Online Supplement for Primary Pharmaceutical Manufacturing Scheduling Problem
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Appendix I: Proof of Propositions

Proof of Proposition 2:

Proof. First, note that the validity of (28) follows from the Time Capacity Constraint (4). On the other hand, a solution of $W_{f,i^*}^{k,t} = m_f^{k,t}$, $W_{f,i}^{k,t} = 0, \forall i \neq i^*$, and $Z_f^{k,t} = 1$ is clearly feasible for (15). But it is infeasible for (28) as $c^{k,t} < p_{f,i^*}^k m_f^{k,t} = p_{f,i^*}^k W_{f,i^*}^{k,t}$. $\square$

Proof of Proposition 3:

Proof. Consider the amount of production $P_{f,i}^{k,t}$ in an optimal solution to the PPMSP. We claim that the production output is eventually either converted into some end products in order to satisfy external demand, or it is converted into the end inventory of an *attractive product* i' , indicated by a negative incremental holding cost $h_{i'}^1 \equiv h_{i'} - \sum_{j \in N_f} b_{j,i'} h_j < 0$. Note that this incremental holding cost $h_{i'}^1$ is the change in the total inventory holding cost (per period) caused by producing one unit of product i' and consuming the inventory of intermediate products that serve as inputs for its production. To see the validity of this claim, suppose that there is some extra amount of production outside of these two cases, which means that the extra amount is eventually converted into the end inventory of some non-attractive product. By simply reducing the production of such a non-attractive product, the total inventory cost can be reduced while keeping the solution feasible. We call the optimal amount of production corresponding to the above-mentioned two cases as the *Production-Driven-by-Demand* (PDD) and *Production-Driven-by-Inventory* (PDI), respectively. In the following, we will derive valid upper bounds for both PDD and PDI, where their summation provides a valid upper bound on $P_{f,i}^{k,t}$.

In order to derive an upper bound value for PDI, we observe that a negative value of incremental holding cost, by itself, does not justify the production of an attractive product. There has to be some initial inventory present, because otherwise the total inventory cost would not be reduced since the second part in the formula of $h_{i'}^1$ would not be realized. Note that it's not necessary to have initial inventories for the intermediate products that are directly consumed as inputs to produce an attractive product. Initial inventories could be present for products further upstream of the BOM relations and it would still justify the production of an attractive product by virtue of reducing total inventory cost. In other words, PDI may include the production of a non-attractive product in case it is required to supply inputs for the production of an attractive product downstream. For the purpose of deriving upper bounds on PDI, we consider the

aggregated amount of production over the planning horizon in a relaxed environment with no external demand, capacity constraint, or setup cost. Furthermore, in order to avoid the complexity of considering multiple attractive products competing for the same set of initial inventories, we adopt the following two-step approach of calculating an upper bound on PDI for any product i , denoted by $\tilde{G}_i$, $\forall f \in F, i \in N$.

Step 1. Consider each attractive product i' individually, only allowing itself and its upstream products to be produced in the aforementioned relaxed problem, and assume that all initial inventory is available for consumption. Determine an optimal production amount of i' , denoted by $\pi_{i'}$, by minimizing the total inventory cost in this specific problem.

Step 2. Determine the required amount of each product i to provide inputs for its downstream attractive products based on their π -values calculated in Step 1. This required amount is then compared with the initial inventory of product i to determine its necessary amount of production, κ_i . If the current product is a non-attractive product, κ_i gives an upper bound on its PDI-value (i.e., $\tilde{G}_i = \kappa_i$); otherwise, the upper bound value is given by $\tilde{G}_i = \max\{\kappa_i, \pi_i\}$.

Note that in an optimal solution to the original PPMSP, PDI may be postponed due to capacity constraints. Nevertheless, the value of $\tilde{G}_i$ provides an upper bound on the amount of PDI in any period $t \in T$.

In order to derive an upper bound on PDD, we first assume that there is no initial inventory, capacity constraint, or setup cost. By assuming no initial inventory, we essentially exclude PDI from the optimal solution of this relaxation. Also, because there is no capacity constraint in this relaxation, production can be carried out as late as possible in order to reduce the inventory holding cost to zero. In other words, all production is carried out in the same period in which the output is due. We denote such a solution as

$\hat{G}_i^t$: the amount of product i that is produced during period t , $\forall t \in T, i \in N$.

Its value can be obtained by solving the following linear program:

$$\begin{aligned} & \text{Minimize} && \sum_{t \in T} \sum_{i \in N} \hat{G}_i^t \\ & \text{subject to:} && \hat{G}_i^t = d_i^t + \sum_{j \in N_f} b_{f,i,j} \hat{G}_i^t, \quad \forall t \in T, f \in F, i \in N_f \\ & && \hat{G}_i^t \geq 0, \quad \forall t \in T, i \in N. \end{aligned}$$

Since capacity constraints are present in the original PPMSP, some amount of PDD is likely scheduled in periods prior to which the demand is due. Nevertheless, for any period $t \in T$, the summation of $\hat{G}_i^t$ over the remaining periods ($\sum_{\tau=t}^{|T|} \hat{G}_i^\tau$) gives an upper bound on PDD for the original PPSMP.

Finally, the combination of PDD and PDI gives the following valid upper bound value:

$$\sum_{\tau=t}^{|T|} \hat{G}_i^\tau + \tilde{G}_i. \quad \square$$

Proof of Proposition 5:

Proof. If $|M^i| = 1$, then $\epsilon_i^{k,t} = \hat{d}_i^t$ for the only bay k in M^i . Hence, inequality (38) reduces to inequality (33), which has been shown to be valid. Hence, suppose that $|M^i| > 1$. We first show that $\hat{d}_i^t \leq \sum_{k \in M^i} \theta_i^{k,t}$. On the contrary, suppose that $\hat{d}_i^t > \sum_{k \in M^i} \theta_i^{k,t}$. We then have

$$\epsilon_i^{k,t} = \hat{d}_i^t - \sum_{\hat{k} \in M^i \setminus \{k\}} \theta_i^{\hat{k},t}, \forall k \in M^i. \text{ Hence,}$$

$$\begin{aligned} \sum_{k \in M^i} \epsilon_i^{k,t} &= \sum_{k \in M^i} \left(\hat{d}_i^t - \sum_{\hat{k} \in M^i \setminus \{k\}} \theta_i^{\hat{k},t} \right) \\ &= \hat{d}_i^t + (|M^i| - 1) \cdot \left(\hat{d}_i^t - \sum_{k \in M^i} \theta_i^{k,t} \right) > \hat{d}_i^t. \end{aligned}$$

This contradicts the assumption that $\sum_{k \in M^i} \epsilon_i^{k,t} \leq \hat{d}_i^t$. Therefore, $\hat{d}_i^t \leq \sum_{k \in M^i} \theta_i^{k,t}$.

We further define $\tilde{M}^i = \{k \in M^i : \epsilon_i^{k,t} > 0, Z_f^{k,t} = 0\}$. If $\tilde{M}^i = \emptyset$, inequality (38) is trivially valid. Hence, suppose that $|\tilde{M}^i| \geq 1$. Note that family f is not in production on the bays of $\tilde{M}^i$. To satisfy the converted demand for product i in period t , we must have

$$\sum_{j \in N_f} \eta_{i,j} I_j^{t-1} \geq \hat{d}_i^t - \sum_{k \in M^i \setminus \tilde{M}^i} \theta_i^{k,t}.$$

But

$$\begin{aligned} &\left(\hat{d}_i^t - \sum_{k \in M^i \setminus \tilde{M}^i} \theta_i^{k,t} \right) - \sum_{k \in \tilde{M}^i} \left(\hat{d}_i^t - \sum_{\hat{k} \in M^i \setminus \{k\}} \theta_i^{\hat{k},t} \right) \\ &= \hat{d}_i^t - \sum_{k \in M^i \setminus \tilde{M}^i} \theta_i^{k,t} - |\tilde{M}^i| \cdot \left(\hat{d}_i^t - \sum_{k \in M^i} \theta_i^{k,t} \right) - \sum_{k \in \tilde{M}^i} \theta_i^{k,t} \\ &= (1 - |\tilde{M}^i|) \cdot \left(\hat{d}_i^t - \sum_{k \in M^i} \theta_i^{k,t} \right) \geq 0. \end{aligned}$$

Therefore,

$$\sum_{j \in N_f} \eta_{i,j} I_j^{t-1} \geq \hat{d}_i^t - \sum_{k \in M^i \setminus \tilde{M}^i} \theta_i^{k,t}$$

$$\geq \sum_{k \in \bar{M}^i} \left(\hat{d}_i^t - \sum_{\hat{k} \in M^i \setminus \{k\}} \theta_i^{\hat{k},t} \right) = \sum_{k \in M^i} (1 - Z_f^{k,t}) \epsilon_i^{k,t}. \quad \square$$

Appendix II: Algorithm for Generalized BOM Ratio

For each $f \in F$:

For each $j \in N_f$:

 Let $\eta_{i,j} = 0, \forall i \in N_f$;

 Define a temporary variable $x_{i,j}, \forall i \in N_f$;

 Let $x_{j,j} = 1$ and $x_{i,j} = 0, \forall i \in N_f; i \neq j$;

While there exists a product $i \in N_f$ such that $x_{i,j} > 0$:

 Let $\eta_{i,j} \leftarrow \eta_{i,j} + x_{i,j}$;

For each $k \in N_f$ such that $b_{k,i} > 0$:

 Let $x_{k,j} \leftarrow x_{k,j} + b_{k,i} x_{i,j}$;

End for

 Let $x_{i,j} = 0$;

End while

End for

End for