin Report	Issue Validated Report	5.0	5.5	6.0
Begin Transfer Method (not an in-house lab)	Method Transferred (in-house)	8.0	8.7	9.5
Phase II Formulation	Final Market Image Established	17.4	17.8	18.1
Phase II Formulation	Final Market Image Established	12.0	12.3	12.6

Figure 4: Cycle Time Output Example

3 RESULTS

The resource planning capability facilitates staffing analysis informed by variability estimates from the target process. It represents the process a new compound can take upon leaving the discovery laboratory all the way through product launch. This capability provides management a more accurate view of resource demands than does a traditional static analysis tool.

Although this simulation capability is not yet fully deployed in this pharmaceutical company at the time of this writing, the model has already delivered tremendous preliminary value in several initial applications:

- Running the shell sub-model, the company developed a deeper understanding of the critical path for its drug projects. In particular, the model showed how the critical path can change based on the variability of key parameters. This understanding had been absent in using previous static project planning tools and illuminated several previously unknown high-value opportunities to reduce cycle time.

- Running the clinical sub-model, the company validated its expected cycle time reduction from a process change initiative in clinical study reporting. They feel much more confident investing substantial resources to implement this change after having proved it in this risk-free virtual environment.
- Running the product development and preclinical sub-models, the company has identified initial resource bottlenecks that will result from a planned future increase in arriving projects. This insight allowed the company to proactively address this looming capacity shortage.

These preliminary findings indicate the model's potential value as a resource planning tool once fully deployed to the pharmaceutical company in this study.

4 CONCLUSIONS

Simulation modeling provides unique insight into highly complex resource planning tasks. As shown through this case study from the pharmaceutical industry, it provides a resource manager an improved capability to predict the effects of critical sources of process variation. The keys to this ability are having a robust user-friendly interface, capturing the variability of the process at a resource constrained level, and providing meaningful outputs. This capability is not provided by the static planning tools routinely used in the pharmaceutical industry. Moreover, this advantage gives simulation modeling unique relevance to managing resources in the drug development process.

REFERENCES

Breckinridge, C. 1998. Information Rx. *Profit*, May 1998. Oracle Corporation.

The Wall Street Journal. 2000. Drug price program notes. August 10, 2000. Dow Jones & Company, Inc.

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