AN AGGREGATION APPROACH FOR CAPACITY PLANNING UNDER UNCERTAINTY FOR THE PHARMACEUTICAL INDUSTRY

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Abstract

Over the last few years, the simultaneous optimisation of the product portfolio and manufacturing capacity has gained increased importance in the Pharmaceutical Industry. The problem of capacity planning under clinical trials uncertainty for the pharmaceutical industry has recently been addressed in the literature. However, there is a need for better solution approaches, as when the potential product portfolio increases, existing models become extremely large and very difficult to solve. Here, a scenario aggregation/disaggregation approach for this problem is presented. The results from the proposed flexible approach are compared with those obtained from a detailed stochastic, multistage, multiperiod model.

Keywords

Scenario aggregation, Pharmaceutical industry, Capacity planning, Portfolio selection, Uncertainty, Clinical trials, Mixed integer optimisation

Introduction

Market pressures, tough sociopolitical regulations and an aggressive competitive environment are among the factors of today's world that are changing the way in which pharmaceutical business is operated. The pharmaceutical industries are faced with the question of the best use of the limited resources available to obtain the highest possible profit from the selected product portfolio. Thus, they are being forced to consider more systematic approaches to optimise their potential product portfolio.

During the optimisation of the product portfolio of a typical pharmaceutical company we must take into account first of all the product characteristics that make it a suitable candidate for manufacturing. Among those there are the R&D cost associated with the development of each new product, potential outcomes of ongoing clinical trials, commercial details of each product (e.g. demand forecast, price, marketing expenses), the lifetime cycle of each drug, etc. The management of manufacturing capacity must also be considered. This is concerned with the allocation of existing capacity for the selected product portfolio and decisions concerning additional investments that may be required to satisfy future demands (Papageorgiou et al, 2001).

The problem of optimisation of the product portfolio and manufacturing capacity subject to a certain source of uncertainty (e.g. demand, clinical trials), has been addressed in the literature (Rotstein et al. (1999), Maravelias and Grossmann (2001)). An optimisation-based approach has already been described (Gatica et al., 2001) capturing the above issues so as to select simultaneously the optimal capacity planning and investment strategy subject to uncertainty of clinical trials for each potential drug. Four possible clinical trial outcomes (High success, Target success, Low success, Failure) for each product are considered as is typical in the industry. As these outcomes have different probabilities of occurrence and the

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information from the trials will become available at different times resulting in a multistage, multiperiod stochastic optimisation problem, which is then reformulated as a large-scale, multi-scenario, mixed integer linear programming (MILP) model. As the resulting detailed model is quite large to tackle, an alternative efficient solution strategy is required without compromising the quality of the final solution. A scenario-based aggregation/disaggregation procedure with a multi-level aggregation scheme is presented here. This approach is based on the detailed stochastic multistage model described by Gatica et al. (2002).

The scenario tree in Figure 1 represents a four product portfolio, 1 deterministic, 3 potential products (with four clinical trial outcomes). For this case, the last stage comprises 64 scenarios.

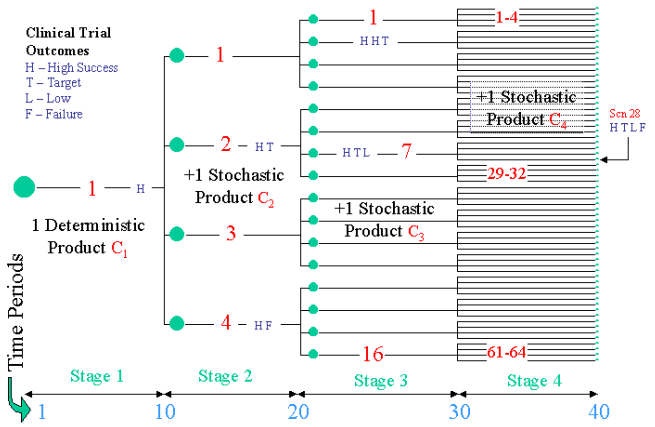

Figure 1. Tree map for all scenarios and stages

The aggregation/disaggregation approach is described in the next section.

Scenario Aggregation Algorithm

The procedure used here is based on the scenario aggregation approach described by Samuelsson (1999). As seen from Figure 2, the algorithm groups the scenarios into predetermined clusters.

Each cluster is composed by a series of **NO** neighbouring scenarios, where **NO** is the number of possible outcomes of the clinical trials considered; four for the present case (o_1,o_2,o_3,o_4), representing different types of success and failure. In every case, the grouping must follow the scenario mapping given by Figure 1. Thus, the groups of two consecutive stages are not related if there is no direct link between scenarios within those stages. As can be noticed, the scenario aggregation takes place within each stage, however it can involve one or more stages. The algorithm gives the possibility of choosing the desired level of aggregation, that is, how many stages are going to be aggregated. Based on the original tree, Figure 3 shows how these clusters are configured for a second aggregation level (Level 2), in this case involving stages 3 and 4, rendering a 1-4-4-16 reduced scenario tree.

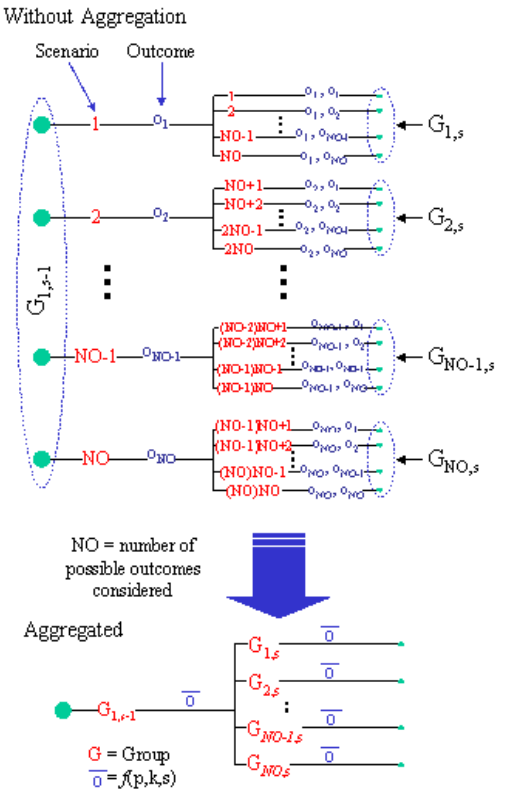

Figure 2. General aggregation scheme

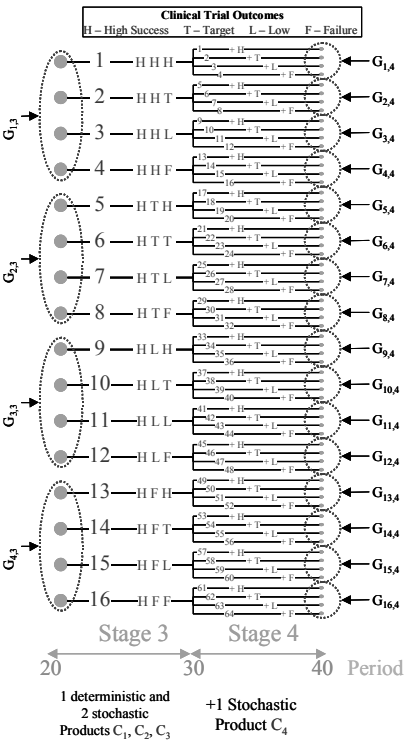

Figure 3. Aggregation for stages 3 and 4

The demands and probabilities within a cluster are changed for each stage according to Equations **1-3**. The new probability is the cumulative probability of the scenarios included in each group. Their demands are adjusted by taking into account the average of the clinical trial outcomes for those scenarios.

$$\overline{\pi}_{ks} = \sum_{k_1 \in G_{ks}} \pi_{k_1 s} \qquad \forall s, k \in KS_s \tag{1}$$

$$\overline{B}_{pks} = \frac{\sum_{k_1 \in G_{ks}} \beta_{k_1}}{NO} \quad \forall s, p \in IP_s, k \in KS_s \tag{2}$$

$$\overline{D}_{ptks} = D_{pt} \overline{B}_{pks} \qquad \forall s, t \in TS_s, p \in IP_s, k \in KS_s \tag{3}$$

The flow diagram for this the scenario aggregation algorithm is shown in Figure 4.

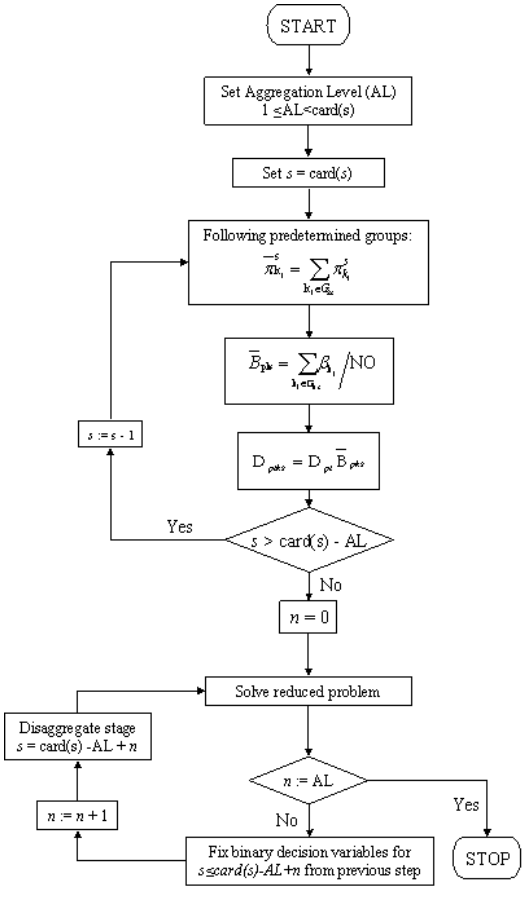

Figure 4. Scenario aggregation algorithm

First, a multiscenario aggregated problem is generated according to equations 1–3. Then a series of reduced problems are solved by applying stage dissagregation iteratively. In particular, the reduced multistage stochastic problem is solved based on the new scenario tree (reduced scenarios) to determine the binary decision variables of the non-aggregated stages. Each reduced scenario is then disaggregated and the resulting tree is solved to find the optimal decisions of the aggregated stages, based on the binary decision variables of the previous stages. If the problem is still too large, the scenarios of the previous stage might be aggregated again, until a solution is obtained. It should be noted that as the scenarios are more aggregated a faster solution can be found. However, this is at the risk of losing information and therefore quality of the final solution.

Illustrative example

In our example, there is one initial existing product C_1 and other three potential drugs (C_2, C_3, C_4). In the first stage, only product C_1 exists for the first 10 time periods, Initially there is one manufacturing suite per production line. In the second stage, which involves product C_1, as well as potential product C_2 (because the trials for C_2 will be completed at the end of stage 1), 4 scenarios are generated. The second stage lasts until time period 20. Then for the third stage, the third potential product is added to the product portfolio at time period 21, giving a total of 16 scenarios until period 31, when the last potential product C_4 is added. The fourth stage then has 64 scenarios. So, for each scenario, additional capacity investment may be made. Additionally, the manufacture of any product with unfavourable outcomes may be suspended, and the available resources reallocated for other products.

Table 1 shows the comparative results of the parameter analysis tests for the detailed model (no aggregation), and two aggregation levels; Level 1 (involving only stage 4) and Level 2 (aggregating both stages 3 and 4).

The results obtained from both aggregation levels were very similar to those obtained by the detailed model alone. In most cases, the CPU computational times were considerably reduced, by up to 60% on average for Level 1 and about 50% for Level 2. The decrease in the final iteration count was also high, of 40% for the Level 1 and about 38% for the Level 2 tests. In that sense, Level 1 rendered a better performance than Level 2 aggregation scheme.

The GAMS (Brooke et al., 1998) system was used to implement the model using Cplex 6.0 MILP optimiser with an optimality gap of 3% to compute the solution using a Sun Ultra60 workstation.

For every case, the solutions included a complete profile of the sales, production amounts, manufacturing times, inventories, wastes and, if needed, investment capacity for each product.

Table 1. Scenario Aggregation results

		No aggregation			Aggregation Level 1			Aggregation Level 2		
	Parameter	eNPV	CPU	Iter.	eNPV	CPU	Iter.	eNPV	CPU	Iter.
1	Reference	892.93	29	15713	892.93	17	11004	892.93	23	10394
2	$R_1 = 4.5$	865.61	933	23987	865.76	412	14791	862.46	676	16833
3	R={4.5,1.5}	845.24	1861	30275	845.52	743	18934	845.99	1144	20818
4	λ={500,600}	847.18	2623	34484	847.61	988	21884	842.76	983	22429
5	σ_3=120	840.24	873	19656	836.26	148	8995	833.11	121	8705
6	$\xi_{L1,2}$=2	722.81	2176	31054	722.46	832	19514	720.44	1098	21073
7	ν_1=18	3403.35	1735	22613	3387.75	635	15593	3399.07	605	12392
8	E_{L1}=0.6	818.91	2220	37979	818.52	883	18932	819.15	7032	21491

Conclusions

The proposed scenario aggregation algorithm has proved to render satisfactory results, especially for the Level 1 case. A substantial improvement in the computational times was achieved by using the aggregation scheme although for the Level 2 aggregation, the results obtained were not as good as for the Level 1. The objective function values of the aggregated procedure for most tests were close enough to the detailed model solution, however an important issue to mention is that after analysing the particular solution for each test we found that the capacity planning decisions taken were slightly different from one case to the other. This indicates that the model is quite robust, and that a wrong decision taken in the last part of the project does not significantly affect the final expected profits.

Nomenclature

k = scenario

s = stages

KS_s = set of included scenarios for stage s

IP_s = set of included products for stage s

TS_s = time periods within stage s

π_{ks} = clinical trial outcome probability for scenario k at stage s

$\bar{\pi}_{ks}$ = cumulative probability for each group $G_{k,s}$ in the aggregation approach

β_k = weight of each outcome for the forecasted demands, 1 for a High Success, 0.95 for a Target Success, 0.65 for Low Success, 0 for Failure.

NO = number of possible outcomes considered

$\bar{B}_{\text{pks}}$ = Adjusted (average) factor β_{ko} for scenario aggregated groups

D_{pt} = demand as forcasted in period t for product p

$\bar{D}_{\text{ptks}}$ = adjusted demand for scenario aggregated group

G_{ks} = set of original scenarios included in the aggregated scenario k for s

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