Report on *"BLUEPHARMA"*

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Executive Summary: A legal obligation for the Pharmaceutical Industry is to monitor the quality of their products during its life cycle. The activity of development new pharmaceutical products (medicines) leads to a high number of batches to test to accomplish with an ICH Stability Program and the time lines are critical. The problem is how to manage and schedule the tests of several projects that run at the same time, to avoid delays in the answers.

1 Introduction

Bluepharma is a pharmaceutical company developing pharmaceutical products that have to be subject to stability tests during their life cycle. Batches from each product are stored at given environmental conditions (temperature and humidity), and 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. Each operation is characterized by its duration, the resources (machines and technicians) it needs, and the precedence relationships it has with other operations. The table in Figure 1 lists every test (Conteúdo, Imp Mét 1, ...) that each batch of a product (Blue002, Blue002 US (25mg), ...) involves, indicating the different operations of each test and the corresponding processing times.

There are two different types of machines: HPLC and Dissolution UV. Before a HPLC machine starts processing a test of a set of batches, some setup operations have to be carried out. Some of these operations are executed by technicians of the laboratory. Figure 2 sketches the sequence of operations of a test (conteúdo) for three batches of a product (blue002) on a HPLC machine. The tests on HPLC machines only require the work of a technician during some period of time. The dissolution' tests on the Dissolution UV machine, on the other hand, require the participation of a technician during the whole process.

The process of submitting, at a given time, a certain number of batches of a product to the tests is called a project. The project starts when the batches are removed from the controlled atmosphere chamber. The table in Figure 3 (*2010 - Stability Plan Schedule*) lists the projects

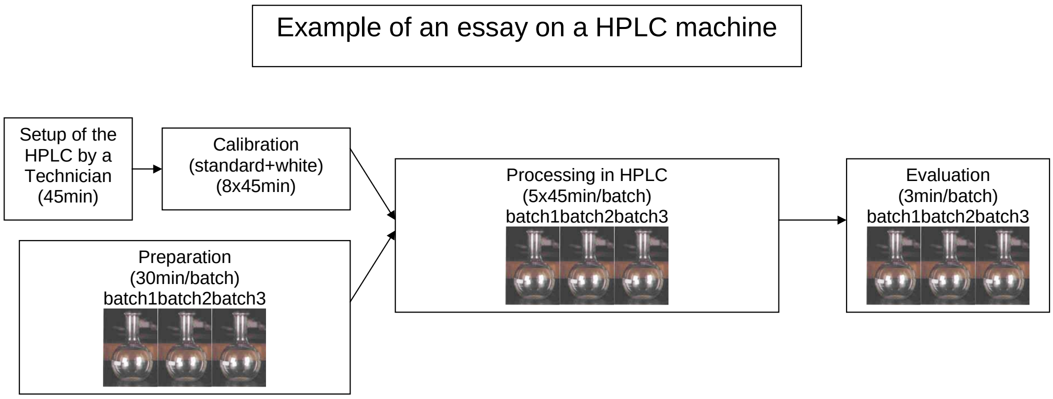
Produto	Conteúdo				Imp Mét 1				Imp Mét 2					Dissolução HPLC					DissoluçãoUV(ma					
	Tempo corrida	Nº inj std+bran	Nº inj spl+cont	TOTAL 1	Tempo corrida	Nº inj std+bran	Nº inj spl+cont	TOTAL 2	Tempo corrida	Nº inj std+bran	Nº inj spl+cont	TOTAL 3	Dissolução	Tempo corrida	Tempos de perf	std+bran	spl+cont	TOTAL 4	Tempo LEITURA	Tempos de perf	std+bran	spl+cont	TOTAL 5	TOTAL HORAS
Blue002	45	8	5	9,8									45											9,8
Blue002 US (25mg)	45	8	5	9,8									45	3	6	7	7	2,45						12,2
Blue007	8	7	3	1,3	60	5	3	8,0					60											9,3
Blue007 Plus	8	7	3	1,3	60	5	3	8,0					45	6	5	7	7	4,2						13,5
Blue008	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	60											13,7
Blue008 Plus	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	60	10	7	7	7	9,33						23,0
Blue009	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	60					0						13,7
Blue009 Plus	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	60	10	7	7	7	9,33						23,0
Blue013	15	11	4	3,8	30	5	3	4,0	30	5	3	4,0	30											11,8
Blue013 Oral Sol	45	11	4	11,3	45	5	3	6,0	20	5	3	2,7												19,9
Blue015	15	7	3	2,5									30											2,5
Blue016	30	13	4	8,5	12	5	3	1,6					30	7	5	7	7	4,9						15,0
BlueA17	40	7	3	6,7	60	6	3	9,0					30						0,5	6	2	6	1	16,3
Blue018	90	8	3	16,5				0,0				0,0						0						16,5
Blue019				0,0				0,0				0,0						0						0,0
Blue020	70	12	4	18,7									60											18,7
Blue022	8	7	3	1,3	60	5	3	8,0					45	6	5	7	7	4,2						13,5
BlueAAA	30	7	3	5,0	60	7	3	10,0				0,0						0						15,0
BlueBBB	30	7	3	5,0	60	7	3	10,0				0,0						0						15,0
BlueCCC	15	7	3	2,5	70	5	3	9,3	40	5	3	5,3	45											17,2
BlueDDD	50	7	3	8,3									45	30	5	4	7	19,5						27,8
BlueEEE	10	7	3	1,7	70	5	3	9,3					30											11,0
BlueFFF	15	7	3	2,5	45	5	3	6,0					60						0,5	5	2	6	1	9,0
BlueGGG	70	7	3	11,7									30	6	4	7	7	3,5						15,2
BlueHHH	3	7	3	0,5	45	6	3	6,8					45	3	5	7	7	2,1						9,4
BlueJJJ	68	7	3	11,3	30	5	3	4,0					30											15,3
BlueKKK	30	7	3	5,0	30	5	3	4,0					30	30	1	7	7	7						16,0
BlueLLL	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	60					0						13,7
BlueMMM	10	7	3	1,7	40	6	3	6,0	40	6	3	6,0	61					0						13,7
BlueNNN	30	7	3	5,0	60	7	3	10,0				0,0						0						15,0
BlueOOO	30	7	3	5,0	60	7	3	10,0				0,0						0						15,0
BluePPP	70	7	3	11,7									30	6	4	7	7	3,5						15,2

Figure 1: Tests and processing times of one batch of each of 32 products.

that are planned to be accomplished in 2010, indicating for each project the number of batches and the week it should start.

Every project should finish before one month after it started. A delay of two months is acceptable but it should not be exceeded.

When defining the schedule of projects, the human interventions being restricted to established labour time periods and other obligations (each technician $\approx$ 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 limited (each HPLC machine $\approx$ 16 h, each Dissolution UV machine $\approx$ 6 h).



Product = blue002
Essay = conteúdo
Number of batches= 3
Processing time=45
Nºinj stand+white=8
Nºinj split+cont=5

Activity	Resources used	Time	observations
Setup	HPLC+Technician	45min	
Calibration	HPLC	8x45min	Time depends on the product
Preparation	Technician	30min/batch	
Processing in HPLC	HPLC	5x45min/batch	Time depends on the product
Evaluation	Technician	3min/batch	

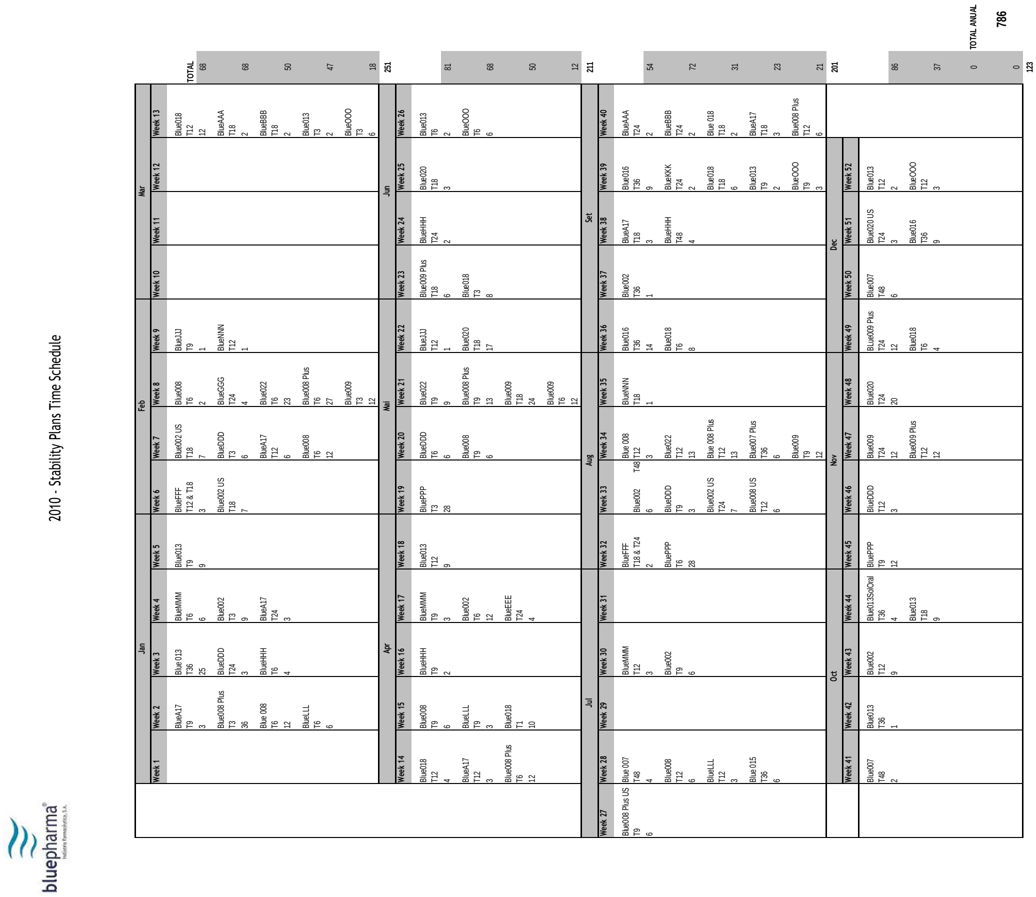
We assume that activities Setup and Calibration can occur simultaneously with Preparation.

Figure 2: A test of three batches of product blue002 on a HPLC machine.

The laboratory wants to know whether it is possible to process all projects without any delay of more than two months. If this is not possible, the laboratory would like to determine minimal additional resources (machines and technicians) that could avoid these type of delays.

The problem is a difficult job shop scheduling with sequence-dependent setups [2, 3], which we suggest being considered at two different time scales. A long term planning approach (several months), in which the tests for each project are weekly assigned to minimize the sum of delays; and a daily planning approach that uses the order defined for the tests to schedule the operations to be performed in each day. If no feasible assignment is determined, the possibility of adding extra resources (machines of each of the two types and additional technicians) is considered.

In Section 2 a 0/1 linear description for the long term planning approach is established. A heuristic algorithm for establish the daily scheduling of operations is described in Section 3. Section 4 reports some computational results. We finish with Section 5, with some conclusions



2010 - Stability Plans Time Schedule

Month	Week	Entries (product / time point / quantity)
Jan	Week 1	
Jan	Week 2	BlueA17 T9 3 Blue008 Plus T3 36 Blue 008 T6 12 BlueLLL T6 6
Jan	Week 3	Blue 013 T36 25 BlueDDD T24 3 BlueHHH T6 4
Jan	Week 4	BlueMMM T6 6 Blue002 T3 9 BlueA17 T24 3
Jan	Week 5	Blue013 T9 9
Feb	Week 6	BlueFFF T12 & T18 3 Blue002 US T18 7
Feb	Week 7	Blue002 US T18 7 BlueDDD T3 6 BlueA17 T12 6 Blue008 T6 12
Feb	Week 8	Blue008 T6 2 BlueGGG T24 4 Blue022 T6 23 Blue008 Plus T6 27 Blue009 T3 12
Feb	Week 9	BlueJJJ T9 1 BlueNNN T12 1
Mar	Week 10	
Mar	Week 11	
Mar	Week 12	
Mar	Week 13	Blue018 T12 12 BlueAAA T18 2 BlueBBB T18 2 Blue013 T3 2 BlueOOO T3 6
Apr	Week 14	Blue018 T12 4 BlueA17 T12 3 Blue008 Plus T6 12
Apr	Week 15	Blue008 T9 6 BlueLLL T9 3 Blue018 T1 10
Apr	Week 16	BlueHHH T9 2
Apr	Week 17	BlueMMM T9 3 Blue002 T6 12 BlueEEE T24 4
Apr	Week 18	Blue013 T12 9
Mai	Week 19	BluePPP T3 28
Mai	Week 20	BlueDDD T6 6 Blue008 T9 6
Mai	Week 21	Blue022 T9 9 Blue008 Plus T9 13 Blue009 T18 24 Blue009 T6 12
Mai	Week 22	BlueJJJ T12 1 Blue020 T18 17
Jun	Week 23	Blue009 Plus T18 6 Blue018 T3 8
Jun	Week 24	BlueHHH T24 2
Jun	Week 25	Blue020 T18 3
Jun	Week 26	Blue013 T6 2 BlueOOO T6 6
Jul	Week 27	Blue008 Plus US T9 6
Jul	Week 28	Blue 007 T48 4 Blue008 T12 6 BlueLLL T12 3 Blue 015 T36 6
Jul	Week 29	
Jul	Week 30	BlueMMM T12 3 Blue002 T9 6
Jul	Week 31	
Aug	Week 32	BlueFFF T18 & T24 2 BluePPP T6 28
Aug	Week 33	Blue002 T48 6 BlueDDD T9 3 Blue002 US T24 7 Blue008 US T12 6
Aug	Week 34	Blue 008 T12 3 Blue022 T12 13 Blue 008 Plus T12 13 Blue007 Plus T36 6 Blue009 T9 12
Aug	Week 35	BlueNNN T18 1
Set	Week 36	Blue016 T36 14 Blue018 T6 8
Set	Week 37	Blue002 T36 1
Set	Week 38	BlueA17 T18 3 BlueHHH T48 4
Set	Week 39	Blue016 T36 9 BlueKKK T24 2 Blue018 T18 6 Blue013 T9 2 BlueOOO T9 3
Set	Week 40	BlueAAA T24 2 BlueBBB T24 2 Blue 018 T18 2 BlueA17 T18 3 Blue008 Plus T12 6
Oct	Week 41	Blue007 T48 2
Oct	Week 42	Blue013 T36 1
Oct	Week 43	Blue002 T12 9
Oct	Week 44	Blue013SolOral T36 4 Blue013 T18 9
Nov	Week 45	BluePPP T9 12
Nov	Week 46	BlueDDD T12 3
Nov	Week 47	Blue009 T24 12 Blue009 Plus T12 12
Nov	Week 48	Blue020 T24 20
Dec	Week 49	BLue009 Plus T24 12 Blue018 T6 4
Dec	Week 50	Blue007 T48 6
Dec	Week 51	Blue020 US T24 3 Blue016 T36 9
Dec	Week 52	Blue013 T12 2 BlueOOO T12 3

Quarter	TOTAL (by row)	Total
Jan–Mar	68, 68, 50, 47, 18	251
Apr–Jun	81, 68, 50, 12	211
Jul–Set	54, 72, 31, 23, 21	201
Oct–Dec	86, 37, 0, 0	123

TOTAL ANUAL 786

Figure 3: Stability Plans Scheduling for 2010: Projects' starting times.

and recommendations.

2 Long term planning approach

We begin introducing the notation that will be used in the 0/1 linear description description for the long term planning approach.

Indices

p Projects.

e Tests.

w Weeks.

Input sets

W	Set of weeks of the considered time period.
P	Set of projects to be considered.
E	Set of tests (contents, impurities, dissolution...).
$E(p)$	Set of all tests involved in project p.
$U = \{1, 2\}$	Set of machine types: 1 for HPLC and 2 for Dissolution UV machine.

Input parameters

K_1	Weekly processing time (in hours) of a HPLC machine.
N_1	Number of available HPLC machines.
TS	Setup time of a HPLC machine. Time (in hours) it takes to prepare a HPLC machine to perform a test. This value does not depend on the project and type of test, and requires the intervention of a technician.
K_2	Weekly processing capacity (in number of dissolutions) of a Dissolution UV machine.
N_2	Number of available Dissolution UV machines.
NT	Number of technicians available to accomplish tests in a HPLC machine.
HT	Weekly working hours of a technician.

For all project $p \in P$:

TI_p	Week in which project p starts.
TF_p	Maximum week in which project p is to be finished. It defines the maximum acceptable delay. We set 3 months, i.e. $TF_p = TI_p + 11$.
L_p	Number of batches of project p.

For all test $e \in E$

U_e	Type of machine in which test e is accomplished.

For all project $p \in P$, and for all test $e \in E(p)$ such that $U_e = 1$ (HPLC machine)

$TC_{p,e}$	Calibration time. Time (in hours) it takes to calibrate a HPLC machine to execute test e of project p.
$TP_{p,e}$	Time (in hours per batch) a technician needs to prepare test e of project p.
$TM_{p,e}$	Time (in hours per batch) it takes to execute the test e of project p.
$TE_{p,e}$	Time (in hours per batch) a technician needs to evaluate the results obtained from test e of project p.

Auxiliar sets

$A = \{(p, e, w) \mid p \in P,\ e \in E(p),\ TI_p \leq w \leq TF_p\}$ Set of all possible allocations of test e of project p to week w.

Variables

$$\forall\ (p,e,w) \in A: \quad x_{pew} = \begin{cases} 1 & \text{if test } e \text{ of project } p \text{ is assigned to week } w; \\ 0 & \text{otherwise.} \end{cases}$$

$$y_0 = \text{Number of new technicians to be engaged.}$$

$$\forall\ u \in U: \quad y_u = \text{Number of new machines of type } u \text{ to be acquired.}$$

$$\forall\ p \in P: \quad f_p = \text{Week in which project } p \text{ is finished.}$$

$$\forall\ p \in P: \quad \delta_p = \text{Delay of project } p.$$

The 0/1 linear formulation for the long term planning approach now follows.

Constraints

- Each test of each project must be allocated to be performed in exactly one of its possible weeks:

$$\sum_{\{w|(p,e,w)\in A\}} x_{pew} = 1,\ \forall\ p \in P,\ \forall\ e \in E(p) \tag{1}$$

- The weekly processing time of HPLC machines must be respected:

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

- The weekly labor force of technicians working with HLPC machines must be respected:

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

- The weekly processing capacity of Dissolution UV machines must be respected:

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

- Defines the final time of each project. The week in which a project is completed can not be earlier than the week in which the last test of the project is performed.

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

- Defines delays of more than 4 weeks for each project.

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

- Sign and integrality constraints:

$$x_{pew} \in \{0,1\},\ \forall\ (p,e,v) \in A \tag{7}$$

$$y_u \in \mathcal{Z},\ \forall\ u \in U \cup \{0\} \tag{8}$$

$$\delta_p \geq 0,\ \forall\ p \in P \tag{9}$$

Objective function

- The goal is to minimize the sum of delays of more than 4 weeks, i.e.,

$$\min \sum_{p \in P} \delta_p. \tag{10}$$

3 Daily planning approach

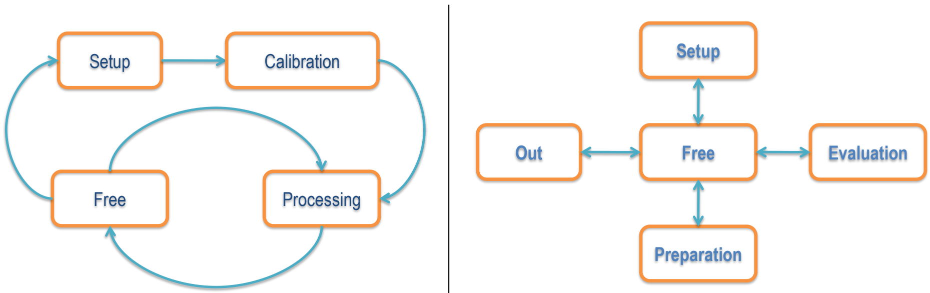
The assignment outcome from the long term planning defines an order on the set of tests for the considered period. Using that order, the daily planning approach establishes a scheduling of every operation of each test for a certain time of a certain day of the period.

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 resources as timed automata. The advantage of the automaton-based approach is that it is a natural framework for modeling scheduling problems [1], and allows a straightforward design of the evolution of the scheduling produced by a step by step procedure.

Figure 4 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 on the current states and on the internal clocks of the technician (machine) 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 available state. The machine remains at the free state, if no technician is in the free state.



(i) HPLC Machine Automaton (ii) Technician Automaton

Figure 4: Generic automata used to model resources.

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

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

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 states.

The whole system evolution, which effectively defines the scheduling that is being constructed is achieved simulating the automata state transitions through time.

4 Computational results

The computational results were obtained with data provided by BluePharma. The list of projects programmed at the beginning of 2010 that figure in document *2010 - Stability Plan Schedule*, depicted in Figure 3, and associating to each project the collection of tests, and corresponding running times, as reported in the table of Figure 1 [1].

We worked under the following specifications regarding weekly maximum working times for HPLC machines and technicians, and number of dissolutions 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 task capacity of each Dissolution UV machine (K_2): 30 dissolutions (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 *conteúdo* and *Dissolução HPLC*, and 0.7 hours for *Imp. Método 1* and *Imp. Método 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*

[1] Actually, the file that we got from BluePharma lacks information on some projects. We complete this information (in red) with simulated data.

(Figure 3), 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) [5] as an integer programming solver for the 0/1 linear model of Section 2, running on an Intel Core2 Duo CPU, 2 GHz, 2Gb RAM. Our implementation ensures that the solutions produced are optimal.

Our first conclusion is that no feasible assignment 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 exceeding 4 weeks (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 (*Projects starting*), the ending projects (*Projects completed*), 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*), for that week.

Additional specifications about the weekly assignment solution are given in the Appendix.

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 that the number of projects initially listed. We thus considered adding to the list of the 105 projects of the *2010 - Stability Plan Schedule* (Figure 3) some randomly generated projects. Each project results from uniformly selecting one product among the 32 products listed in the table of Figure 1, 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*. 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 instance. We have also included the solution described in Table 1 for

Table 1: Weekly assignment obtained for 105 projects, 4 HPLC machines, 1 Dissolution HV machine and 3 technicians.

Week	Projects starting					Projects completed					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	P12	P13		48,77	10,00	90,33
7	P14	P15	P16	P17		P14	P15	P16	P17		90,93	20,00	82,67
8	P18	P19	P20	P21	P22	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	P27	P28	P29	P25	P26	P27	P28	P29	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	P46	P47		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	P59	P60		P57	P58	P59	P60		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	P70	P71	P72	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	P81	P82	P83	P79	P80	P81	P82	P83	57,72	0,00	62,67
40	P84	P85	P86	P87	P88	P84	P85	P86	P87	P88	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	P102	P103				P102	P103				32,02	0,00	32,67
52	P104	P105				P104	P105				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	nEss(HPLC + DissUV)	nHPLC M.	nDissUV M.	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

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 dissolutions on the Dissolution UV machines (*nTests (HPLC + DissUV)*); the numbers of available HPLC machines (*nHPLC M.*), of Dissolution UV machines (*nDissUV M.*) and of technicians operating tests on the HPLC machines (*nTech*); and the minimum sum of delays exceeding four weeks 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 of more than 4 weeks.

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, working with the solution (depicted in Tables 1, 3–8 and 9–11) that the long term planning approach outcome for the 105 projects in the *2010 - Stability Plan Schedule* (Figure 3), using 4 HPLC machines, 1 Dissolution HV machines and 3 technicians.

The durations of the operations of each test of one batch of a product are those specified in the table of Figure 1, and we considered the daily working period for the technicians as being 9 to 12 A.M. and 2 to 6 PM.

The automata-based algorithm was implemented in Mathematica 7, and Microsoft Outlook was used for displaying the schedules.

The solution obtained is outcome as a sequence of timetables for every week of the period. Figure 5 shows the scheduling for the 6th week. The operations scheduled for Tuesday can be read in Figure 6. In the figures $M1, M2, M3, M4$ and $W1, W2, W3$ refer to each of the 4 HPLC machines and to each of the 3 technicians, respectively.

5 Conclusions and recommendations

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 period.

For the weekly assignment we designed a 0/1 linear model that allows to obtain, on reasonable computational times, feasible solutions 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 precise schedule for all operations in the whole period, is a timed automaton-based heuristic which respects the order of tests determined in phase one. It is possible that the algorithm outcome unfeasible schedules (projects exceeding three months), although schedules without unacceptable delays may exist. To attempt for attaining feasibility it is possible to slightly change the order of tests considering first tests of those projects which are currently having larger delays. This certainly would not substantially increase the running times.

Finally, we would like to refer that having a more detailed pattern of the type of projects that are often added during the year to the initial list for that year, would permit to predict the ideal number of unities of each type of resource, and therefore producing a better final schedule.

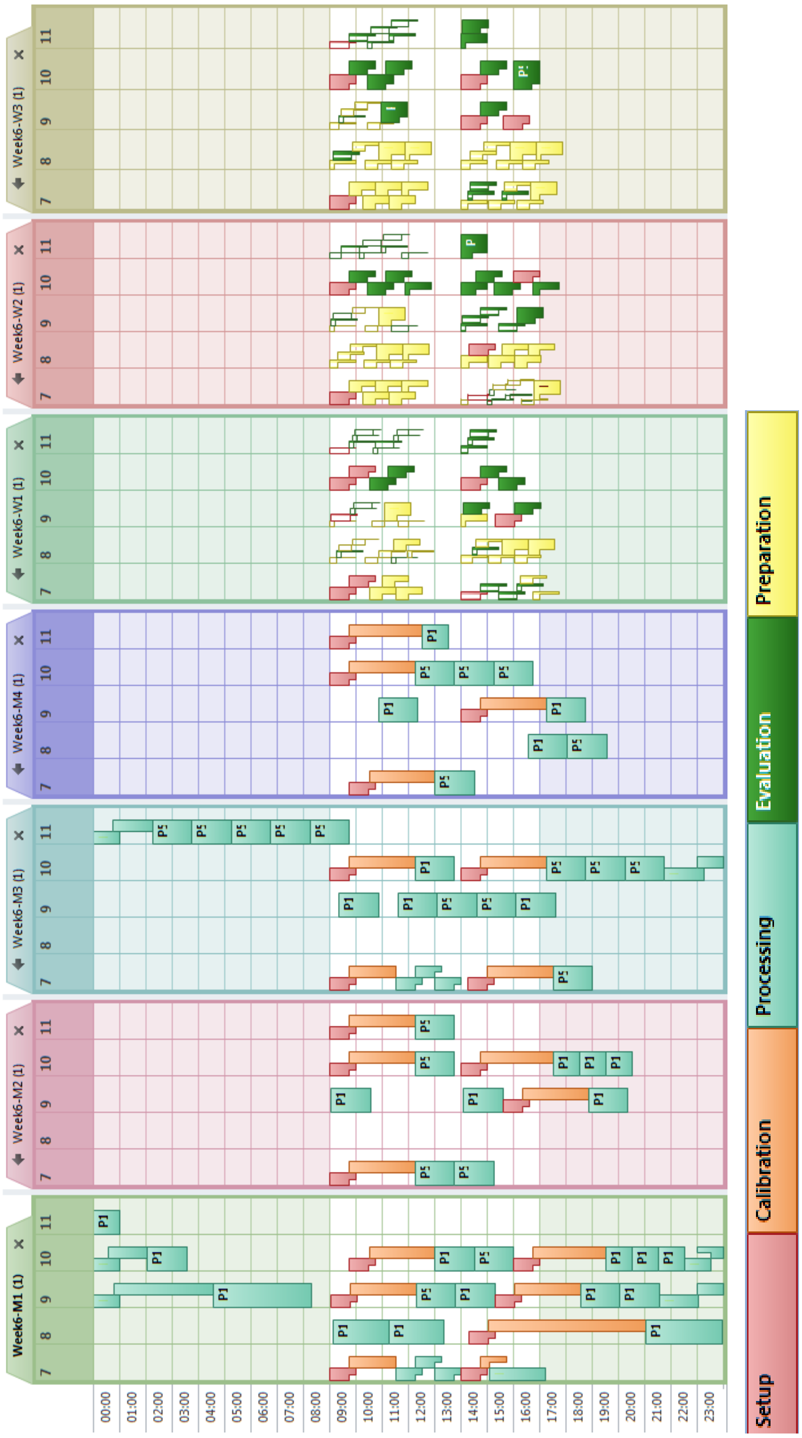


Figure 5: Scheduling obtained for the 6th week.

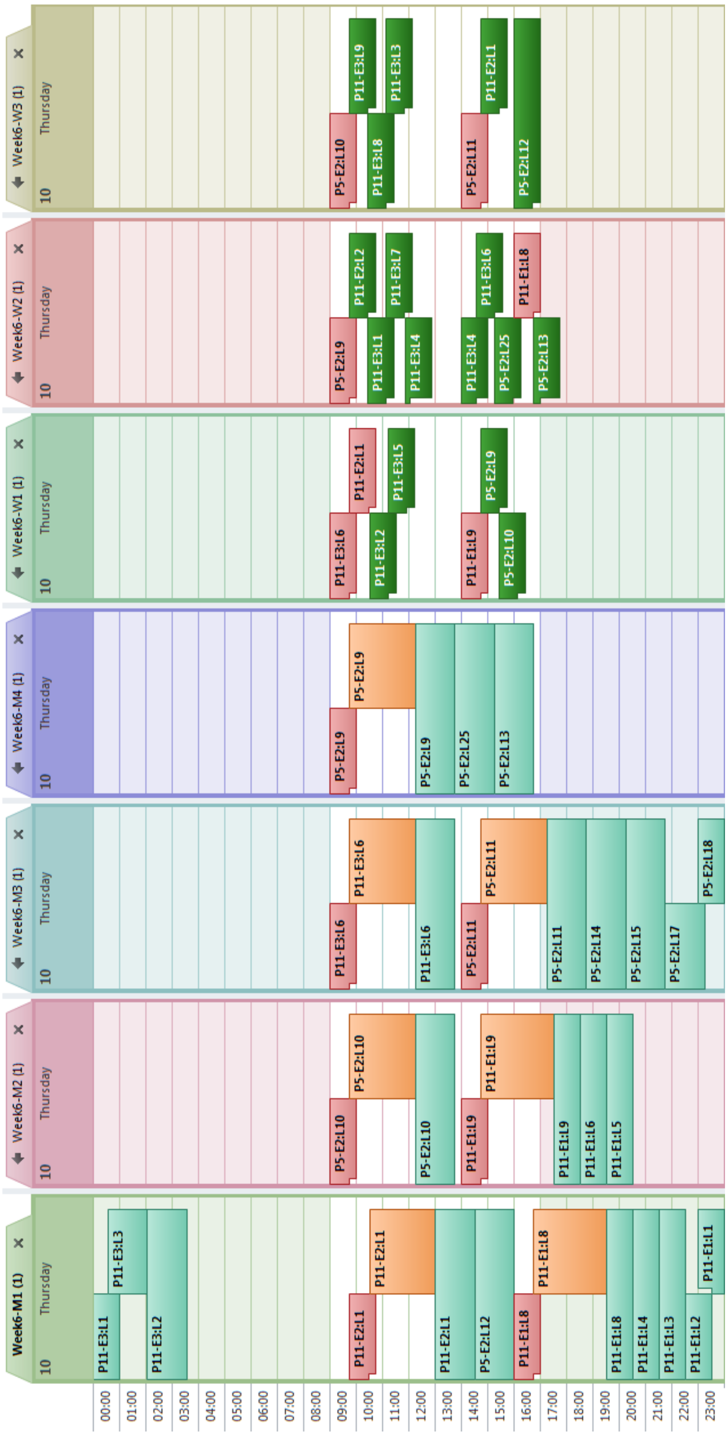


Figure 6: Scheduling for Tuesday of the 6th week.

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Appendix

Here we give details on the weekly assignment solution obtained for the 105 projects in the *2010 - Stability Plan Schedule* (Figure 3), using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians.

Tables 3 to 8 indicate for each of the 105 projects (*Proj*) the number of batches (*#bat*), the week in which the project starts (*Wstart*) and the week where it finishes (*Wend*), the usage of resources: number of hours in the HPLC machines (*hHPLC*), number of dissolutions in the Dissolution UV machines (*#Diss*), number of hours of technicians' work (*hTech*) and, for every test (*Test*), the week where it should be processed (*Wproc*). Tests $E1, E2, E3, E4$ and $E5$ refer to tests *Conteúdo*, *Impureza 1*, *Impureza 2*, *Dissolution HPLC* and *Dissolution UV*, respectively.

Finally, Tables 9, 10 and 11 specify the week in which each project starts (*WPstart*) and the week in which each test of the project is to be processed (*WEproc*).

Table 3: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: I.

Proj	#nbat	Wstart	Wend	hHPLC	#Diss	hTech	Test	Wproc
P1	12	2	3	66.17	0	39	E3	2
							E1	3
							E2	3
P2	36	2	5	469.46	0	132.6	E3	2
							E2	4
							E1	5
							E4	5
P3	3	2	2	28.67	3	8.4	E1	2
							E2	2
							E5	2
P4	6	2	2	39.17	0	21	E1	2
							E2	2
							E3	2
P5	25	3	6	110.75	0	78	E1	3
							E3	3
							E2	6
P6	3	3	3	70.83	0	6.6	E1	3
							E4	3
P7	4	3	3	24.8	0	12.6	E1	3
							E2	3
							E4	3
P8	9	4	4	42.75	0	8.4	E1	4
P9	3	4	4	28.67	3	8.4	E1	4
							E2	4
							E5	4
P10	6	4	4	39.17	0	21	E1	4
							E2	4
							E3	4
P11	9	5	6	46.75	0	30	E1	6
							E2	6
							E3	6
P12	7	6	6	50.3	0	11.4	E1	6
							E4	6
P13	3	6	6	17.5	3	8.4	E1	6
							E2	6
							E5	6
P14	7	7	7	50.3	0	11.4	E1	7
							E4	7
P15	12	7	7	66.17	0	39	E1	7
							E2	7
							E3	7
P16	6	7	7	43.67	6	13.8	E1	7
							E2	7
							E5	7

Table 4: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: II.

Proj	#nbat	Wstart	Wend	hHPLC	#Diss	hTech	Test	Wproc
P17	6	7	7	130.83	0	10.2	E1	7
							E4	7
P18	2	8	8	21.17	0	9	E1	8
							E2	8
							E3	8
P19	27	8	10	355.43	0	100.2	E3	8
							E1	10
							E2	10
							E4	10
P20	12	8	8	66.17	0	39	E1	8
							E2	8
							E3	8
P21	23	8	9	168.33	0	58.2	E1	9
							E2	9
							E4	9
P22	4	8	8	37.07	0	7.8	E1	8
							E4	8
P23	1	9	9	18.33	0	4.8	E1	9
							E2	9
P24	1	9	9	18	0	4.8	E1	9
							E2	9
P25	2	13	13	18.75	0	9	E1	13
							E2	13
							E3	13
P26	12	13	13	69	0	10.2	E1	13
P27	2	13	13	22.5	0	6.6	E1	13
							E2	13
P28	2	13	13	22.5	0	6.6	E1	13
							E2	13
P29	6	13	13	40.5	0	13.8	E1	13
							E2	13
P30	12	14	14	165.38	0	46.2	E1	14
							E2	14
							E3	14
							E4	14
P31	3	14	14	28.67	3	8.4	E1	14
							E2	14
							E5	14
P32	4	14	14	33	0	5.4	E1	14
P33	6	15	15	39.17	0	21	E1	15
							E2	15
							E3	15
P34	10	15	15	60	0	9	E1	15

Table 5: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: III.

Proj	#nbat	Wstart	Wend	hHPLC	#Diss	hTech	Test	Wproc
P35	3	15	15	25.67	0	12	E1	15
							E2	15
							E3	15
P36	2	16	16	16.5	0	7.8	E1	16
							E2	16
							E4	16
P37	12	17	17	54	0	10.2	E1	17
P38	4	17	17	90.83	0	7.8	E1	17
							E4	17
P39	3	17	17	25.67	0	12	E1	17
							E2	17
							E3	17
P40	9	18	18	46.75	0	30	E1	18
							E2	18
							E3	18
P41	28	19	19	188.27	0	36.6	E1	19
							E4	19
P42	6	20	20	39.17	0	21	E1	20
							E2	20
							E3	20
P43	6	20	20	130.83	0	10.2	E1	20
							E4	20
P44	13	21	22	178.05	0	49.8	E3	21
							E1	22
							E2	22
							E4	22
P45	24	21	23	120.17	0	75	E2	22
							E1	23
							E3	23
P46	12	21	21	165.38	0	46.2	E1	21
							E2	21
							E3	21
							E4	21
P47	9	21	21	71.73	0	24.6	E1	21
							E2	21
							E4	21
P48	17	22	22	96.39	0	13.2	E1	22
P49	1	22	22	18.33	0	4.8	E1	22
							E2	22
P50	6	23	23	89.36	0	24.6	E1	23
							E2	23
							E3	23
							E4	23

Table 6: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: IV.

Proj	#nbat	Wstart	Wend	hHPLC	#Diss	hTech	Test	Wproc
P51	8	23	23	51	0	7.8	E1	23
P52	2	24	24	16.5	0	7.8	E1	24
							E2	24
							E4	24
P53	3	25	25	31.01	0	4.8	E1	25
P54	2	26	26	18.75	0	9	E1	26
							E2	26
							E3	26
P55	6	26	26	40.5	0	13.8	E1	26
							E2	26
P56	6	27	27	89.36	0	24.6	E1	27
							E2	27
							E3	27
							E4	27
P57	4	28	28	22.53	0	10.2	E1	28
							E2	28
P58	6	28	28	39.17	0	21	E1	28
							E2	28
							E3	28
P59	6	28	28	9.25	0	6.6	E1	28
P60	3	28	28	25.67	0	12	E1	28
							E2	28
							E3	28
P61	6	30	30	31.5	0	6.6	E1	30
P62	3	30	30	25.67	0	12	E1	30
							E2	30
							E3	30
P63	2	32	32	14.5	2	6.6	E1	32
							E2	32
							E5	32
P64	28	32	32	188.27	0	36.6	E1	32
							E4	32
P65	13	33	33	57.75	0	10.8	E1	33
P66	6	33	33	39.17	0	21	E1	33
							E2	33
							E3	33
P67	3	33	33	70.83	0	6.6	E1	33
							E4	33
P68	6	34	34	51.03	0	17.4	E1	34
							E2	34
							E4	34
P69	3	34	34	25.67	0	12	E1	34
							E2	34
							E3	34

Table 7: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: V.

Proj	#nbat	Wstart	Wend	hHPLC	#Diss	hTech	Test	Wproc
P70	13	34	35	70.67	0	42	E1	34
							E2	34
							E3	35
P71	12	34	35	165.38	0	46.2	E1	35
							E2	35
							E3	35
							E4	35
P72	13	34	34	99.33	0	34.2	E1	34
							E2	34
							E4	34
P73	1	35	35	18	0	4.8	E1	35
							E2	35
P74	14	36	36	104.84	0	36.6	E1	36
							E2	36
							E4	36
P75	8	36	36	51	0	7.8	E1	36
P76	1	37	37	12.75	0	3.6	E1	37
P77	3	38	38	28.67	3	8.4	E1	38
							E2	38
							E5	38
P78	4	38	38	24.8	0	12.6	E1	38
							E2	38
							E4	38
P79	2	39	39	18.75	0	9	E1	39
							E2	39
							E3	39
P80	9	39	39	71.44	0	24.6	E1	39
							E2	39
							E4	39
P81	6	39	39	42	0	6.6	E1	39
P82	2	39	39	25.5	0	7.8	E1	39
							E2	39
							E4	39
P83	3	39	39	27	0	8.4	E1	39
							E2	39
P84	6	40	40	89.36	0	24.6	E1	40
							E2	40
							E3	40
							E4	40
P85	3	40	40	28.67	3	8.4	E1	40
							E2	40
							E5	40
P86	2	40	40	24	0	4.2	E1	40

Table 8: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: VI.

Proj	n bat	WOut	WEnd	HPLC	Diss	Tech	Test	Wproc
P87	2	40	40	22.5	0	6.6	E1	40
							E2	40
P88	2	40	40	22.5	0	6.6	E1	40
							E2	40
P89	2	41	41	15.73	0	6.6	E1	41
							E2	41
P90	1	42	42	14.75	0	6	E1	42
							E2	42
							E3	42
P91	9	43	43	42.75	0	8.4	E1	43
P92	9	44	44	46.75	0	30	E1	44
							E2	44
							E3	44
P93	4	44	44	41.67	0	15	E1	44
							E2	44
							E3	44
P94	12	45	45	87.47	0	17.4	E1	45
							E4	45
P95	3	46	46	70.83	0	6.6	E1	46
							E4	46
P96	12	47	47	66.17	0	39	E1	47
							E2	47
							E3	47
P97	12	47	47	165.38	0	46.2	E1	47
							E2	47
							E3	47
							E4	47
P98	20	48	48	110.4	0	15	E1	48
P99	12	49	49	165.38	0	46.2	E1	49
							E2	49
							E3	49
							E4	49
P100	4	49	49	33	0	5.4	E1	49
P101	6	50	50	29.33	0	13.8	E1	50
							E2	50
P102	9	51	51	71.44	0	24.6	E1	51
							E2	51
							E4	51
P103	3	51	51	31.01	0	4.8	E1	51
P104	2	52	52	18.75	0	9	E1	52
							E2	52
							E3	52
P105	3	52	52	27	0	8.4	E1	52
							E2	52

Table 9: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: VII.

Proj Test	WPstart	WEproc	Proj Test	WPstart	WEproc
P1 E3	2	2	P17 E1	7	7
P2 E3	2	2	P17 E4	7	7
P3 E1	2	2	P18 E1	8	8
P3 E2	2	2	P18 E2	8	8
P3 E5	2	2	P18 E3	8	8
P4 E1	2	2	P19 E3	8	8
P4 E2	2	2	P20 E1	8	8
P4 E3	2	2	P20 E2	8	8
P1 E1	2	3	P20 E3	8	8
P1 E2	2	3	P22 E1	8	8
P5 E1	3	3	P22 E4	8	8
P5 E3	3	3	P21 E1	8	9
P6 E1	3	3	P21 E2	8	9
P6 E4	3	3	P21 E4	8	9
P7 E1	3	3	P23 E1	9	9
P7 E2	3	3	P23 E2	9	9
P7 E4	3	3	P24 E1	9	9
P2 E2	2	4	P24 E2	9	9
P8 E1	4	4	P19 E1	8	10
P9 E1	4	4	P19 E2	8	10
P9 E2	4	4	P19 E4	8	10
P9 E5	4	4	P25 E1	13	13
P10 E1	4	4	P25 E2	13	13
P10 E2	4	4	P25 E3	13	13
P10 E3	4	4	P26 E1	13	13
P2 E1	2	5	P27 E1	13	13
P2 E4	2	5	P27 E2	13	13
P5 E2	3	6	P28 E1	13	13
P11 E1	5	6	P28 E2	13	13
P11 E2	5	6	P29 E1	13	13
P11 E3	5	6	P29 E2	13	13
P12 E1	6	6	P30 E1	14	14
P12 E4	6	6	P30 E2	14	14
P13 E1	6	6	P30 E3	14	14
P13 E2	6	6	P30 E4	14	14
P13 E5	6	6	P31 E1	14	14
P14 E1	7	7	P31 E2	14	14
P14 E4	7	7	P31 E5	14	14
P15 E1	7	7	P32 E1	14	14
P15 E2	7	7	P33 E1	15	15
P15 E3	7	7	P33 E2	15	15
P16 E1	7	7	P33 E3	15	15
P16 E2	7	7	P34 E1	15	15
P16 E5	7	7	P35 E1	15	15

Table 10: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: VIII.

Proj Test	WPstart	WEproc	Proj Test	WPstart	WEproc
P35 E2	15	15	P52 E2	24	24
P35 E3	15	15	P52 E4	24	24
P36 E1	16	16	P53 E1	25	25
P36 E2	16	16	P54 E1	26	26
P36 E4	16	16	P54 E2	26	26
P37 E1	17	17	P54 E3	26	26
P38 E1	17	17	P55 E1	26	26
P38 E4	17	17	P55 E2	26	26
P39 E1	17	17	P56 E1	27	27
P39 E2	17	17	P56 E2	27	27
P39 E3	17	17	P56 E3	27	27
P40 E1	18	18	P56 E4	27	27
P40 E2	18	18	P57 E1	28	28
P40 E3	18	18	P57 E2	28	28
P41 E1	19	19	P58 E1	28	28
P41 E4	19	19	P58 E2	28	28
P42 E1	20	20	P58 E3	28	28
P42 E2	20	20	P59 E1	28	28
P42 E3	20	20	P60 E1	28	28
P43 E1	20	20	P60 E2	28	28
P43 E4	20	20	P60 E3	28	28
P44 E3	21	21	P61 E1	30	30
P46 E1	21	21	P62 E1	30	30
P46 E2	21	21	P62 E2	30	30
P46 E3	21	21	P62 E3	30	30
P46 E4	21	21	P63 E1	32	32
P47 E1	21	21	P63 E2	32	32
P47 E2	21	21	P63 E5	32	32
P47 E4	21	21	P64 E1	32	32
P44 E1	21	22	P64 E4	32	32
P44 E2	21	22	P65 E1	33	33
P44 E4	21	22	P66 E1	33	33
P45 E2	21	22	P66 E2	33	33
P48 E1	22	22	P66 E3	33	33
P49 E1	22	22	P67 E1	33	33
P49 E2	22	22	P67 E4	33	33
P45 E1	21	23	P68 E1	34	34
P45 E3	21	23	P68 E2	34	34
P50 E1	23	23	P68 E4	34	34
P50 E2	23	23	P69 E1	34	34
P50 E3	23	23	P69 E2	34	34
P50 E4	23	23	P69 E3	34	34
P51 E1	23	23	P70 E1	34	34
P52 E1	24	24	P70 E2	34	34

Table 11: Solution for *2010 - Stability Plan Schedule*, using 4 HPLC machines, 1 Dissolution HV machine and 3 technicians: IX.

Proj Test	WPstart	WEproc	Proj Test	WPstart	WEproc
P72 E1	34	34	P88 E1	40	40
P72 E2	34	34	P88 E2	40	40
P72 E4	34	34	P89 E1	41	41
P70 E3	34	35	P89 E2	41	41
P71 E1	34	35	P90 E1	42	42
P71 E2	34	35	P90 E2	42	42
P71 E3	34	35	P90 E3	42	42
P71 E4	34	35	P91 E1	43	43
P73 E1	35	35	P92 E1	44	44
P73 E2	35	35	P92 E2	44	44
P74 E1	36	36	P92 E3	44	44
P74 E2	36	36	P93 E1	44	44
P74 E4	36	36	P93 E2	44	44
P75 E1	36	36	P93 E3	44	44
P76 E1	37	37	P94 E1	45	45
P77 E1	38	38	P94 E4	45	45
P77 E2	38	38	P95 E1	46	46
P77 E5	38	38	P95 E4	46	46
P78 E1	38	38	P96 E1	47	47
P78 E2	38	38	P96 E2	47	47
P78 E4	38	38	P96 E3	47	47
P79 E1	39	39	P97 E1	47	47
P79 E2	39	39	P97 E2	47	47
P79 E3	39	39	P97 E3	47	47
P80 E1	39	39	P97 E4	47	47
P80 E2	39	39	P98 E1	48	48
P80 E4	39	39	P99 E1	49	49
P81 E1	39	39	P99 E2	49	49
P82 E1	39	39	P99 E3	49	49
P82 E2	39	39	P99 E4	49	49
P82 E4	39	39	P100 E1	49	49
P83 E1	39	39	P101 E1	50	50
P83 E2	39	39	P101 E2	50	50
P84 E1	40	40	P102 E1	51	51
P84 E2	40	40	P102 E2	51	51
P84 E3	40	40	P102 E4	51	51
P84 E4	40	40	P103 E1	51	51
P85 E1	40	40	P104 E1	52	52
P85 E2	40	40	P104 E2	52	52
P85 E5	40	40	P104 E3	52	52
P86 E1	40	40	P105 E1	52	52
P87 E1	40	40	P105 E2	52	52
P87 E2	40	40			