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Job scheduling for stability testing of pharmaceutical products using mathematical model

Kantanat Pridaphatrakun[1], Nuchanad Bunkerd[1], Netnawee Umin[2], Narueporn Sutanthavibul[1], Wipawee Tharmmaphornphilas[2], Phanphen Wattanaarsakit[1]*

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand, [2]Department of Industrial Engineering, Faculty of Engineering, Chulalongkorn University, Bangkok 10330, Thailand

Corresponding Author:
Phanphen Wattanaarsakit, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.
E-mail address: phanphen.a@chula.ac.th

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ABSTRACT

The pharmaceutical industry plays an important role in the nation's economy and society since pharmaceutical products are one of the factors that affect people's lives and their health. At present, the domestic pharmaceutical industry is developing and adapting to meet the needs of customers and is also very competitive. Therefore, each stage of the production process must be as efficient as possible to achieve competitive advantages without compromising the product quality. One important process in production is pharmaceutical product stability testing, which ensures that the products have the necessary quality, efficacy, and safety. Managing time in a way that maximizes the efficiency of limited staff and testing equipment is one of many challenges. This research demonstrates efficient job scheduling for staff and testing equipment using mathematical formulae and IBM ILOG CPLEX Optimization Studio (CPLEX), which is a set of tools to help model and solve optimization problems. The result will be a job schedule for pharmaceutical product stability testing which includes the start and end date, which is a way of managing time for available resources as efficiently as possible.

Keywords: Job scheduling, stability testing of pharmaceutical products, optimization problem

INTRODUCTION

The stability testing of pharmaceutical products is in every process of pharmaceutical production, including research, testing, recipe, registration, and production (as shown in Figure 1).

Testing must be conducted in accordance with relevant regulations and with the International Conference on Harmonization Guidelines to obtain quality, efficacy, and safety throughout the lifecycle of the pharmaceutical products. In addition to these reasons, stability testing must be an efficient process in order to minimize cost which will benefit customers and allow the products to compete in the market.[1] The previous research titled "Capacity Planning for Stability Testing of Pharmaceutical Products" (which will be referred to as "previous research" for simplicity) demonstrates capacity planning for stability testing for a certain pharmaceutical manufacturer to obtain the number of staff and machines for the testing process, the list of pharmaceutical products, and the number of lots that must be tested in each month that will minimize the production cost.[2] The next problem that must be addressed is the order in which the pharmaceutical products must be tested to use the limited time and resources most efficiently. This can be done by conducting job scheduling. Furthermore, job scheduling can help prove whether the capacity planning from the previous research is appropriate or not. Generally, job scheduling is conducted using simple methods, such as completing tasks in the order they were assigned or randomly selecting tasks to work on without considering the fact that time and resources must be managed in a way that will result in the most efficiency. Job scheduling is difficult and complicated in practice. For example, in the stability testing process for pharmaceutical products, there is a variety of products that must be tested in each month which may come in different forms, such as injection, solution, tablets, capsules, and cream/ointment.

This means that each pharmaceutical product has a unique stability testing process which requires varying amounts of time, staff, and machines. If the order in which the products must be tested is inappropriate, it is possible that the staff must wait for another testing equipment which is currently be used to test another product, which will result in waiting time. An appropriate job schedule will help solve this problem. This research is conducted after the capacity planning process by using the original data from the previous research as input.

Job scheduling for the stability testing of pharmaceutical products to allocate time most efficiently can be done by using mathematical models. In general, algorithms for the optimization process can be divided into two categories according to international standards: Conventional optimization algorithms and approximate optimization algorithms. Conventional optimization algorithms are used as a way to find the most reliable solution using mathematical programming, which can be divided into linear programming, integer programming, mixed integer programming, and nonlinear programming. If the model is highly complex and may take a very long time to process, approximate optimization algorithms will be used instead. Even though the solutions found using approximate optimization algorithms might not be as accurate as those obtained from conventional optimization algorithms, these algorithms will find the best solution in a reasonable amount of time. Approximate optimization algorithms can be divided into heuristic and meta-heuristic. In this research, we have proposed a method for job scheduling for the stability testing of pharmaceutical products using conventional optimization algorithms, since the model is not highly complex and can be processed in a reasonable amount of time. Since nonlinear variables are used in the model, nonlinear programming is used for job scheduling using the number of pharmaceutical products that must be tested in Jan 2019 from the previous research. The objective is to use the working time most efficiently, which means that overtime (OT) must be minimized as represented by the objective function as follows:

$$Minimize\,OT = \max_{p \in P} EndNB_p - workingDayPerMonth$$

The $EndNB_p$ is the last day for the testing of pharmaceutical product p and the *working Day Per Month* is the number of working days for the month that needs job scheduling.

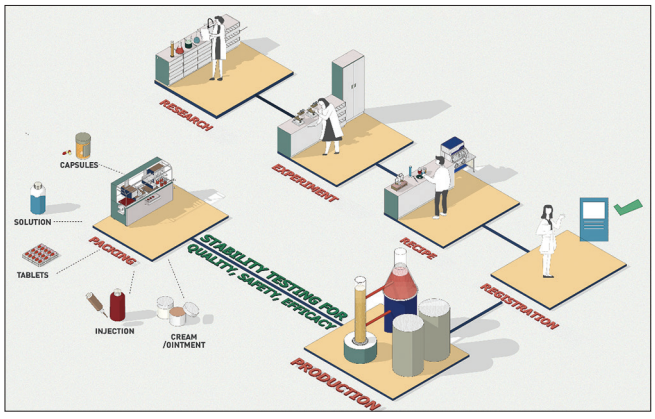

Figure 1: The pharmaceutical production process

Optimization Programming Language (OPL), which is an algebraic modeling language for mathematical optimization models, is used because it is tailored for and is a part of the CPLEX software package.[3-6]

METHOD

Data Collection

Input data are data from the previous research which is obtained from the testing department of a certain pharmaceutical manufacturer from January 2019 to December 2019 as well as the results from capacity planning in the previous research. The data includes the number of optimal resources in Table 1 and the list of pharmaceutical products that should be tested in each month.

This paper will use a sample of pharmaceutical products that should be tested from January, which is the month with the highest number, 65, of products that must be tested. The testing process for each pharmaceutical product consists of three streams that can be done in parallel which includes Assay, Impurity, and Dissolution. The process is shown in Figure 2.

All three streams must be completed for the stability testing of some pharmaceutical products, while only one or two must be completed for other products. Therefore, the number of required staff depends on the number of streams required for testing the corresponding product. Each stream may require the same or a different testing machine, and the amount of time used for the testing process is the amount of time used by the stream that takes the longest. These conditions are summarized in Table 2.

Formulate a Mathematical Formula

In January 2019, there are 20 working days. The goal is to create a job schedule for the pharmaceutical product testing process that requires the minimum number of days and that minimizes overtime using the number of optimal resources obtained from the previous research. The first step is to define the indices that will be used in the mathematical formula. The next step is to define the variables used for known information which are called parameters. The variables used for unknown information are known as decision variables. The following step is to define the objective function and constraints between variables. Then, Optimization Programming Language (OPL), and CPLEX is used to model and solve the formula.[7,8]

Indices

D =set of working date {0.31}

P =set of pharmaceutical products to be tested {1.65}

Table 1: Optimal resources obtained from the previous research

Optimal resources				
Staff	**Testing equipment**			
	HPLC	**Spectrophotometer**	**GC**	**Distillator**
13	11	1	1	1

HPLC: Hight performance liquid chromatography, GC: Gas chromatography

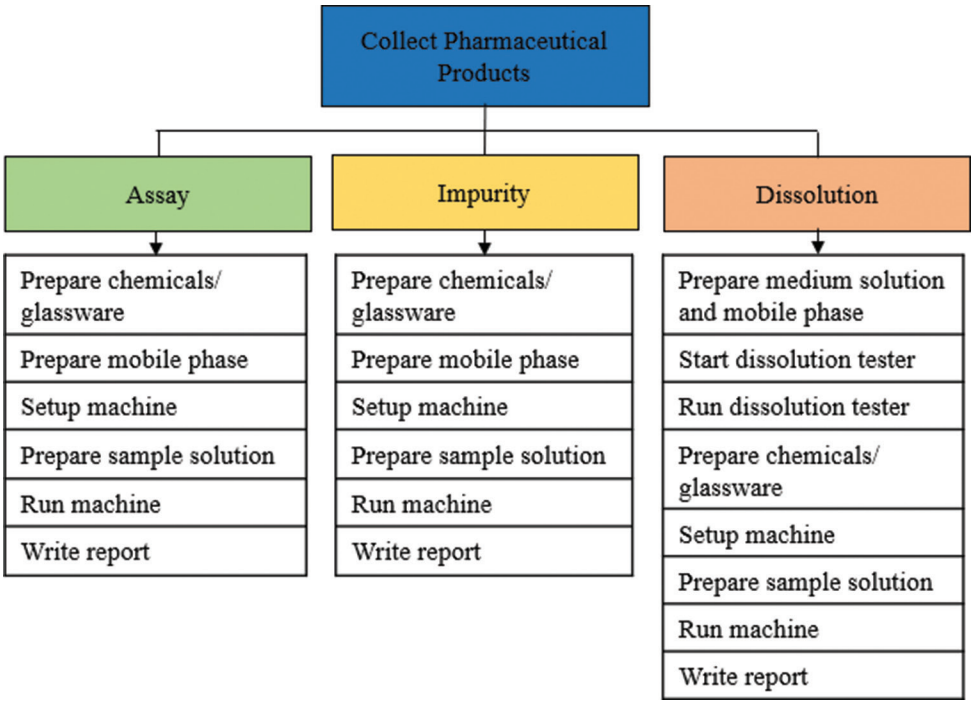

Figure 2: The process for the stability testing of pharmaceutical products

Table 2: An example of the amount of time and number of resources required to test each pharmaceutical product in January 2019 (19 of 65)

Product	Time and resources needed to test each product					
	Time (days)	Staff	HPLC	Spectrophotometer	GC	Distillator
A02	2.7	1	1	0	0	0
A03	2.6	2	2	0	0	0
A04	1.4	1	1	0	0	0
A05	1.3	1	2	0	0	0
A06	2.8	1	1	0	0	0
A07	2.5	2	2	0	0	0
A08	1.4	1	1	0	0	0
A09	0.8	1	0	0	1	0
A10	1.4	2	2	0	0	0
A11	1.4	1	1	0	0	0
B01	2.5	2	2	0	0	0
B02	1.5	1	1	0	0	0
B03	1.5	1	0	1	0	0
C01	1.5	1	1	0	0	0
C02	1.5	1	1	0	0	0
C03	1.4	2	2	0	0	0
C06	1.4	1	1	0	0	0
D02	1.6	2	2	0	0	0
D03	1.5	1	1	0	0	0

HPLC: Hight performance liquid chromatography, GC: Gas chromatography

Parameters

day_p = Number of days used to test pharmaceutical product p (decimal number)

$staff_p$ = Number of staff used to test pharmaceutical product p

$hplc_p p$ = Number of High Performance Liquid

Chromatography (HPLC) machines used to test pharmaceutical product p

gc_p = Number of Gas Chromatography (GC) machines used to test pharmaceutical product p

$spectro_p$ = Number of Spectrophotometers (Spectro) used to test pharmaceutical product p

$buchi_p$ = Number of Distillation Units used to test pharmaceutical product p

nbStaff = Optimal number of staff obtained from the previous paper

nbHplc = Optimal number of HPLC machines obtained from the previous paper

nbGc = Optimal number of GC machines obtained from the previous paper

nbSpectro = Optimal number of Spectrophotometers obtained from the previous paper

nbBuchi = Optimal number of Distillator machines obtained from the previous paper

workingDayPerMonth = Number of working days for the month that needs job scheduling

Decision Variables

$DayRoundUp_p$ = Number of days used to test pharmaceutical product p rounded up to the nearest integer

$Time_{pd}$ = Time required (day) for testing product p on working date d, such as 1 day or 0.7 day

$Test_{pd}$ = 1 if pharmaceutical product p is tested on working date d

0 otherwise

$Start_{pd}$ = 1 if working date d is the starting date for the testing of pharmaceutical product p

0 otherwise

End_{pd} = 1 if working date d is the ending date for the testing of pharmaceutical product p

0 otherwise

$StartNB_p$ = Is the starting date for the testing of pharmaceutical product p, such as day 10 or day 20

$EndNB_p$ = Is the last day for the testing of pharmaceutical product p, such as day 12 or day 23

OT = The difference between the number of days required for testing and the number of working days for the specified month

Objective Function

The objective is to arrange time for resources in a way that is most efficient, which means that OT (the difference between the number of days required for testing and the number of working days in each month) is minimized according to the function below.

$$\text{Minimize } OT = \max_{p \in P} EndNB_p - workingDayPerMonth; \forall_{p \in P}$$

Constraints

Calculate the nearest integer value from rounding up the number of days used for testing of pharmaceutical product *p*.

$$DayRoundUp_p \geq day_p; \forall_{p \in P}$$

$$DayRoundUp_p < day_p + 1; \forall_{p \in P}$$

The number of days used to test each pharmaceutical product must be equal to the number of days needed to test that product.

$$\sum_{d \in D} Test_{pd} = DayRoundUp_p; \forall_{p \in P}$$

Find the starting date for the testing of pharmaceutical product using the method shown in the following example. Suppose pharmaceutical product takes 3 days to test, which are working dates 4, 5, and 6. The variable $Test_{pd}$ will be as shown in Table 3.

$Test_{pd}$ will have a value of 1 on the testing days, which are days 4, 5, and 6, and will have a value of 0 on all other days. It can be seen that the first testing day of pharmaceutical product is the first day that $Test_{pd}$ has a value of 1. Therefore, $Start_{pd}$, which represents the first testing date of pharmaceutical product will have a value of 1 when $Test_{pd}$ has a value of 1 and $Test_{p,d-1}$ has a value of 0, which is shown in the formula below.

$$Start_{pd} = (Test_{pd} - Test_{p,d-1}) \cdot Test_{pd}; \forall_{p \in P, d \in D: d \geq 1}$$

$$Test_{p,0} = 0; \forall_{p \in P}$$

From the example in Table 3, the value of $Start_{pd}$ will be as shown in Table 4.

It can be seen that $Start_{pd}$ has a value of 1 on day 4, which is the starting day for the testing of pharmaceutical product p, and is the day that $Test_{pd}$ changes to 1 when it was 0 the day before.

Nevertheless, to prevent the case of inconsecutive testing days, such as in Table 5, there must be a formula that prevent this case from occurring. Inconsecutive testing days, such as in Table 5, where testing occurs on working days 4 and 5 and jumps to working day 7, lead to the holding of resources.

From Table 5, $Start_{pd}$ will have a value of 1 twice, which occurs in the case that there is a change in the value of $Test_{pd}$ from 0 to 1, which occurs twice. Therefore, if it is determined that $Start_{pd}$ of each pharmaceutical product can occur only once, according to the formula below, the product will be tested on consecutive days.

$$\sum_{d \in D} Start_{pd} = 1; \forall_{p \in P}$$

In the last day of testing, each pharmaceutical product may not utilize the resource for the entire day. For example, pharmaceutical products that require 2.7 days for testing will use only 0.7 days on the last day of testing. To accurately calculate the number of resources required for testing in each

Table 3: Value of $Test_{pd}$ when the working dates for testing pharmaceutical product *P* are 4, 5, and 6

d	1	2	3	4	5	6	7	8	9	10
$Test_{pd}$	0	0	0	1	1	1	0	0	0	0

Table 4: Value of $Start_{pd}$ when the working dates for testing pharmaceutical product *p* are 4, 5, and 6

d	1	2	3	4	5	6	7	8	9	10
$Start_{pd}$	0	0	0	1	0	0	0	0	0	0

Table 5: Values of $Test_{pd}$ and $Start_{pd}$ when the working dates for testing pharmaceutical product p are 4, 5, and 7

d	1	2	3	4	5	6	7	8	9	10
$Test_{pd}$	0	0	0	1	1	0	1	0	0	0
$Start_{pd}$	0	0	0	1	0	0	1	0	0	0

Table 6: Value of End_{pd} when the working dates for testing pharmaceutical product p are 4, 5, and 6

d	1	2	3	4	5	6	7	8	9	10
End_{pd}	0	0	0	0	0	1	0	0	0	0

Table 7: Value of $Time_{pd}$ when the number of days used for testing pharmaceutical product p is 2.7 days and testing begins on day 4

	1	2	3	4	5	6	7	8	9	10
$Time_{pd}$	0	0	0	1	1	0.7	0	0	0	0

day, the amount of time required for testing in each day for each pharmaceutical product must be calculated. First, the last day of testing pharmaceutical product must be calculated and will have a value of 1 when $Test_{pd}$ changes from 1 to 0 according to the formula below.

$$End_{pd} = (Test_{pd} - \ Test_{p,d+1}) \cdot Test_{pd}; \forall_{p \in P, d \in D: d \leq 30}$$

$$Test_{p,31} \ = \ 0; \forall_{p \in P}$$

Using the example from Table 3, the value of End_{pd} will be as shown in Table 6.

The time used for testing each pharmaceutical product in each day can be calculated by the formula:

$$Time_{pd} = Test_{pd} - End_{pd} * \left(DayRoundUp_{p} - day_{p}\right); \forall_{p \in P, d \in D}$$

If the number of days used for testing pharmaceutical product is 2.7 days, and testing begins on day 4, the value of $Time_{pd}$ will be as shown in Table 7.

The number of resources used to test pharmaceutical products in each day must not exceed the number of available resources.

$$\sum_{p \in P} \left(Time_{pd} \cdot staff_{p}\right) \leq nbStaff; \forall_{d \in D}$$

$$\sum_{p \in P} \left(Time_{pd} \cdot hplc_{p}\right) \leq nbHplc; \forall_{d \in D}$$

Table 8: Output from CPLEX shows the optimal job schedule for pharmaceutical product stability testing in January 2019

Product	Testing date		Product	Testing date		Product	Testing date	
	Start	End		Start	End		Start	End
H02	1	2	A06	10	12	F06	16	18
A02	1	3	N04	11	12	C03	17	18
S02	1	3	L07	11	13	C06	17	18
S05	1	3	M01	11	13	F05	17	19
T02	1	3	A04	12	13	B02	18	19
V04	1	3	E01	12	13	C01	18	19
L05	3	4	M06	12	13	C02	18	19
A07	3	5	M09	12	13	D03	18	19
Q02	4	6	S06	12	14	D05	18	19
T04	5	6	I04	13	14	F03	18	19
M11	5	7	M10	13	14	D04	18	21
P05	6	8	I08	13	15	M07	19	20
P07	6	8	D02	14	15	A03	19	21
R03	6	8	L04	14	15	B01	19	21
H03	7	9	M03	14	15	A05	20	21
P08	7	9	I07	14	16	A08	20	21
P01	7	10	I01	14	17	A10	20	21
M12	8	11	F07	15	17	A11	20	21
P04	9	10	G01	15	17	B03	20	21
E02	9	11	G05	15	17	A09	21	21
P02	9	11	G02	16	17	S07	21	21
O01	10	11	S01	16	17			

CPLEX: IBM ILOG CPLEX Optimization Studio

$$\sum_{p\in P}\left(\text{Time}_{pd}\cdot \text{gc}_{p}\right) \le \text{nbGc}; \forall_{d\in D}$$

$$\sum_{p\in P}\left(\text{Time}_{pd}\cdot \text{spectro}_{p}\right) \le \text{nbSpectro}; \forall_{d\in D}$$

$$\sum_{p\in P}\left(\text{Time}_{pd}\cdot \text{buchi}_{p}\right) \le \text{nbBuchi}; \forall_{d\in D}$$

The formula below is used to find the starting testing date for pharmaceutical product p.

$$\text{StartNB}_{p} = \sum_{d\in D}\text{Start}_{pd}\cdot d; \forall_{p\in P}$$

The formula below is used to find the last day of testing for pharmaceutical product p.

$$\text{EndNB}_{p} = \text{StartNB}_{p} + \text{DayRoundUp}_{p} - 1; \forall_{p\in P}$$

Declare the type of decision variables.

$$\text{DayRoundUp}_{p} \in \text{Integer+}; \forall_{p\in P}$$

$$\text{Time}_{pd} \in \text{Real+}; \forall_{p\in P, d\in D}$$

$$\text{Test}_{pd} \in \text{Binary}; \forall_{p\in P, d\in D}$$

$$\text{Start}_{pd} \in \text{Binary}; \forall_{p\in P, d\in D}$$

$$\text{End}_{pd} \in \text{Binary}; \forall_{p\in P, d\in D}$$

$$\text{StartNB}_{p} \in \text{Integer+}; \forall_{p\in P}$$

$$\text{EndNB}_{p} \in \text{Integer+}; \forall_{p\in P}$$

$$OT \in URS$$

Processing using CPLEX

Using OPL to model and solve, the testing schedule for January 2019 is obtained as shown in Table 8.

The OT in each month is displayed in Table 9, which is compared with the number of pharmaceutical products that should be tested in each month from the previous research. Negative OT values represent the number of days required for testing that less than the number of working days.

RESULTS

By creating a mathematical model and using optimization tools such as CPLEX, an optimal job schedule which matches the objective can be obtained. That is, overtime is minimized, which means that the working time and resources are utilized in the most efficient way. Table 8 shows the starting and last working days for testing each pharmaceutical product which follow the constraints in the model, such as working using available resources within the specified working time. This table will help make job assignment easier for the assigners, and they can also be certain that the jobs are assigned efficiently and will be done in a timely manner which is different from when using the original methods. Table 9 displays OT in each

Table 9: Output from CPLEX shows optimal overtime in each month

Topic	January	February	March	April	May	June	July	August	September	October	November	December
Number of pharmaceutical products that should be tested	65	53	54	57	44	42	30	43	36	30	42	32
Number of working days	20	18	20	20	20	20	20	20	20	20	20	20
Number of days required for testing	21	20	20	20	18	19	12	16	10	11	15	11
OT (days)	1	2	0	0	−2	−1	−8	−4	−10	−9	−5	−9

OT: Overtime, CPLEX: IBM ILOG CPLEX Optimization Studio

month which varies according to the number of pharmaceutical products that should be tested in that month. In January and February, there is a large number of pharmaceutical products that should be tested which results in OT. In May to December, there are fewer pharmaceutical products that should be tested which leads to working days with no work. There can be up to 10 days of unproductive working days which occurs in September.

DISCUSSION AND CONCLUSION

The testing department in the manufacturer used in the study has five staff members to conduct the testing and eight testing machines which cannot successfully test the products on time. For example, in January 2019, only 18 products were tested from 65 products that need to be tested. Even if all holidays are used for OT, not all pharmaceutical products can be tested on time. Therefore, capacity planning is conducted in the previous research, and the results obtained show that 13 staff members and 14 testing machines are required for a chance of completing the testing on time. To utilize the resources obtained from the previous paper in the most efficient manner, this research has taken the output, or number of resources obtained from the previous research, to conduct job scheduling. The results show that it is possible for all pharmaceutical products to be completed in each month. For some months that have a large number of products that must be tested, such as January, only a small amount of OT is required. Furthermore, from simulations, taking the number of resources from the previous research and assigning work randomly results in testing time that is up to 30% greater than that obtained from conducting job scheduling. For example, in January, assigning work randomly results in 27 working days, or 7 OT days required. Using job scheduling results in only 21 working days, or 1 OT day required. Even though the optimal job scheduling obtained from this research helps increase the work efficiency, the data from Table 9, suggests that the work efficiency can be further improved. That is, OT varies significantly from month to month with a maximum of 2 day and a minimum of -10 days. Since OT varies according to the number of pharmaceutical products that should be tested, if the number of products is about the same in each month, the large amount of OT in certain months can be lowered. Another observation that should be made is most OT values are negative which means that the number of resources obtained from capacity planning in the previous research is too large. This might result from the large number of resources' idle time used for the calculation in the year that data was collected. During that period, resources, both staff and machine, were insufficient which often leads to one waiting for the other. If there are more resources, idle time might be reduced. Therefore, in practice, the number of various resources should be gradually increased, and OT should be allowed to a certain extent. Then, data should be collected to conduct capacity planning again which will result in a more appropriate number of resources. In the previous research and in this research, mathematical models and optimization tools are used to help with capacity planning and job scheduling for the pharmaceutical product stability testing of a certain pharmaceutical manufacturer. Capacity planning demonstrates the optimal way to manage resources, while job scheduling demonstrates the way of creating a job schedule that uses the available resources from the capacity planning in the most productive way. These two processes certainly reduce the operation cost. Both research papers also show that capacity planning and job scheduling for pharmaceutical product testing are not complex, the mathematical models that are used are not complicated, the optimization tools that are used can be found and applied easily and that the processing time is very fast (measured in minutes). Therefore, investment in these two processes in the pharmaceutical industry is very cost-effective since they lead to maximum productivity in the stability testing portion of the production process.

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