Strategic Supply Chain Optimization for the Pharmaceutical Industries

Lazaros G. Papageorgiou,*,†,‡ Guillermo E. Rotstein,‡,§ and Nilay Shah‡

Department of Chemical Engineering, University College London, Torrington Place, London WC1E 7JE, U.K., and Centre for Process Systems Engineering, Imperial College, Prince Consort Road, London SW7 2BY, U.K.

Pharmaceutical companies are undergoing major changes to cope with the new challenges of the modern economy. The globalization of the business, the diversity and complexity of new drugs, the increasing tightness of capital, and the diminishing protection provided by patents are some of the factors driving these changes. All stages of the business value chain are affected: from the development of new drugs to the management of the manufacturing and marketing networks. This paper describes an optimization-based approach to selecting both a product development and introduction strategy and a capacity planning and investment strategy. The overall problem is formulated as a mixed-integer linear programming (MILP) model. This takes account of both the particular features of pharmaceutical active ingredient manufacturing and the global trading structures. An illustrative example is presented to demonstrate the applicability of the proposed model.

1. Introduction

Pharmaceutical companies are undergoing major changes to cope with the new challenges of the modern economy. The internationalization of the business, the diversity and complexity of new drugs, and the diminishing protection provided by patents are some of the factors driving these changes. All stages of the business value chain are affected: from the development of new drugs to the management of the manufacturing and supply networks.

Market pressures are also forcing pharmaceutical companies to take a more holistic view of their product portfolio. The typical life cycles of new drugs are becoming shorter. It may take 8 years to develop a new product, and the investment on it must be recovered quickly because generic equivalents can appear later in the market, reducing its profitability. Companies are constantly faced with the question of the best use of the limited financial resources available. For instance, consider the following situation. A company is manufacturing and selling an established product (product A) and has developed a new product (product B) which will be ready to be launched in about a year. It is also starting to develop another product (product C) which will demand significant investment in research and development (R&D) and require up to 6 years of development time. The company must somehow decide on the best structure for its future portfolio. One option is to invest simultaneously in manufacturing capacity and R&D to build up a large portfolio with the three products. Alternatively, it could plan to invest in R&D while gradually phasing out product A and launching product B, in such a way that no significant investment in capacity is required. Several other options exist, each of which differs in the investment required and the potential return of the resulting portfolio. The challenge is then to optimize some performance criterion of the portfolio while avoiding unnecessary capital commitments.

This problem has typically been addressed in the pharmaceutical industry in a somewhat simplistic fashion. The value of the product portfolio is estimated based on R&D costs and the potential value estimated for the products in the market. Manufacturing costs were usually considered to be negligible. However, new drugs require more complex production paths, and their manufacturing costs are increasing and can nowadays often absorb 10−20% of the final value of a drug.[1] There is therefore a need to develop an approach that can simultaneously consider (a) the R&D cost associated with the development of potential new products, (b) the commercial characteristics of each product (e.g., demand forecast, price, marketing expenses, etc.), (c) the decisions associated with multiple sites, e.g. where to install/expand capacity, which product to produce at which site, etc., (d) the manufacturing costs and capacity requirements for the product portfolio [in the pharmaceutical industry, the idle time for switching production from one product to another is usually very significant and therefore complex portfolios (i.e., with many products) at a single site often result in considerable reduction of manufacturing efficiency], (e) the trading structure of the company (most companies nowadays manufacture and sell internationally; different commercial and production business centers will work under different tax regimes; the allocation of the portfolio profits among these centers is therefore important because it affects the overall profitability expected from the portfolio).

The problem is obviously very challenging because the aim is to bridge the gap currently existing between decision makers in traditionally isolated areas, such as product development, manufacturing, accounting, and commercialization.

This paper presents a mathematical programming model that captures all of these issues simultaneously,

* To whom all correspondence should be addressed. Tel: +44-20-76792563. Fax: +44-20-73832348. E-mail: l.papageorgiou@ucl.ac.uk.

† University College London.

‡ Imperial College.

§ Current address: i2 Technologies, The Priory, Burnham, Berkshire SL1 7LL, U.K.

10.1021/ie990870t CCC: $20.00
Published on Web 12/08/2000

thus providing an effective support for a holistic approach to decision making.

Various aspects of this problem, each of them in isolation, have been considered in the past.

One area is multisite planning and distribution in the process industries. Here, it is expected that large benefits stem from coordinated planning across sites, in terms of costs and market effectiveness. Most business processes dictate that a degree of autonomy is required at each manufacturing and distribution site, but pressures to coordinate responses to global demand while minimizing cost imply that simultaneous planning of production and distribution across plants and warehouses should be undertaken. The need for such coordinated planning has long been recognized in the management science and operations research literature. For example, ref 2 surveyed a series of heuristics for production–distribution scheduling in multisite systems for different network structures. There are two general weaknesses with research in this domain: (i) steady-state demands are assumed; (ii) simple expressions or even constants are used for plant capacity. In practice, demands are usually time-varying and the capacity of a flexible manufacturing facility cannot be known a priori but is rather a function of the product mix and the details of planning.

A potential problem with this approach as recognized in ref 3 is the very large problem sizes that will ensue. A secondary issue is that the development of a central plan to a very fine level of detail is probably unnecessary, leading to the development of an aggregation procedure. The aim is to capture production and distribution capacities accurately without considering detailed scheduling. The method involves aggregating the many discrete intervals into fewer, longer intervals known as aggregated time periods (ATPs). This technique has been applied by ref 4 to a continent-wide industrial case study. This involved optimally planning the production and distribution of a system with 3 factories and 14 market warehouses and over 100 products. A great deal of flexibility existed in the network which, in principle, enables the production of products for each market at each manufacturing site. It was found that the ability of the technique to capture effects such as multipurpose operation, intermediate storage, and setups gave rise to counterintuitive results, such as producing materials further away from demand points than would be expected.

A similar problem suitable for multiple facilities which effectively produce products on single-stage continuous lines for a number of geographically distributed customers is described in ref 5. Their basic model is of multiperiod linear programming (LP) form and takes account of available processing time on all lines, transportation costs, and shortage costs. An approximation is used for the inventory costs, and product transitions are not modeled. The model is extended to include minimum run lengths (which requires the inclusion of binary variables). They include a number of additional supply chain related constraints such as single sourcing, internal sourcing, and transportation times. This type of aggregate model is prevalent in the literature.

Other planning models of this type do not consider each product in isolation but rather group products that place similar demands on resources into families and base the higher level planning function on these families. This forms the basis of many hierarchical production planning systems (see, e.g., ref 6). More sophisticated models exist in the process systems literature. A model which selects processes to operate from an integrated network is decribed in ref 7 while ensuring that the network capacity constraints are not exceeded. Means of improving the solution efficiency of this class of problems can be found in refs 8 and 9.

Although these approaches have some degree of relevance to this work, in particular to relate investments in capacity to the overall ability to produce at certain levels, considerable work remains to be done to capture the salient details relevant to the selection and long-term manufacture of pharmaceutical active ingredients at multiple sites.

The model we propose is based on a family of strategic planning problems that we have worked on during the last 3 years. Most elements of it are quite generic, but, of course, some (e.g., trading structure) will vary between organizations.

The rest of the paper is structured as follows. In section 2, the main characteristics of the problem are discussed. The proposed mathematical model together with the key assumptions are described in section 3. An illustrative multisite example is presented in section 4 to demonstrate the applicability of the model. Finally, some concluding remarks are given in section 5.

2. Problem Statement

This paper considers the development of models that can support a holistic approach to product portfolio management in the pharmaceutical industry. There are three main issues that are to be considered during the optimization of the product portfolio of a typical pharmaceutical industry.

Product Management. This is concerned with the main features of each product considered as a suitable candidate for manufacturing and commercialization.

Capacity Management. This is concerned with the allocation of the existing capacity (at more than one site) for the selected product portfolio and decisions concerning additional investments that may be required to satisfy future demands.

Trading Structure. This is concerned with decisions related to the financial flows between different components of the company, in particular, transfer pricing issues among the various manufacturing and commercialization business centers.

These issues are discussed in the next three subsections.

2.1. Product Management. Pharmaceutical products are made in two main stages (“primary” or “secondary” manufacture). The first stage produces small quantities of the active ingredient (AI), a high-quality, high-value chemical. The second stage converts this AI into a product for final use (e.g., as tablets, vials, etc.). The primary stage is the critical one for portfolio planning; it is this component that we shall consider further in this paper.

The starting point of the analysis is the “candidate portfolio”, a set of products that are being considered for development, manufacturing, and commercialization. The following data are required for the analysis of the role of these products within the portfolio:

(a) Demand forecasts: the quantities of material that are expected to be sold year by year within the time horizon considered. These are, in the general case, stochastic. In this work, we treat them as deterministic and indicate how a capacity plan can be selected for such forecasts. Future work will consider stochastic demand forecasts dependent on clinical trial outcomes.

(b) Clinical trials supply: the quantities of material that are required for clinical trials (product testing) within the time horizon considered.

(c) Price profile: this is the forecasted selling price for each product. Often the price is expected to decrease with time as the product matures.

(d) Manufacturing cost: this is the cost to produce a given amount of the product, usually determined by its bill of materials.

(e) Royalties: this is the fraction of the revenues of each product to be paid to third parties. This is common in the pharmaceutical companies where products may be developed in a cooperative fashion between generators of new chemical entities, licensors, and manufacturers.

(f) Development cost: this is the investment required for the development of each product in the candidate portfolio.

2.2. Capacity Management. Once the details of each product in the candidate portfolio are known, the next step is to identify the capacity needs for each individual product and the impact on the capacity of a plant when several products are manufactured in it. The latter is of significant importance in the pharmaceutical industry because long setup times between different products (e.g., 1 month) are not unusual. The plants usually operate in campaigns, and each additional product manufactured in the plant introduces significant capacity losses. The following data are therefore required for an accurate analysis of the capacity needs:

(a) Capital costs: this is the investment required for each new individual manufacturing facility and/or cost associated with expansion by a prespecified amount. Also, the associated depreciation rate is taken into account.

(b) Construction lead times: this is the time required either for building of a facility or for future expansions by adding extra equipment. Note that, once the facility is in place, future expansions can be relatively fast.

(c) Fixed operating costs: overheads required to run a particular facility in 1 year. These may be very relatively large in the pharmaceutical industry, where significant laboratory and analytical support is required.

(d) Production rates per product: this is the rate at which a product can be manufactured during a campaign in a particular facility.

(e) Setup time: this is the time required to switch a facility from the manufacturing of one product to another.

(f) Scale-up time: the first time a product is manufactured in a facility, there is some time required to go through the "learning curve" and achieve the desired quality targets. This introduces significant capacity losses when a new product is first manufactured in a plant.

(g) Qualification time: once scale-up is completed, a minimum amount (nominally, five consecutive batches) of each product must be manufactured to comply with standard regulatory requirements.

2.2.1. Manufacturing Components. The manufacturing equipment at each site is organized into blocks. Each block contains two types of entities: suites and service centers. A suite, in turn, comprises a production line and its coupled purification line. These suites are available in identical capacities and known fixed cost. Each block makes use of services such as utilities, administration, and analytical/laboratory facilities. We assume here that at most four suites can share one service center, creating a block as shown in Figure 1. The first suite to be attached to a block is denoted the "header" suite. Then, with a number of existing blocks, the problem is then essentially to select the products for manufacture over the horizon as well as when to start investing in new blocks or in projects to upgrade existing blocks. Each block need not have all of its suites constructed at the same time, while the investment strategy must take account of the lead times associated with construction and commissioning. Additionally, the product-to-suite assignment should take account of the complexity introduced if too many different products are to be manufactured in the same facility.

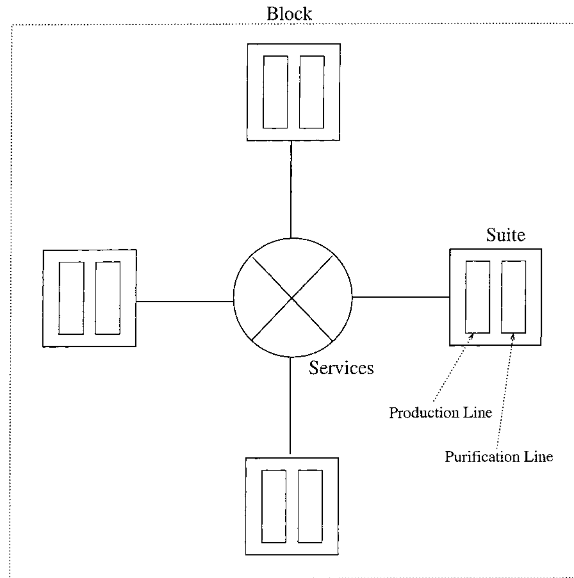

Figure 1. Block with one service center and four suites.

2.2.2. Processing Considerations. The processing of the products in the suites has a number of characteristics. First of all, before a campaign of a particular product is started in a suite, the suite must be cleaned thoroughly. This takes a long time (e.g., 1 month). Then, the campaign length is usually subject to minimum and maximum durations. Although products are produced at a nominal rate during the campaign, production loss factors need to be included to account for actual production levels that tend to be lower than the nominal ones. When a product is made for the first time in a new geographical location (site), it must first undergo a scale-up activity. This reflects that it takes some time for the new site to learn to produce the product in a satisfactorily repeatable fashion. Finally, once this has been achieved, the first few batches of the product ever produced at a site (the qualification amount) must be sent to the relevant regulatory authorities for approval.

2.3. Trading Structure. In general, models dealing with the management of manufacturing and capacity planning ignore the internal trade and transfer pricing that takes place within any corporation. However, this internal trading structure often has a large impact on the after-tax profitability of the portfolio. Also, it may largely affect decisions concerning the location of a new plant, for instance, when locations with differential tax rates are considered. Three main business centers are

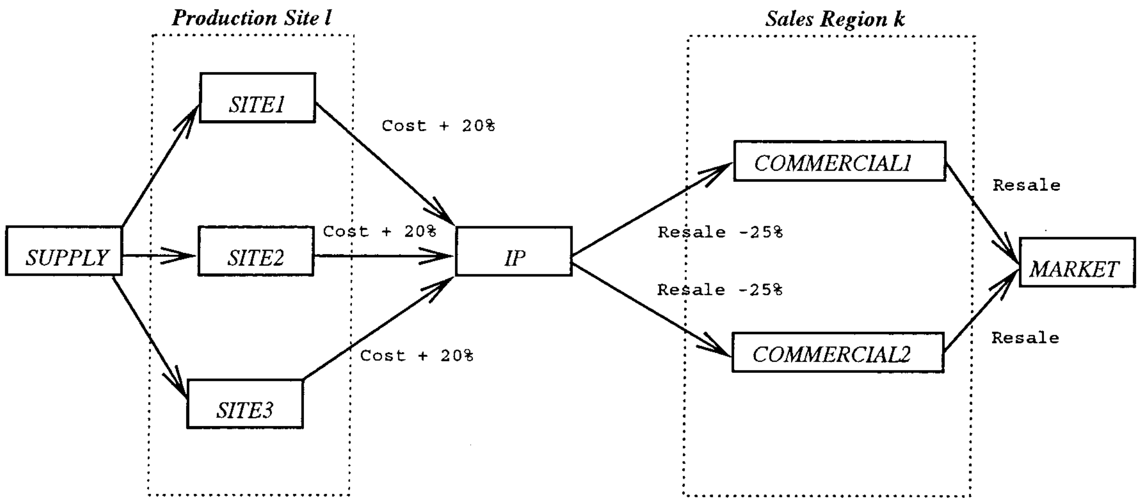

Figure 2. Typical internal trading structure.

usually present in one form or another within the supply chain network of the company:

(a) Intellectual property (IP) owner: this is the sector of the organization responsible for the funding and development of new products.

(b) Production sites: these are the production locations responsible for product manufacturing.

(c) Sales regions: these are the sectors of the company responsible for the marketing and sales efforts required to sell the products.

Significant financial flows take place among these centers, and the transfer pricing structure adopted (i.e., the internal selling prices) may have a significant impact on the profits made at each center and therefore the taxes paid at the corresponding center location. The operating mode of each center can be defined as follows:

Profit center: here significant profits are realized. Usually, their products are sold according to a "resale minus" formula (i.e., the final selling price minus a predetermined percentage).

Cost center: these centers usually only cover their own costs plus a small profit. Therefore, the internal selling price for the product is established according to the fully absorbed costs (including capital depreciation) plus a small percentage.

Figure 2 shows a typical trading structure for a pharmaceutical company. In this case, all production sites work as cost centers (similar to contract manufacturing), while the IP owner and the sales regions work as business centers and retain most of the profits. In the figure, the IP owner buys the product at cost + 20% and sells it at a price of resale − 25% (i.e., the final selling price minus 25%).

A Comprehensive Model. We are now in a position to state the problem formally. The following items are assumed to be known:

1. A set of potential products (the candidate product portfolio).
2. The demand forecasts (in kilograms per year) for each active ingredient product in the candidate portfolio.
3. The minimum demand fulfillment for any product launched into the market.
4. The forecasted product market price for each year.
5. The commercialization costs to be paid, such as royalties and marketing.
6. Variable (marginal) and fixed manufacturing costs.
7. Expected production losses.
8. The shelf-life of each product.
9. Other manufacturing costs such as setups or scale-up.
10. Internal interest rates and expected inflation rates.
11. Production rates for each product.
12. The time required for manufacturing activities such as setups and scale-up.
13. Construction lead times.
14. Minimum and/or maximum production times.
15. The trading structure of the company (organization into cost and profit centers) and the taxation rate at each center.
16. Depreciation rates for capital investments.

On the basis of the data above, we seek to develop a mathematical optimization model which can determine the following quantities:

1. The product portfolio (i.e., products from the candidate portfolio that are developed and launched).
2. What manufacturing capacity to invest in over the time horizon.
3. Timing for scale-up and qualification runs for each product.
4. Production plans per year for each product, including product allocation to manufacturing sites and the amount manufactured (campaign lengths).
5. Sales and inventory planning.

Finally, an objective function must be stated. Here, we optimize an overall performance citerion (e.g., maximize the net present value).

3. Mathematical Formulation

The indices, parameters, and sets associated with the product portfolio optimization problem are listed.

Indices

p = product
t = year
i, j = suites
l = production location
k = sales region

Parameters

M = maximum number of suites being served by each laboratory (block)
L_p = production losses of product p
ζ_p = lifetime of product p

α_p = qualification amount of product p
r^l_{ip} = production rate of product p in suite i at production site l
H_t = available production time over time period t
$T^{l,\min}_{ip}$ = minimum production time of product p in suite i at production site l
$T^{l,\max}_{ip}$ = maximum production time of product p in suite i at production site l
$\bar{\tau}$ = setup time
$\hat{\tau}_p$ = scale-up time for product p
D^k_{pt} = demand of product p at period t at sales region k
δ^l_i = construction time of suite i at production site l

Sets

P^k = set of products for sales region k
R^p = set of sales regions where there is a market for product p
I^l = set of suites at production site l
F^l = set of header suites at production site l, cf. section 2.2.1; (card(F^l) = card(I^l) $DIV\ M$)
N^l_i = set of suites that belong to the same laboratory as header suite $i \in F^l$ ($N^l_i = \{j \in I^l\colon\ j = i + 1, ..., i + M - 1\}$)

Next, the key variables of the formulation are described by referring first to the ones that are "global" (i.e., those not associated with specific production sites or sales regions).

Binary Variables

U_p = 1 if product p is selected for development and manufacturing and 0 otherwise

Continuous Variables

I_{pt} = amount of product p in global inventories at the end of period t
W_{pt} = amount of product p wasted at period t

Each production site l is characterized by the following binary variables:

V^l_p = 1 if product p is selected for development and manufacturing and 0 otherwise
$\hat{Z}^l_{pt}$ = 1 if scale-up of product p takes place over period t and 0 otherwise
X^l_{pt} = 1 if product p is first produced (qualification run) over period t and 0 otherwise
Z^l_{ipt} = 1 if scale-up of product p takes place in suite i over period t and 0 otherwise
Y^l_{ipt} = 1 if product p is produced in suite i over period t and 0 otherwise
E^l_{it} = 1 if suite i is invested in at period t and 0 otherwise
A^l_{it} = 1 if suite i is available at period t and 0 otherwise

Each production site l is characterized by the following continuous variables:

T^l_{it} = production time of suite i during period t
T^l_{ipt} = production time of product p in suite i during period t
B^l_{ipt} = amount of product p produced in suite i during period t

Finally, each sales region k is solely characterized by the amount of product p sold at period t, S^k_{pt}.

All resource characteristics (e.g., capacity and construction time) as well as production requirements are assumed to be known. The time horizon is discretized into T time intervals of equal duration. Generally speaking, the process dynamics (e.g., activity durations) and decision-making cycle mean that a 1-year discretization interval is suitable. Startup and shutdown periods are considered to be negligible compared to the duration of each time interval. For the purposes of this paper, all data are assumed to be deterministic.

Next, we describe the model constraints.

3.1. Product and Suite Existence Constraints. If a product is not selected for development and manufacturing *globally* (i.e., $U_p = 0$), then this product should be excluded from any candidate production site. Mathematically, we have

$$V^l_p \le U_p \qquad \forall\ l, p \tag{1}$$

When an investment decision for any suite is taken, a construction time is required before that suite becomes available. This can be modeled as follows:

$$A^l_{it} = A^l_{i,t-1} + E^l_{i,t-\delta_i} \qquad \forall\ l, i \in I^l, t \tag{2}$$

3.2. Block Constraints. Each production site is organized into many blocks. Each block can serve up to a maximum number of suites, M (here, 4 suites/block). Usually, the construction time of the header suite of each block is larger than that of the rest of the suites which belong to the same block. Therefore, a relation between the header suite, $i \in F$, and the other constituent suites of the same block, $j \in N_i$, should be established:

$$\sum_{\theta=1}^{t-(\delta^l_i-\delta^l_j)} E^l_{i\theta} \ge E^l_{jt} \qquad \forall\ l, i \in F^l, j \in N^l_i, t \tag{3}$$

This ensures that a constituent suite j can be invested in at time period t only if the header suite i has been invested in *at least* $\delta^l_i - \delta^l_j$ time periods before period t.

3.3. Investment Degeneracy Constraints. Usually, the final optimal solution will include fewer suites than the maximum allowed. In such cases, there will be significant solution degeneracy because different investment suite combinations based on identical suites would result in the same objective function value. This source of degeneracy can further be eliminated by allowing suite i to be potentially invested in at time period t *only if* suite $i - 1$ has already been invested in at any previous time period. This can be written mathematically as

$$\sum_{\theta=1}^{t} E^l_{i\theta} \ge E^l_{i+1,t} \qquad \forall\ l, i = 1, ..., I^l - 1, t \tag{4}$$

The above constraints implicitly assume that all suites require the same construction time. In general, every suite may have its own construction time, and therefore constraints (4) could further be generalized to

$$\sum_{\theta=1}^{t-(\delta^l_i-\delta^l_{i+1})} E^l_{i\theta} \ge E^l_{i+1,t} \qquad \forall\ l, i = I^l - 1, t \tag{5}$$

These constraints are similar to constraints (3), where the header of each block is related to the rest of the suites which belong to the same block while the ones described in this subsection are written for successive suites which may belong to the same or different blocks.

3.4. Production Constraints. Each product can be produced in a specific suite only if that suite is available:

$$\sum_p Y^l_{ipt} \le \mathrm{card}(p)\, A^l_{it} \qquad \forall\, l, i \in I^l, t \tag{6}$$

Of course, constraints (6) may be disaggregated to provide a "tighter" alternative at the expense of a larger problem:

$$Y^l_{ipt} \le A^l_{it} \qquad \forall\, l, i \in I^l, p, t$$

The amount of each product produced within each available suite is given by the following equalities:

$$B^l_{ipt} = r^l_{ip} T^l_{ipt} \qquad \forall\, l, i \in I^l, p, t \tag{7}$$

Furthermore, when a product is qualified (i.e., $X^l_{pt} = 1$), a minimum amount, α_p, must be produced:

$$\sum_{i \in I^l} B^l_{ipt} \ge \alpha_p X^l_{pt} \qquad \forall\, l, p, t \tag{8}$$

It should be added that the minimum required amount should be produced within a single period; otherwise, the above constraints (8) should be extended to include more than one time period.

3.5. Inventory Constraints. The amount of product p stored *globally* at the end of period t will be equal to the amount at the previous period $t - 1$ plus the net amount produced during period t (taking into account production losses) by all producer sites minus the amount sold to different customer regions minus the amount wasted due to the limited product lifetime. Thus, we obtain

$$I_{pt} = I_{p,t-1} + (1 - L_p)\sum_l \sum_{i \in I^l} B^l_{ipt} - \sum_k S^k_{pt} - W_{pt} \qquad \forall\, p, t \tag{9}$$

Because we consider relatively long time periods, we ignore any transportation effects. It should also be added that, despite the fact that the time period is rather long, the above constraints are important by providing planned year-end inventories, which companies always find useful.

3.6. Product Lifetime Constraints. In the previous subsection, we introduced the W_{pt} variables in order to maintain feasibility in the case of limited product lifetimes. However, constraints are required to guarantee that the amount stored in each period cannot be used after the next ζ_p time periods:

$$I_{pt} \le \sum_k \sum_{\theta = t+1}^{t+\zeta_p} S^k_{p\theta} \qquad \forall\, p, t \tag{10}$$

3.7. Timing Constraints. Once a product is to be produced, then appropriate minimum and maximum production times (campaign lengths) should be enforced:

$$T^l_{ipt} \ge T^{l,\min}_{ip} Y^l_{ipt} \qquad \forall\, l, i \in I^l, p, t \tag{11}$$

and

$$T^l_{ipt} \le T^{l,\max}_{ip} Y^l_{ipt} \qquad \forall\, l, i \in I^l, p, t \tag{12}$$

These constraints are only active if the Y^l_{ipt} variables are equal to 1; otherwise (i.e., $Y^l_{ipt} = 0$), the T^l_{ipt} values are forced to zero.

The total production time for every suite over each period (i.e., the total time that the suite is busy producing products), T^l_{it}, is simply the summation of the individual product production times, T^l_{ipt}:

$$T^l_{it} = \sum_p T^l_{ipt} \qquad \forall\, l, i \in I^l, t \tag{13}$$

Also, the total production time, T^l_{it}, cannot exceed the total available production time, H_t, minus the time required for any necessary setups, $\bar{\tau}$, and scale-ups, $\hat{\tau}_p$:

$$T^l_{it} \le H_t - \bar{\tau}\left(\sum_p Y^l_{ipt} - A^l_{it}\right) - \sum_p \hat{\tau}_p Z^l_{ipt} \qquad \forall\, l, i \in I^l, t \tag{14}$$

3.8. Scale-Up Constraints. Every *new* product introduced at each production site must undergo a scale-up procedure for a certain period of time, $\hat{\tau}_p$ (for example, 3 months), before starting commercial production. This scale-up time reflects technology transfer from a laboratory or different production site to the new one.

Every product is allowed to be produced during a certain period *only if* scale-up has taken place up to that period. This can be expressed as

$$\sum_{\theta=1}^{t} \hat{Z}^l_{p\theta} \ge Y^l_{ipt} \qquad \forall\, l, i \in I^l, p, t \tag{15}$$

If scale-up occurs (i.e., $\hat{Z}^l_{pt} = 1$), then it should be performed within a single suite:

$$\sum_{i \in I^l} Z^l_{ipt} = \hat{Z}^l_{pt} \qquad \forall\, l, p, t \tag{16}$$

Finally, a suite can be used for scale-up purposes only if it is available:

$$\sum_p Z^l_{ipt} \le \mathrm{card}(p)\, A^l_{it} \qquad \forall\, l, i \in I^l, t \tag{17}$$

Constraints (17) can be disaggregated to result in a tighter form similarly to constraints (6).

3.9. Qualification Constraints. After the scale-up procedure, each selected product should be "qualified" to verify that the plant is capable of producing that product according to the satisfaction of the regulatory authorities. The first batches produced of each product are called *qualification* batches and must coincide with the first time that production of that product occurs:

$$X^l_{pt} \ge Y^l_{ipt} - \sum_j \sum_{\theta=1}^{t-1} Y^l_{jp\theta} \qquad \forall\, l, i \in I^l, p, t \tag{18}$$

The above constraints ensure that the first time a product is produced ($Y^l_{ipt} = 1$ and all $Y^l_{jp\theta} = 0$ for $\theta = 1, ..., t - 1$), X^l_{pt} must take a value of 1. At all subsequent time intervals, the right-hand sides of constraints (18) will be zero or negative.

Thus, to ensure that every product is qualified only once, the following constaints should be included:

$$\sum_t X^l_{pt} \le V^l_p \qquad \forall\, l, p \tag{19}$$

It should be noted that constraints (19) are not required if there are costs associated with the X^l_{pt}

variables within the objective function (see subsection A.1.6). In this case, the optimization algorithm will force as many as possible of these X^l_{pt} variables to zero.

3.10. Sales Constraints. Different sales strategies could be adopted to reflect alternative marketing policies of the company. Here, we simply assume that the amount sold at each time period does not exceed the forecasted demand of that product:

$$S^k_{pt} \le D^k_{pt} \qquad \forall\ k, p \in P^k, t \tag{20}$$

In some cases, the forecasted demand, D^k_{pt}, may not be met by sales, S^k_{pt}. We define their difference as the *sales gap*. A conservative marketing policy could be adopted by reducing the forecasted demand of the next time periods by the largest sales gap having been experienced before (this reflects the fact that it is difficult to recapture market share). Thus, the optimization algorithm is forced to maximize the corresponding sales in order to minimize future lost opportunities.

To model the above policy, we first introduce new continuous variables, G^k_{pt}, along with the following constraints:

$$G^k_{pt} \ge D^k_{p\theta} - S^k_{p\theta} \qquad \forall\ k, p \in P^k, \theta < t \tag{21}$$

while constraints (20) should replaced by

$$S^k_{pt} \le D^k_{pt} - G^k_{pt} \qquad \forall\ k, p \in P^k, t$$

It should be noted that the previous policy should be used with caution because, in certain cases where there are sharp changes in demand, constraints (21) may give rise to infeasibilities.

An alternative marketing policy could require a nondecreasing percentage of sales over demands:

$$\frac{S^k_{pt}}{D^k_{pt}} \le \frac{S^k_{p,t+1}}{D^k_{p,t+1}} \qquad \forall\ k, p \in P^k, t = \hat{t}^k_p + 1, ..., T - 1 \tag{22}$$

It is implicitly assumed in the above that, after the first nonzero forecasted demand of product p at time period $\hat{t}^k_p$ (i.e., $D^k_{p,\hat{t}^k_p} \neq 0$), then all subsequent forecasted demands are also nonzero, i.e., $D^k_{p\theta} \neq 0$ ($\forall\ \theta = \hat{t}^k_p + 1, ..., T$).

3.11. Objective Function. The model can accommodate a variety of performance criteria usually based on economics. In this paper, we adopt the maximization of the net present value (NPV) over a fairly long horizon of interest (e.g., 10–15 years) as a typical objective function, before or after taxes, Φ^B or Φ^A, respectively, as decribed in Appendix A.

3.12. Summary of Formulation. In conclusion, the entire formulation described in this paper is then outlined.

$$\begin{aligned}\max \Phi^A = {} & \textstyle\sum_t \epsilon_t \Sigma_k \{\mathrm{SR}^k_t[1 - \psi^k_t \rho^k - \psi^{\mathrm{IP}}_t (1 - \rho^k)] - \\ & \mathrm{MC}^k_t (1 - \psi^k_t)\} - \textstyle\sum_t \epsilon_t (\mathrm{RC}^{\mathrm{IP}}_t + \mathrm{RDC}^{\mathrm{IP}}_t)(1 - \psi^{\mathrm{IP}}_t) - \\ & \textstyle\sum_t \epsilon_t \sum_l (\mathrm{OC}^l_t + \mathrm{CSQR}^l_t)[1 + \psi^l_t \rho^l - \psi^{\mathrm{IP}}_t (1 + \rho^l)] + \\ & \textstyle\sum_t \epsilon_t \sum_l \mathrm{DC}^l_t (\psi^{\mathrm{IP}}_t (1 + \rho^l) - \psi^l_t \rho^l) - \sum_t \epsilon_t \sum_l \mathrm{CI}^l_t\end{aligned}$$

subject to

Product and Suite Existence Constraints

$$V^l_p \le U_p \qquad \forall\ l, p$$

$$A^l_{it} = A^l_{i,t-1} + E^l_{i,t-\delta_i} \qquad \forall\ l, i \in I^l, t$$

Block Constraints

$$\textstyle\sum_{\theta=1}^{t-(\delta^l_i - \delta^l_j)} E^l_{i\theta} \ge E^l_{jt} \qquad \forall\ l, i \in F^l, j \in N^l_i, t$$

Investment Degeneracy Constraints

$$\textstyle\sum_{\theta=1}^{t-(\delta^l_i - \delta^l_{i+1})} E^l_{i\theta} \ge E^l_{i+1,t} \qquad \forall\ l, i = 1, ..., I^l - 1, t$$

Production Constraints

$$Y^l_{ipt} \le A^l_{it} \qquad \forall\ l, i \in I^l, p, t$$

$$B^l_{ipt} = r^l_{ip} T^l_{ipt} \qquad \forall\ l, i \in I^l, p, t$$

$$\textstyle\sum_{i \in I^l} B^l_{ipt} \ge \alpha_p X^l_{pt} \qquad \forall\ l, p, t$$

Inventory Constraints

$$I_{pt} = I_{p,t-1} + (1 - L_p) \textstyle\sum_l \sum_{i \in I^l} B^l_{ipt} - \sum_k S^k_{pt} - W_{pt} \qquad \forall\ p, t$$

Product Lifetime Constraints

$$I_{pt} \le \textstyle\sum_k \sum_{\theta=t+1}^{t+\zeta_p} S^k_{p\theta} \qquad \forall\ p, t$$

Timing Constraints

$$T^l_{ipt} \ge T^{l,\min}_{ip} Y^l_{ipt} \qquad \forall\ l, i \in I^l, p, t$$

$$T^l_{ipt} \le T^{l,\max}_{ip} Y^l_{ipt} \qquad \forall\ l, i \in I^l, p, t$$

$$T^l_{it} = \textstyle\sum_p T^l_{ipt} \qquad \forall\ l, i \in I^l, t$$

$$T^l_{it} \le H_t - \bar{\tau}(\textstyle\sum_p Y^l_{ipt} - A^l_{it}) - \sum_p \hat{\tau}_p Z^l_{ipt} \qquad \forall\ l, i \in I^l, t$$

Scale-Up Constraints

$$\textstyle\sum_{\theta=1}^{t} \hat{Z}^l_{p\theta} \ge Y^l_{ipt} \qquad \forall\ l, i \in I^l, p, t$$

$$\textstyle\sum_{i \in I^l} Z^l_{ipt} = \hat{Z}^l_{pt} \qquad \forall\ l, p, t$$

$$Z^l_{ipt} \le A^l_{it} \qquad \forall\ l, i \in I^l, p, t$$

Qualification Constraints

$$X^l_{pt} \ge Y^l_{ipt} - \textstyle\sum_j \sum_{\theta=1}^{t-1} Y^l_{jp\theta} \qquad \forall\ l, i \in I^l, p, t$$

$$\textstyle\sum_t X^l_{pt} \le V^l_p \qquad \forall\ l, p$$

Sales Constraints

$$S^k_{pt} \le D^k_{pt} \qquad \forall\ k, p \in P^k, t$$

4. An Illustrative Example

Here, we consider a company which can produce 7 products (P1–P7) over a planning horizon of 10 years (2000–2009). A discretization interval of 1 year is used for our mathematical model, resulting in 10 time periods. The data used in the example are modified versions of actual data based on a family of respiratory, dermatology, and arthritis products of a major pharmaceutical company.

Table 1. Tax Regions

location	tax rate profile		relative operating cost	relative capital cost
A	0.28	$\forall t$		
B	0.28	$\forall t$	1.00	1.00
C	0.00	$t = 1-4$	1.10	1.10
	0.20	$t = 5-10$	1.10	1.10
D	0.30	$\forall t$	0.27	1.30

Table 2. Product Data

product	α_p	r^l_{ip}	$T^{l,\min}_{ip}$	ν^k_p	λ^k_p	σ_{p1}	ξ^B_{ip}
P1	6.1	2.2	1.8	4	0.10	40	0.165
P2	2.5	0.9	1.6	4	0.12	45	0.220
P3	2.5	0.9	1.7	4	0.10	25	0.220
P4	3.8	0.7	2.4	3	0.40	20	0.165
P5	5.1	1.9	1.8	2	0.20	40	0.330
P6	2.5	0.9	1.5	5	0.15	50	0.165
P7	1.4	1.5	1.1	2	0.20	60	0.550

There are four alternative locations (A–D), where A and B are sales regions; A is the IP center, while B–D are the potential production sites as shown in Figure 2. As already mentioned, in this paper, we assume that the trading structure is given together with the internal pricing policies ($\rho^l = 0.20$ and $\rho^k = 0.25$). Inflation and interest rates of 3% and 15%, respectively, are used for NPV calculations. The tax rate profiles as well as the relative operating and capital costs for all locations are described in Table 1.

Note that location C offers a very significant incentive of no tax over the first 4 years at the expense of increased operating and capital costs. Also, location D constitutes an expensive investment alternative. On the other hand, the significantly cheaper operating cost may force the optimization algorithm toward the selection of that location.

Every plant operates up to 11 months over each year because 1 month/year is required for general plant maintenance. Setup and scale-up durations are 1 and 2 months, respectively, which are quite common for highly regulated and aseptic processes. The lifetime for all products is given equal to 4 years, while production losses of 10% are assumed for all production sites. Data related to the qualification amounts, production rates, minimum production times, and sales prices for all products are given in Table 2.

Note that production rates and minimum production times are assumed to be location and suite invariant (i.e., their values depend only on the product). In addition, we assume that the selling price and royalties for all products are the same for both sales regions (A and B). We further assume that the R&D cost for all products is sufficiently captured by the initial capital cost.

The marketing cost fraction (μ^k_{pt}) for both sales regions is time-dependent: 0.15 from the startup to the fourth year of demand and 0.05 for the rest of the planning horizon. The above marketing policy depicts a more intensive marketing effort during the first years of sales of each product.

Each construction block comprises up to four production suites. A lead time of 2 years is required for all suites regardless of the location, while 3 years is needed for the header suite. Two suites are assumed to be available at location B at the start of the planning horizon. Also given are the maximum number of suites to be invested in at each production location: eight, four, and four suites for locations B–D, respectively. However, the optimization algorithm will determine whether, where, and the number of additional suites that are required for every production location.

All header suites at location B cost 100 rmu (≡relative money units – U.K. pounds appropriately scaled), while the rest of the suites at the same location cost 45 rmu. In addition, the fixed operating costs for location B, η^B_i, are 22 and 11 rmu/suite for the header and remaining suites, respectively. The variable operating costs, ξ^B_{ip}, are given in Table 2. It should be added that the associated costs for other locations rather than B can be found by multiplying the relevant costs of B with the relative operating and capital costs as shown in Table 1. Scale-up and qualification costs are assumed to be negligible in this paper, although their appropriate timings are taken into account.

Finally, the demand patterns for the two sales regions are given in Table 3. Note that products P1, P2, P4, and P6 are sold in sales region A, while products P3, P5, and P8 are sold at B.

The above example was modeled using the GAMS modeling system[10] coupled with CPLEX 6.0 for the MILP optimization. A 5% margin of optimality was used during the branch-and-bound solution procedure using a Sun Ultra60 workstation.

The resulting mathematical model, which comprises 3008 binary and 2718 continuous variables, was solved in 653 s. The optimal solution (within the 5% margin) has an NPV value of 837 rmu. The detailed breakdown of the objective function is shown in Table 4.

The optimization algorithm has selected five products out of the seven potential ones, rejecting products P2 and P4 as nonpromising. Also, production locations B and D have been selected for further capacity investments without allocating any capacity at location C. In total, six additional suites (apart from the initial two at location B) are going to be invested in, thus resulting in a cumulative production capacity of eight suites between locations B and D. Two of these suites will be added to location B and the rest to location D.

Table 5 shows the scale-up and qualification timings as determined by the algorithm for both selected production locations.

Finally, the optimal flows of material for all selected products are illustrated in Figures 3–7. It can be seen from these figures that most of the demand of the selected products is satisfied apart from product P3.

Table 3. Products Demand

product	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
P1	4.2	9.0	22.4	21.6	22.2	22.2	22.2	22.2	22.2	22.2
P2	0	1.0	4.4	8.6	9.0	11.0	11.0	11.0	11.0	11.0
P3	2.2	6.4	10.4	13.6	16.0	16.2	16.2	16.2	16.2	16.2
P4	0	3.8	7.2	12.2	18.6	21.4	21.4	21.4	21.4	21.4
P5	0	0	5.0	11.0	21.4	24.4	28.2	28.2	30.8	31.6
P6	4.0	7.2	9.6	15.2	20.2	23.8	23.0	22.0	20.2	20.2
P7	14.4	15.0	16.8	18.6	20.8	21.0	21.0	21.0	21.0	21.0

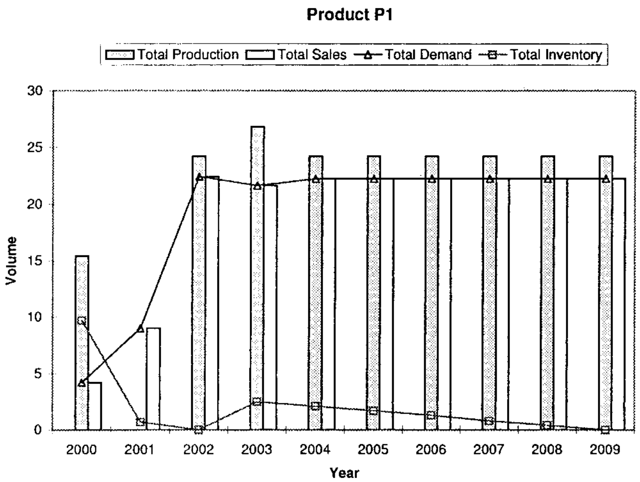

Figure 3. Profile for product P1.

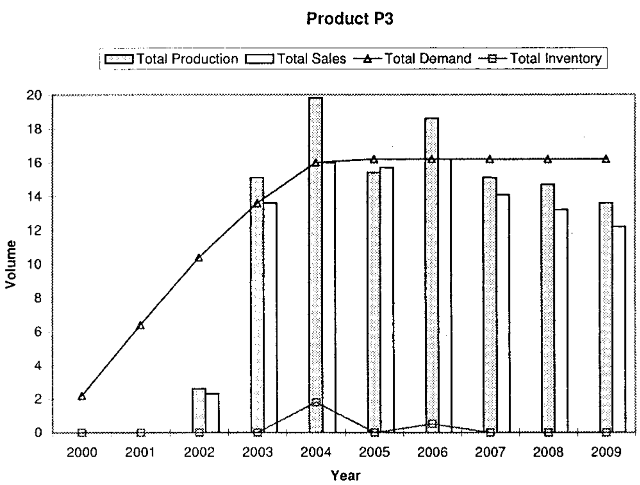

Figure 4. Profile for product P3.

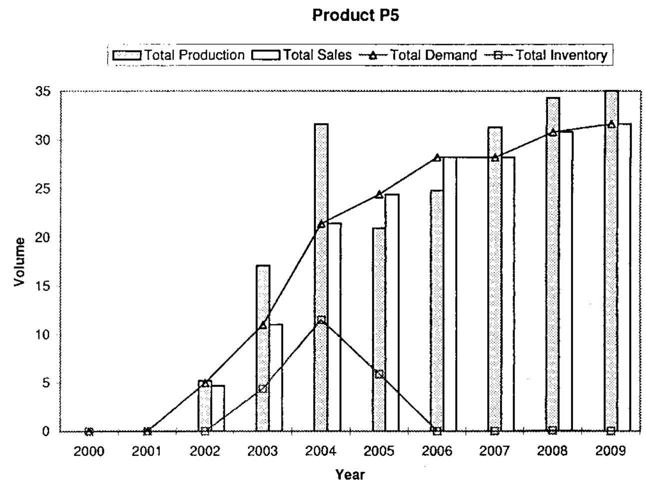

Figure 5. Profile for product P5.

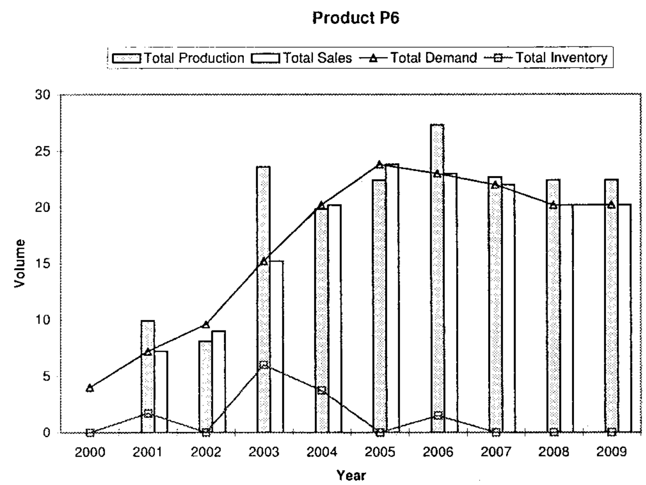

Figure 6. Profile for product P6.

Table 4. Objective Function Breakdown

sales	2582
marketing cost	235
royalties and R&D costs	742
operating costs	325
costs of scale-up and qualification runs	0
depreciation cost	66
capital investment	377
NPV	837

5. Concluding Remarks

In this paper, the main objective was to apply mathematical programming techniques so as to facilitate the strategic supply chain decision-making process for pharmaceutical industries. An optimization-based approach has been presented to select both the optimal product development and introduction strategy together with long-term capacity planning and investment strategy at multiple sites. The developed mathematical model considers many aspects especially related to pharmaceutical sector (e.g., scale-up, qualification, product lifetime constraints).

The overall problem has been formulated as an MILP model which can then be solved to global optimality provided that the model size is tractable. The applicability of the proposed model has been demonstrated by one illustrative example.

In realistic case studies, the resulting model size might be prohibitively large and alternative solution approaches are worth investigation. Our current research focuses on the development of aggregated mathematical models coupled with a hierarchical solution procedure for the efficient solution of the resulting MILP model. Another interesting extension of our work is to include the considerable demand uncertainty which exists in this industry. For example, the uncertainty on the outcome of the clinical trials of all candidate products could be incorporated within our existing

Table 5. Scale-Up and Qualification Timings[a]

	production site B			production site D						
product	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
P1	X+			X+						
P3			X+	X			+			
P5			X+	X+						
P6	X	+							X+	
P7	X+			X+						

[a] X: scale-up. +: qualification.

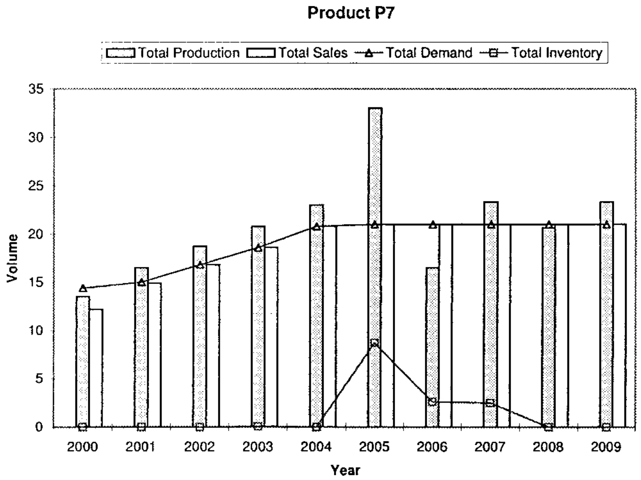

Figure 7. Profile for product P7.

framework (see, for example, ref 12, which deals with the single-site case). Finally, we have assumed a given trading structure with fixed parameters. In some cases, either or both of these may be optimized as well.

Appendix: Derivation of the Objective Function

A.1. Objective Function (before Taxes). The objective function includes revenues from sales, capital investment, R&D costs, operating costs, and costs of scale-up and qualification runs.

Next, we consider each of these terms in sequence.

A.1.1. Sales Revenue. The revenue due to product sales in region k over period t, SR_t^k, can simply be stated as:

$$SR_t^k = \sum_{p \in P^k} \nu_p^k S_{pt}^k \qquad \forall\ k, t \tag{23}$$

where ν_p^k is the sales price for product p at region k.

A.1.2. Sales-Based Costs. Furthermore, the above amount, SR_t^k, should be reduced accordingly in order to capture royalties for IP, RC_t^{IP}, usually to third party companies, as well as marketing contributions for sales center k, MC_t^k. Both of these terms are assumed to be proportional to the amounts sold. Therefore, we obtain

$$RC_t^{IP} = \sum_k \sum_{p \in P^k} \lambda_p^k \nu_p^k S_{pt}^k \qquad \forall\ t \tag{24}$$

and

$$MC_t^k = \sum_{p \in P^k} \mu_{pt}^k \nu_p^k S_{pt}^k \qquad \forall\ k, t \tag{25}$$

where λ_p^k and μ_{pt}^k are the royalties and marketing costs (as fractions of the selling price) for each product at each sales region, respectively. The latter cost coefficient is time-dependent to capture the case where a more intensive marketing effort is required during the launch of each product.

A.1.3. Capital Investment. The capital investment related to production site l in period t, CI_t^l, depends on the cost of each suite i of each production site l, ω_i^l:

$$CI_t^l = \sum_{i \in I^l} \omega_i^l E_{it}^l \qquad \forall\ l, t \tag{26}$$

The relevant cost of header suites (i.e., $i \in F^l$) is higher than those of the others in order to take account of lab construction cost required for each new block.

A.1.4. R&D Cost. Also, the cost spent at the IP associated with the R&D over period t, RDC_t^{IP}, should be included:

$$RDC_t^{IP} = \sum_p \sigma_{pt} U_p \qquad \forall\ t \tag{27}$$

where σ_{pt} is the corresponding time-varying R&D cost of product p.

Although the above summation indicates a time-varying investment on R&D, it is usually considered as an initial capital cost ($\sigma_{p1} \neq 0$ and $\sigma_{pt} = 0$ for $t > 1$).

A.1.5. Operating Cost. The operating cost of production site l in period t, OC_t^l, associated with each suite i at each location l comprises two terms. The first one is a fixed amount, η_i^l, paid each time period if suite i exists (i.e., $A_{it}^l = 1$):

$$\sum_{i \in I^l} \eta_i^l A_{it}^l \qquad \forall\ l, t$$

The second term depends on the actual amount of product p produced at suite i at location l during period t, B_{ipt}^l:

$$\sum_p \sum_{i \in I^l} \xi_{ip}^l B_{ipt}^l \qquad \forall\ l, t$$

where ξ_{ip}^l is the corresponding cost of producing product p in suite i of location l.

Therefore, the total operating cost per time period will be given by

$$OC_t^l = \sum_{i \in I^l} (\eta_i^l A_{it}^l + \sum_p \xi_{ip}^l B_{ipt}^l) \qquad \forall\ l, t \tag{28}$$

A.1.6. Cost of Scale-Up and Qualification Runs. The cost associated with scale-up and qualification runs at production site l over period t, $CSQR_t^l$, can be described mathematically as

$$CSQR_t^l = \sum_p (\beta_{pt}^l \hat{Z}_{pt}^l + \gamma_{pt}^l X_{pt}^l) \qquad \forall\ l, t \tag{29}$$

where β_{pt}^l and γ_{pt}^l represent scale-up and qualification costs, respectively.

Finally, for NPV calculations, we must introduce a discount factor, ϵ_t. This factor is associated with the inflation rate, f, and interest rate, g, according to the following formula:

$$\epsilon_t \equiv \left(\frac{1+f}{1+g}\right)^{t-1} \qquad \forall\ t$$

NPV is based on a common currency (e.g., US$). Hence, f and g are assumed to be independent of location.

Overall, the objective function, Φ^B, being maximized is the following:

$$\Phi^B \equiv \max \sum_t \epsilon_t [\sum_k (SR_t^k - MC_t^k) - \sum_l (CI_t^l + OC_t^l + CSQR_t^l) - RC_t^{IP} - RDC_t^{IP}] \tag{30}$$

So far, we have not considered taxes, and general issues associated with trading structures have not been taken into consideration. In the next section, we describe how taxes and the trading structure affect the performance of the supply chain.

A.2. Objective Function (after Taxes). In this paper, we shall adopt the trading structure illustrated in Figure 2. It can clearly be seen from the figure that there are three distinctive center types: production site (l), intellectual property owner (IP), and sales region (k). The trading structure and especially the transfer pricing structure adopted may have a significant impact on the taxes paid by each center, thus affecting the after-tax profits made at each center. It should be recalled that the production sites are considered as cost centers and the sales regions as profit centers.

In general, the objective function after taxes, Φ^{A}, will be equal to Φ^{B} minus the taxes paid by each center, $\bar{T}_t^k$, $\bar{T}_t^l$, and $\bar{T}_t^{IP}$. Overall, we have

$$\Phi^{A} = \Phi^{B} - \sum_t \epsilon_t \left(\sum_k \bar{T}_t^k + \sum_l \bar{T}_t^l + \bar{T}_t^{IP}\right) \qquad (31)$$

Next, we examine each center in turn to determine its individual tax component.

A.2.1. Sales Region. Each sales center has associated sales revenue (SR_t^k) and marketing cost (MC_t^k) components as described in the previous section. In addition, an "internal" cost is paid from each sales center to IP based on the product selling price minus a predetermined margin, ρ^k, i.e., $(1 - \rho^k)SR_t^k$. Therefore, the profit of each sales center over period t, Π_t^k, is given by

$$\Pi_t^k = SR_t^k - MC_t^k - (1 - \rho^k)SR_t^k \qquad \forall\, k, t \quad (32)$$

Then, the tax paid by each center at period t, $\bar{T}_t^k$, can be calculated by

$$\bar{T}_t^k = \psi_t^k\, \Pi_t^k \qquad \forall\, k, t \qquad (33)$$

or by using constraints (32) to eliminate the Π_t^k variables:

$$\bar{T}_t^k = \psi_t^k(\rho^k SR_t^k - MC_t^k) \qquad \forall\, k, t \qquad (34)$$

where ψ_t^k is the tax rate for sales region k during time period t. Note that different taxation policies over location and time may play a very important role during optimization.

A.2.2. Production Site. Each production suite incurs the operating costs (OC_t^l), cost for scale-up and qualification runs ($CSQR_t^l$), and capital investment (CI_t^l) costs as described in the previous section. To calculate the tax related to each production site at each time period, $\bar{T}_t^l$, capital investment is not included but depreciation cost is taken into account as explained next.

In after-tax calculations, we need to include depreciation components, DC_t^l. Depreciation can simply be considered as a governmental tax incentive which represents a tax-free annual expense due to equipment decay. Each government allows companies to deduct part of the capital investment for a given tax life period, ϕ^l, from their profits. Here, we adopt the *straight line* depreciation model for ϕ^l time periods after an equipment item becomes *available*. Therefore, the corresponding depreciation, DC_t^l, component will be

$$DC_t^l = \sum_{i \in I^l} \sum_{\theta = t - \delta_i^l - \phi^l + 1}^{t - \delta_i^l} \frac{\omega_i^l}{\phi^l} E_{i\theta}^l \qquad \forall\, l, t \qquad (35)$$

The internal selling price from the production site center to IP is based on incurred cost plus a predetermined margin, ρ^l, i.e., $(1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l)$. Therefore, the profit of each production site center at period t, Π_t^l, is given by

$$\Pi_t^l = (1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l) - DC_t^l - OC_t^l - CSQR_t^l \qquad \forall\, l, t \quad (36)$$

The tax paid by each production center at period t, $\bar{T}_t^k$, is as follows:

$$\bar{T}_t^l = \psi_t^l\, \Pi_t^l \qquad \forall\, l, t \qquad (37)$$

or by using constraints (36) to eliminate Π_t^l variables:

$$\bar{T}_t^l = \psi_t^l \rho^l (DC_t^l + OC_t^l + CSQR_t^l) \qquad \forall\, l, t \qquad (38)$$

where ψ_t^l is the relevant tax rate.

A.2.3. Intellectual Property. The profit generated at the intellectual property, IP, center is due to the "internal" product selling, first, from IP to sales regions (i.e., $\Sigma_k(1 - \rho^k)SR_t^k$ and, second, from production sites to IP [i.e., $\Sigma_l(1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l)$]. Of course, the costs associated with royalties and R&D should also be included. Therefore, the profit for the IP center over period t, Π_t^{IP}, is given by

$$\Pi_t^{IP} = \sum_k (1 - \rho^k)SR_t^k - \sum_l (1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l) - RC_t^{IP} - RDC_t^{IP} \qquad \forall\, t \quad (39)$$

while the corresponding tax, $\bar{T}_t^{IP}$, paid by IP will be

$$\bar{T}_t^{IP} = \psi_t^{IP}\, \Pi_t^{IP} \qquad \forall\, t \qquad (40)$$

or

$$\bar{T}_t^{IP} = \psi_t^{IP}\left[\sum_k (1 - \rho^k)SR_t^k - \sum_l (1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l)\right] - \psi_t^{IP}(RC_t^{IP} + RDC_t^{IP}) \qquad \forall\, t \quad (41)$$

where ψ_t^{IP} is the IP tax rate.

In conclusion, the objective function, Φ^{A}, to be maximized, by appropriately eliminating the taxation terms from constraints (31) and applying constraints (34), (38), and (41), is the following:

$$\Phi^{A} = \Phi^{B} - \sum_t \epsilon_t \sum_k \psi_t^k(\rho^k\, SR_t^k - MC_t^k) - \sum_t \epsilon_t \sum_l \psi_t^l \rho^l (DC_t^l + OC_t^l + CSQR_t^l) - \sum_t \epsilon_t \{\psi_t^{IP}[\sum_k (1 - \rho^k)SR_t^k - \sum_l (1 + \rho^l)(DC_t^l + OC_t^l + CSQR_t^l)]\} + \sum_t \epsilon_t [\psi_t^{IP}(RC_t^{IP} + RDC_t^{IP})] \quad (42)$$

Finally, if we substitute Φ^{B} by relations described in section A.1, then eq 42 can be rewritten as

$$\Phi^{A} = \text{Sales}$$
$$\sum_t \epsilon_t \sum_k \mathrm{SR}_t^k [1 - \psi_t^k \rho^k - \psi_t^{\mathrm{IP}}(1 - \rho^k)]$$
$$\text{Marketing Cost}$$
$$- \sum_t \epsilon_t \sum_k \mathrm{MC}_t^k (1 - \psi_t^k)$$
$$\text{Royalties and R\&D Costs}$$
$$- \sum_t \epsilon_t (\mathrm{RC}_t^{\mathrm{IP}} + \mathrm{RDC}_t^{\mathrm{IP}})\,(1 - \psi_t^{\mathrm{IP}})$$
$$\text{Operating Cost}$$
$$- \sum_t \epsilon_t \sum_l \mathrm{OC}_t^l [1 + \psi_t^l \rho^l - \psi_t^{\mathrm{IP}}(1 + \rho^l)]$$
$$\text{Costs of Scale-Up and Qualification Runs}$$
$$- \sum_t \epsilon_t \sum_l \mathrm{CSQR}_t^l [1 + \psi_t^l \rho^l - \psi_t^{\mathrm{IP}}(1 + \rho^l)]$$
$$\text{Depreciation Cost}$$
$$+ \sum_t \epsilon_t \sum_l \mathrm{DC}_t^l [\psi_t^{\mathrm{IP}}(1 + \rho^l) - \psi_t^l \rho^l]$$
$$\text{Capital Investment}$$
$$- \sum_t \epsilon_t \sum_l \mathrm{CI}_t^l \qquad (43)$$

It should be noted that if all centers are located at the same place (i.e., $\psi_t^l = \psi_t^{\mathrm{IP}} = \psi_t^k \equiv \psi_t$, then constraint (43) becomes

$$\max \Phi^{A} = \sum_t \epsilon_t \sum_k (\mathrm{SR}_t^k - \mathrm{MC}_t^k - \mathrm{RC}_t^{\mathrm{IP}} - \mathrm{RDC}_t^{\mathrm{IP}} - \mathrm{OC}_t^l - \mathrm{CSQR}_t^l)(1 - \psi_t) + \sum_t \epsilon_t \sum_l \mathrm{DC}_t^l \psi_t - \sum_t \epsilon_t \sum_l \mathrm{CI}_t^l \qquad (44)$$

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Received for review December 1, 1999
Accepted October 10, 2000

IE990870T