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Scheduling with sequence-dependent batch setup times: planning tests for a pharmaceutical industry

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Abstract: In this work we propose an approach for a real sequence-dependent batch setup times scheduling problem arising in a pharmaceutical company. A legal obligation for the pharmaceutical industry is to monitor the quality of their products during its life cycle. The development of new pharmaceutical products (medicines) leads to a high number of batches to be tested in order to accomplish with certain regulatory obligations regarding maintaining safeguards on quality and safety. The time lines are critical in this process. The problem is how to manage and schedule a number of tests, that require setups and obey to certain precedence relations, to avoid delays in the answers.

Keywords: scheduling, sequence-dependent setup times, case study

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1 Introduction

In this paper we consider a real scheduling problem with sequence-dependent batch setup times proposed by a pharmaceutical company, the Bluepharma - Indústria Farmacêutica S.A. (www.bluepharma.pt). Bluepharma is a pharmaceutical company developing pharmaceutical products that have to be subjected to stability tests during their life cycle, to accomplish to the norms of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, <http://www.ich.org/cache/compo/276-254-1.html>) Stability Program. Batches from each product are stored at given environmental conditions (temperature and humidity). At established time periods (3 months, 6 months, ...) a certain number of batches are removed from the controlled atmosphere chamber and submitted to independent tests. Each test consists of different operations (e.g. setup, calibration, preparation processing, evaluation) and each operation is characterized by its duration, the resources (machines and technicians) it needs, and the precedence relationships with other operations. For each batch of a product a set of predefined tests must be accomplished. The type of a product defines the set of tests and the type of a test determines the machine that should be used. There are two different types of machines: HPLC and Dissolution UV. Before a HPLC machine starts performing a test of a set of batches, some setup and calibration operations have to be carried out. Some of these operations are executed by technicians of the laboratory. Figure 1 sketches the sequence of operations of a test (*Cont.*) for three batches of a product (blue002) on a HPLC machine. Besides these setup times, a precedence relation must be satisfied as whenever a test is to be performed on a machine some operations (e.g. preparations by a technician) must have been accomplished. A test on a HPLC machine requires the work of a technician only during some periods of time. A dissolution test on a Dissolution UV machine, on the other hand, requires the presence of a technician during the whole process, and does not require setup and calibration operations.

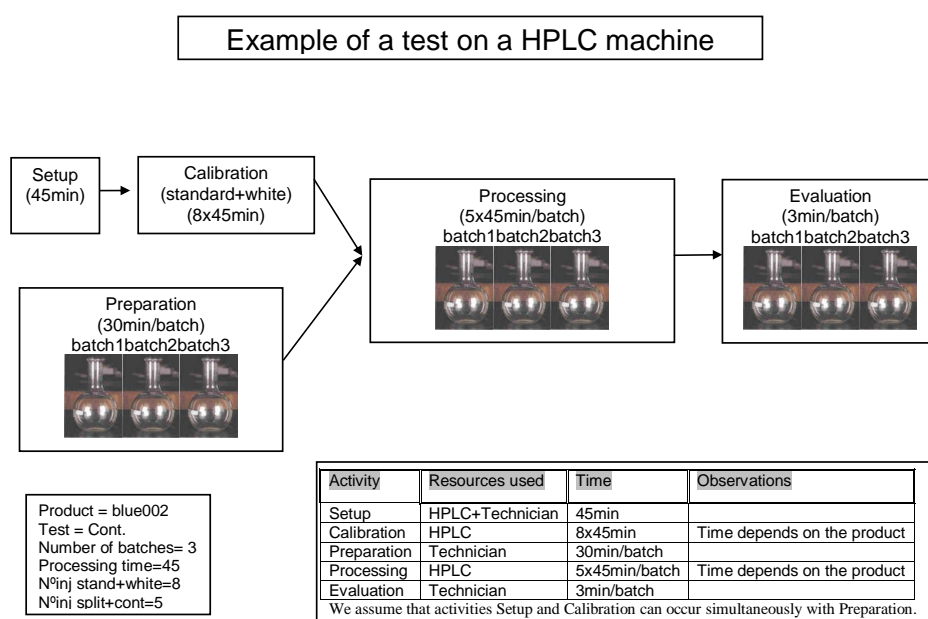


Figure 1 A test of three batches of product blue002 on a HPLC machine according to pharmaceutical specifications.

The process of submitting, at a given time, a number of batches of a certain product to a set of tests is called, in this work, a project. The project starts when the batches of the product are removed from the controlled atmosphere chamber.

At the beginning of each year, a Stability Plan Schedule lists the projects (defined according to ICH Stability Program) that are planned for the current year. This plan indicates for each project: the product, the number of batches and the week it should start. Due to external unpredictable demands, the number of projects for the year may increase.

A project ends when all its set of tests have been completed for all its batches. A project should be finished before one month after it started. A delay of two months is acceptable but it must not be exceeded.

When defining the schedule of projects, the human interventions being restricted to established labor time periods and other obligations (each technician ≈ 6 h/day, 5 days a week) should be accounted. Since technicians interfere on the work of the machines, the daily processing time of the machines is also limited (each HPLC machine ≈ 16 h, each Dissolution UV machine ≈ 6 h).

The pharmaceutical company wants to know whether there is a feasible plan, i.e., a plan where all projects committed during the year are processed without unacceptable delays (delays exceeding two months), and if so, which is the minimum value for the sum of the (acceptable) delays. In addition, the company would like to determine the minimal number of additional resources (machines and/or technicians) that could avoid any delay.

This is a scheduling problem requesting to minimize total delay/tardiness in the presence of sequence-dependent batch setup times. Sequence-dependent setup times play an effective task on the management of the manufacturing capacity and are widely present in industrial applications [6, 9, 13].

Scheduling problems with separate setup times (or costs) have been considered in several studies and approaches including branch and bound, dynamic programming and a number of heuristic procedures have been proposed. We refer [2] and more recently [3] for surveys on this type of scheduling problems.

To solve the pharmaceutical company problem we propose a time decomposition approach which breaks down the scheduling problem into two time-scaled phases. In the first phase, a long term planning (a set of months) approach defines a planning where the tests for each project are weekly assigned to minimize the sum of acceptable delays. The possibility of adding extra resources (machines and/or technicians) is also considered. The weekly planning produced in the first phase is considered in a subsequent phase where a short term planning (a set of weeks) approach is applied. This approach generates a daily planning that schedules, for each machine and for each technician, the operations to be performed in each day. Besides being part of the decomposition strategy, a daily planning tool permits to deal with the existence of possible additional external demands that we have previously mentioned. A mixed integer linear programming model is applied in the long term planning while a greedy heuristic is used in the short term planning.

Decomposition approaches have been successfully applied to some optimization problems [4, 8, 12] as an attempt to deal with the huge size of instances as well as with the complexity involved in the decision-making process.

In Section 2 a mixed integer linear model for the long term planning approach is proposed. A heuristic algorithm for establishing the daily scheduling of operations is described in Section 3. Section 4 reports some computational results. We finish with some conclusions in Section 5.

2 Long term planning approach

The *principles of group technology* [3] is a conventional assumption for scheduling problems with setup times. According to this principle, all batches from the same project are contiguously scheduled. This assumption is considered on the long term planning approach.

We begin by introducing the notation that will be used in the mixed integer linear formulation for the long term planning approach. Let W and P be, respectively, the set of weeks of the considered time period and the set of projects to be executed. Also, let E denote the set of all tests (e.g. *Cont.*, *Imp. 1*, *Imp. 2*, *Diss. HPLC*, *Diss. UV*) accomplished by the pharmaceutical company. Let w , p and e stand for an element in sets W , P and E , respectively. We denote by $E(p)$ the set of all tests involved in project p . Let $U = \{1, 2\}$ stand for the set of machine types: 1 for HPLC and 2 for Dissolution UV machine. Next, we define all the input parameters to be used in the formulation.

K_1 : The weekly processing time (in hours) of a HPLC machine.

N_1 : The number of available HPLC machines.

TS : The setup time of a HPLC machine, i.e, the time (in hours) it takes to configure a HPLC machine to perform a test. This value does not depend neither on the project nor on the type of test.

K_2 : The weekly processing capacity (in number of tests) of a Dissolution UV machine.

N_2 : The number of available Dissolution UV machines.

NT : The number of technicians available to accomplish tests in a HPLC machine.

HT : The weekly working hours of a technician.

For each project $p \in P$ we define:

TI_p : The week in which project p starts.

TF_p : The maximum week in which project p must be finished. This value defines the maximum acceptable delay; for Bluepharma study case $TF_p = TI_p + 11$, which means a maximum acceptable period of twelve weeks to accomplish the tests.

L_p : The number of batches of project p .

For each test $e \in E$ we define:

U_e : Machine type in which test e is accomplished.

For each project $p \in P$ and for each test $e \in E(p)$ such that $U_e = 1$ (HPLC machine) we define:

$TC_{p,e}$: The calibration time, i.e., the time (in hours) it takes to set a HPLC machine to execute test e of project p .

$TP_{p,e}$: The preparation time, i.e., the time (in hours per batch) a technician needs to prepare test e of project p .

$TM_{p,e}$: The processing time, i.e., the time (in hours per batch) it takes to execute the test e of project p .

$TE_{p,e}$: The evaluation time, i.e., the time (in hours per batch) a technician needs to evaluate the results obtained from test e of project p .

Additionally, we denote by $A = \{(p, e, w) \mid p \in P, e \in E(p), TI_p \leq w \leq TF_p\}$ the set of all possible allocations of a test e from a project p to a week w .

Consider a set of binary variables $x \in \{0, 1\}^{|A|}$, a set of integer variables $y \in \mathbb{Z}_+^{|U \cup \{0\}|}$ and two sets of continuous variables $f, \delta \in \mathbb{R}_+^{|P|}$ defined as follows

$$\begin{aligned}
\forall (p, e, w) \in A, \quad x_{pew} &: \begin{cases} 1, & \text{if test } e \text{ of project } p \text{ is assigned to week } w; \\ 0, & \text{otherwise;} \end{cases} \\
y_0 &: \text{number of new technicians to be engaged;} \\
\forall u \in U, \quad y_u &: \text{number of new machines of type } u \text{ to be acquired;} \\
\forall p \in P, \quad f_p &: \text{week in which project } p \text{ is finished;} \\
\forall p \in P, \quad \delta_p &: \text{delay of project } p.
\end{aligned}$$

The following mixed integer linear formulation determines the long term planning.

$$\min \sum_{p \in P} \delta_p$$

$$\text{s. t.} \quad \sum_{\{w | (p,e,w) \in A\}} x_{pew} = 1, \quad \forall p \in P, \forall e \in E(p), \quad (1)$$

$$\sum_{\{p,e | (p,e,w) \in A, U_e=1\}} (TS + TC_{p,e} + L_p \times TM_{p,e}) x_{pew} \leq K_1(N_1 + y_1), \quad \forall w \in W, \quad (2)$$

$$\sum_{\{p,e | (p,e,w) \in A, U_e=1\}} (TS + L_p(TP_{p,e} + TE_{p,e})) x_{pew} \leq HT(NT + y_0), \quad \forall w \in W, \quad (3)$$

$$\sum_{\{p,e | (p,e,w) \in A, U_e=2\}} L_p \times x_{pew} \leq K_2(N_2 + y_2), \quad \forall w \in W, \quad (4)$$

$$f_p \geq w \times x_{pew}, \quad \forall (p, e, w) \in A, \quad (5)$$

$$\delta_p \geq f_p - (TI_p + 3), \quad \forall p \in P, \quad (6)$$

$$TI_p \leq f_p \leq TF_p, \quad \forall p \in P, \quad (7)$$

$$x_{pew} \in \{0, 1\}, \quad \forall (p, e, w) \in A, \quad (8)$$

$$y_u \in \mathcal{Z}_+^1, \quad \forall u \in U \cup \{0\}, \quad (9)$$

$$f_p \geq 0, \quad \forall p \in P \quad (10)$$

$$\delta_p \geq 0, \quad \forall p \in P. \quad (11)$$

Constraints (1) ensure that each test, of each project, is allocated to exactly one week. The weekly processing time of HPLC machines and Dissolution UV machines are forced to be respected by constraints (2) and (4), respectively. Likewise, constraints (3) guarantee that the weekly labor force of technicians working with HLPC machines is respected. Note that we do not have a similar inequality to the UV machine as it has a dedicated technician. Constraints (5)–(7) set a feasible lower bound for the final time and for the delay of each project, respectively. Notice that, the objective function forces these bounds to be tight whenever a project is on delay. Constraints (8)–(11) impose sign and integrality restrictions on the variables defined. Finally, the objective function minimizes the total sum of delays.

3 Daily planning approach

The assignment outcome from the long term planning defines an order on the set of tests for the considered period. Using that order, the daily planning approach establishes a scheduling of every operation of each test for a certain time of a certain day of the period.

We recall that, each operation is characterized by its duration, the resources (machines and technicians) it needs, and the precedence relationships it has with other operations.

We modeled the resources as timed automata. **At each time instant, the state of an automaton indicates an operation being conducted by the corresponding resource or its availability to start one. State transitions occur when a resource starts, interrupts or finishes an operation.** The advantage of the automata-based approach is that it is a natural framework for modeling scheduling problems [1]. Besides that, it allows a straightforward design of the evolution of the scheduling produced by a step by step procedure.

Figure 2 depicts the automata for a generic HPLC machine and for a technician. In our model, the time instants in which transitions of states of each machine (technician) automaton occur depend **directly on its current state as well on the states of the other machines and technicians automata.** As an example, the transition from the free to the setup state on a HPLC machine only takes place if some technician is in the free state. The machine remains at the free state, if no technician is in the free state.

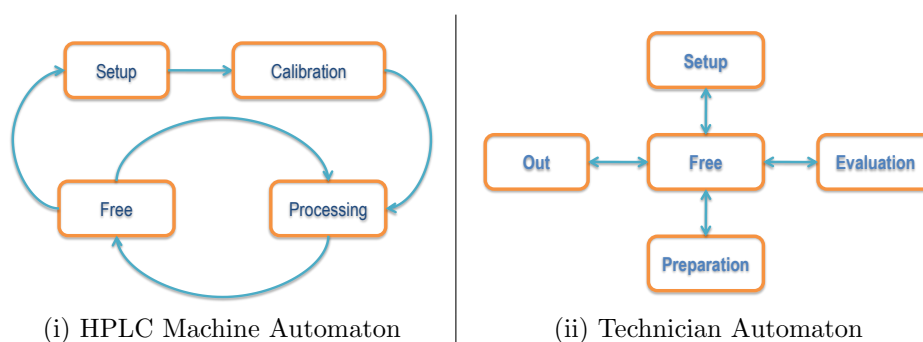


Figure 2 Generic automata used to model resources.

Each test of one batch of each project is conducted according to a specific protocol which defines and rules the operations involved on the test. Each protocol is characterized by

- the set of operations to conduct the test.
Example: $\{Setup, Preparation, Calibration, Processing, Evaluation\}$;
- for each operation, the type of resources needed.
Examples: the operation *Setup* requires a technician and a HPLC machine; the operation *Evaluation* only requires a technician;

- the duration of each operation;
- the time dependencies of each operation from the others.
Examples: the operation *Processing* can only start after *Calibration* and *Preparation* have been finished; the operation *Evaluation* cannot start before *Processing* is completed.

Technicians rest periods (lunch break, leisure, week ends, ...) impose additional restrictions on the scheduling, since operations that require human intervention cannot start in this period.

Some operations can be paused and later resumed. For example, *Preparations* and *Evaluations* can be left in standby and be resumed later. Other operations, however, cannot be interrupted. *Setup* cannot start if there is not enough time to complete the task before the lunch break or by the end of the day. Scheduling of uninterruptible operations, such as *Setup*, require available time windows large enough to completely accommodate the task.

The algorithm that we designed picks tests from the ordered list and sends the corresponding operations to the appropriate automata, according to the protocols and other constraints, minimizing the periods in which the automata stay in the free state. **More precisely, the ordered list of tests is initially transformed into a list of operations, by specifying for each test the sequence of required operations. Then a global procedure cyclically tries to assign to each available machine and/or technician automaton the first compatible operation on that list.**

The whole system evolution, which effectively defines the scheduling that is being constructed is achieved simulating the automata state transitions through time. **This simulation is controlled by a global clock that advances in discrete ticks. At each clock tick, a next tick is computed as the minimum of all the possible future time instants an automaton state transition may occur.**

4 Computational results

The computational results were obtained with data provided by Bluepharma: the list of projects programmed at the beginning of 2010 in document *2010 - Stability Plan Schedule* containing 105 projects and a list of 32 products with the corresponding collection of tests and running times.

We worked under the following specifications regarding weekly maximum working times for HPLC machines and technicians, and number of tests in the Dissolution UV machines, which we will refer as weekly time and task capacities. Weekly time capacity of each HPLC machine (K_1): 80h (16h/day); weekly time capacity of each technician (HT): 30h (6h/day); and weekly time task capacity of each Dissolution UV machine (K_2): 30 tests (6diss/day). We defined the setup time of a HPLC machine (TS) as being equal to 0.75 hours. For every test e of every project p , we set the time a technician takes to prepare a batch ($TP_{p,e}$) equal to 0.5 hours. Finally, the time to evaluate results of each batch ($TE_{p,e}$) was set equal to 0.1 hours for tests *Cont.* and *Diss. HPLC*, and 0.7 hours for tests *Imp. 1* and *Imp. 2*, for every project.

4.1 Long term planning

We considered a 55 weeks planning period (1 year=52 weeks, plus 3 additional weeks to accommodate possible delays) for the 105 projects included in the *2010 - Stability Plan Schedule*, consisting of 786 batches of products, requiring 2053 tests: 2027 tests in the HPLC machines and 26 in the Dissolution UV machines.

We used Xpress Release 2009 (Xpress-Optimizer 20.00.05 and Xpress-Mosel 3.0.0) [7] as an integer programming solver for the mixed integer linear programming model of Section 2, running on an Intel(R) Core(TM)2 Duo CPU 2.00 GHz processor and 1.99Gb of RAM. Our implementation ensures that the solutions produced are optimal.

Our first conclusion is that no feasible plan exists for 3 HPLC machines, 1 Dissolution UV machine and 3 technicians operating tests on the HPLC machines (the resources existing at Bluepharma in 2009). With these resources some inequalities (2) are violated. However, for 4 HPLC machines, and maintaining 1 Dissolution UV machine and the 3 technicians, the algorithm found a feasible solution with no delays (i.e., the corresponding objective value $\sum \delta_p$ equals to zero). Table 1 specifies the weekly usage of the resources determined by the obtained solution. Each line indicates, for a given week, the starting projects, the ending projects, and the percentage of usage of the resources' capacities: HPLC machines (*HPLC*), Dissolution UV machines (*DissUV*) and technicians operating tests on the HPLC machines (*Tech*).

Additional specifications about the weekly assignment can be consulted in the *Bluepharma Report* [5].

Further computational tests were performed with data produced as follows. Bluepharma starts every year with a list of projects for that year. During the year, other projects are added to that list, so that the number of projects executed each year is larger than the number of projects initially listed. We thus considered adding to the list of the 105 projects of the *2010 - Stability Plan Schedule* some randomly generated projects. Each project results from uniformly selecting one product among the list of the 32 products, a number of batches between 3 and 36, and a starting week. In this way, we generated three fictitious lists of annual projects adding to the *2010 - Stability Plan Schedule* 5 (5%), 10 (10%) and 21 (20%) of randomly generated projects. We also considered duplicating every project of the *2010 - Stability Plan Schedule*. Unlike the previous three fictitious lists, in which the additional projects were randomly generated (product, number of batches, starting week), in this last fictitious list, each project was duplicated (same product, same number of batches, same starting week). For each of the four lists of projects several instances were considered varying the numbers of different resources.

In Table 2 we show the main features of the solutions produced from the long term model approach with these instances. We have also included the solution described in Table 1 for the 105 projects of the *2010 - Stability Plan Schedule*. Each line indicates the percentage of projects (*%added Proj*) that were added to the list *2010 - Stability Plan Schedule*; the number of projects (*nProj*) (the number of generated projects plus the 105 projects in *2010 - Stability Plan Schedule*); the total number of batches (*nBat*); the number of tests on the HPLC machines and tests on the Dissolution UV machines (*nTests (HPLC + DissUV)*); the number of available HPLC machines (*nHPLC*), of Dissolution UV machines (*nDissUV*) and

Table 1 Weekly assignment obtained for 105 projects, 4 HPLC machines, 1 Dissolution UV machine and 3 technicians to accomplish tests in HPLC machines.

Week	Starting projects	Ending projects	HPLC	DissUV	Tech
1			0,00	0,00	0,00
2	P1 P2 P3 P4	P3 P4	54,40	10,00	99,17
3	P5 P6 P7	P1 P6 P7	62,98	0,00	98,67
4	P8 P9 P10	P8 P9 P10	58,54	10,00	90,83
5	P11	P2	98,74	0,00	49,67
6	P12 P13	P5 P11 P12P13	48,77	10,00	90,33
7	P14 P15 P16P17	P14 P15 P16P17	90,93	20,00	82,67
8	P18 P19 P20P21P22	P18 P20 P22	57,47	0,00	99,67
9	P23 P24	P21 P23 P24	63,72	0,00	74,50
10		P19	92,71	0,00	74,50
11			0,00	0,00	0,00
12			0,00	0,00	0,00
13	P25 P26 P27P28P29	P25 P26 P27P28P29	54,14	0,00	51,33
14	P30 P31 P32	P30 P31 P32	70,95	10,00	66,67
15	P33 P34 P35	P33 P34 P35	39,01	0,00	46,67
16	P36	P36	5,16	0,00	8,67
17	P37 P38 P39	P37 P38 P39	53,28	0,00	33,33
18	P40	P40	14,61	0,00	33,33
19	P41	P41	58,83	0,00	40,67
20	P42 P43	P42 P43	53,13	0,00	34,67
21	P44 P45 P46P47	P46 P47	83,94	0,00	97,67
22	P48 P49	P44 P48 P49	98,37	0,00	90,00
23	P50 P51	P45 P50 P51	64,70	0,00	85,67
24	P52	P52	5,16	0,00	8,67
25	P53	P53	9,69	0,00	5,33
26	P54 P55	P54 P55	18,52	0,00	25,33
27	P56	P56	27,93	0,00	27,33
28	P57 P58 P59P60	P57 P58 P59P60	30,19	0,00	55,33
29			0,00	0,00	0,00
30	P61 P62	P61 P62	17,87	0,00	20,67
31			0,00	0,00	0,00
32	P63 P64	P63 P64	63,37	6,67	48,00
33	P65 P66 P67	P65 P66 P67	52,42	0,00	42,67
34	P68 P69 P70P71P72	P68 P69 P72	67,48	0,00	99,17
35	P73	P70 P71 P73	66,92	0,00	74,83
36	P74 P75	P74 P75	48,70	0,00	49,33
37	P76	P76	3,98	0,00	4,00
38	P77 P78	P77 P78	16,71	10,00	23,33
39	P79 P80 P81P82P83	P79 P80 P81P82P83	57,72	0,00	62,67
40	P84 P85 P86P87P88	P84 P85 P86P87P88	58,45	10,00	56,00
41	P89	P89	4,92	0,00	7,33
42	P90	P90	4,61	0,00	6,67
43	P91	P91	13,36	0,00	9,33
44	P92 P93	P92 P93	27,63	0,00	50,00
45	P94	P94	27,33	0,00	19,33
46	P95	P95	22,13	0,00	7,33
47	P96 P97	P96 P97	72,36	0,00	94,67
48	P98	P98	34,50	0,00	16,67
49	P99 P100	P99 P100	61,99	0,00	57,33
50	P101	P101	9,17	0,00	15,33
51	P102P103	P102P103	32,02	0,00	32,67
52	P104P105	P104P105	14,30	0,00	19,33

Table 2 Results on instances obtained augmenting the *2010 - Stability Plan Schedule* with random projects.

%add Proj	nProj	nBat	nTests (HPLC + DissUV)	nHPLC	nDissUV	nTech	$\sum \delta$
0%	105	786	2053 (2027+26)	4	1	3	0
5%	110	892	2368 (2342+26)	6	1	3	10
				6	1	4	1
				6	1	5	0
10%	115	983	2428 (2376+52)	4	1	3	1
				4	1	4	0
20%	126	1234	3042 (2970+72)	5	2	3	3
				5	2	4	1
				5	2	5	0
100%	210	1572	4106 (4054+52)	4	1	3	253
				4	1	4	138
				4	1	5	94
				5	1	5	28
				6	1	5	11
				6	1	6	3
				6	1	7	1
				7	1	6	1
				7	1	7	0

technicians operating tests on the HPLC machines ($nTech$); and the minimum sum of delays for that instance ($\sum \delta$).

The resources were gradually increased, thus minimizing the sum of the delays, till an instance was reached where there are no delays ($\sum \delta_p = 0$).

The CPU time taken to run each instance did not exceed 2 hours. After 15 minutes an optimal assignment was found. The remaining time was spent proving that the current solution is indeed an optimal one.

4.2 Daily planning

Here we present some results produced by the automata-based model of Section 3. The automata-based model is working with the solution (depicted in Table 1) that the long term planning approach outcome for the 105 projects in the *2010 - Stability Plan Schedule*, using 4 HPLC machines and 3 technicians.

The solution obtained is outcome as a sequence of timetables for every week of the period. As an example, the operations scheduled for Tuesday of the 6th week can be read in Figure 4. In the figure $M1, M2, M3, M4$ and $W1, W2, W3$ refer to each of the 4 HPLC machines and to each of the 3 technicians, respectively.

In order to access the adequacy of the weekly assignments provided by the long term planning, each set of tests to be conducted in a week was independently fed into the scheduling automata-based program. There were 19 weeks (among the 52) in which some tests were not accommodated during the work period. For those weeks, some tests were scheduled for the beginning of the following week. Therefore, some additional days are needed for the completion of the assigned tests. Those weeks and the additional days needed for the conclusion of the last evaluation (E) of a project (by a technician) are depicted in Figure 3. The same figure also shows that

only for 6 weeks (out of 52 weeks), besides the evaluation, there were processing (P) tasks by HPLC machines scheduled into the following week.

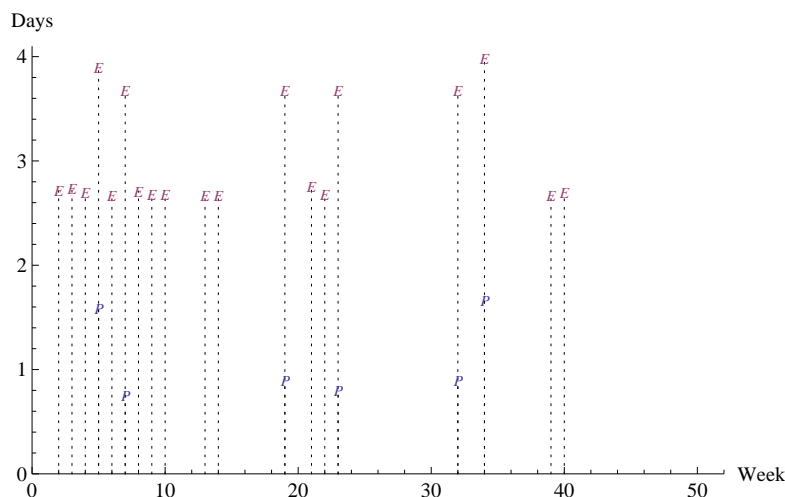


Figure 3 Additional days needed for evaluation (E) and processing (P) resulting from the daily planning.

The automata-based algorithm was implemented in Mathematica 7, and Microsoft Outlook was used for displaying the schedules. Establishing the daily planning for all the 105 projects took less than 2 minutes of CPU time on a computer equipped with an Intel(R) Core(TM)2 DUO 2.53GHz processor and 4GB of RAM.

5 Conclusions

The planning of stability tests for medicines in pharmaceutical industry is a complex task asking for combined operations from different types of resources. We propose to tackle the problem by a two phase procedure. Phase one defines, for a certain period of time (say one year), and based on estimated weekly working capacities of the resources, the week in which each test will be handled. Phase two establishes the schedule of every operation for the considered time period.

For the long term planning we designed a mixed integer linear model that allows to obtain, on reasonable computational times, weekly assignments whose sums of acceptable delays (less than two months) are as small as possible. The model permits to consider varying number of unities for each type of resource which allows to assess the impact that additional resources could have in reducing the delays.

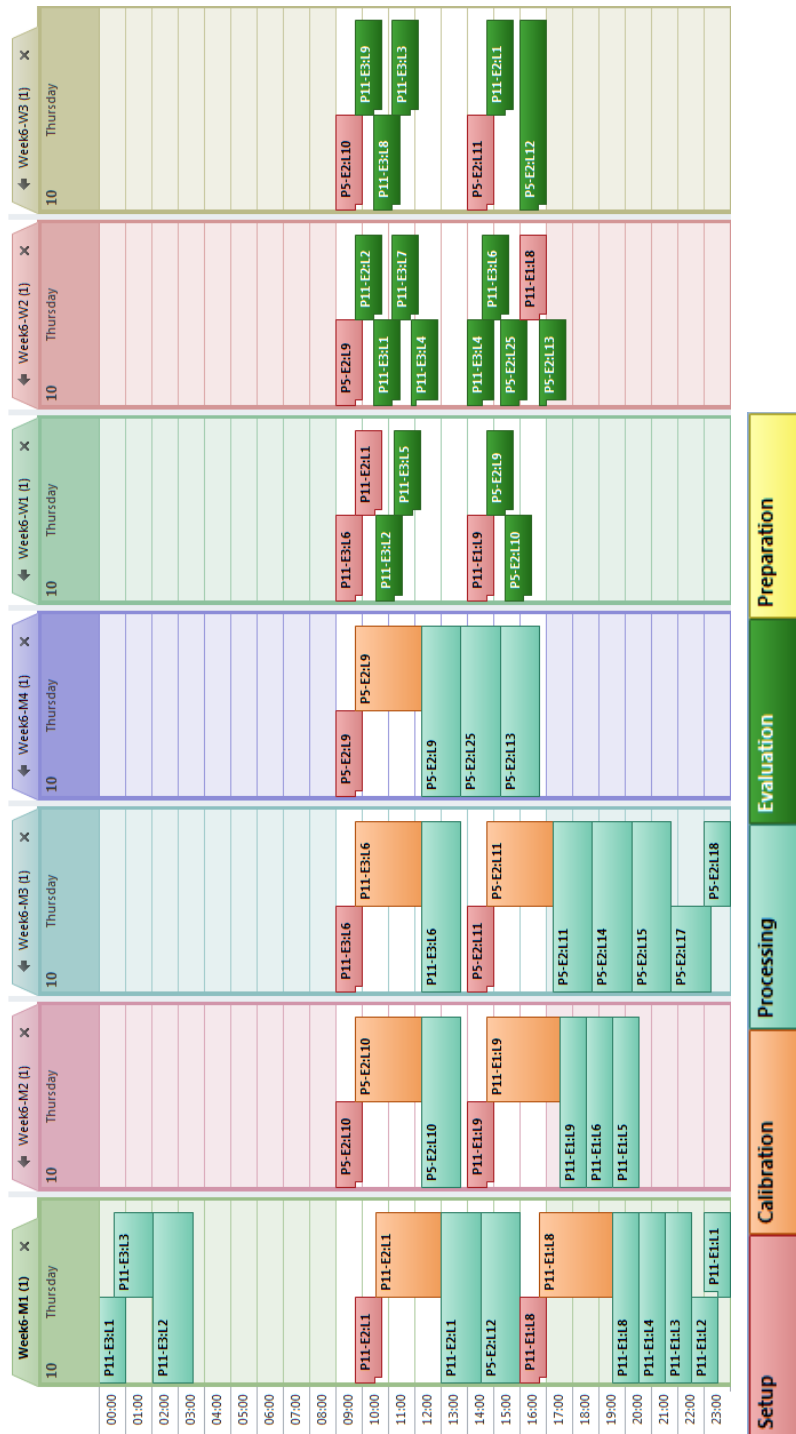
The algorithm that defines, in phase two, a schedule for all operations in the whole period, is a timed automaton-based heuristic which respects the order of tests determined in phase one.

A direction for continuing research is to conceive a model that permits to solve to optimality the schedule problem in phase two. In addition, it is also thought to

develop an integrated tool for the two phases that could handle non-feasibilities in an expedite way.

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