Online Supplement for “Incentivizing Resilient Supply Chain Design to Prevent Drug Shortages: Policy Analysis Using Two- and Multi-Stage Stochastic Programs” by Emily L. Tucker, Mark S. Daskin, Burgunda V. Sweet, and Wallace J. Hopp

Section 1 presents detail on the data used for the parameter values, and Section 2 presents the sensitivity and scenario analysis results. Section 3 includes proofs of the lemmas and theorem presented in the text.

1. Parameters

1.1. Distribution of time to recover

We have three recovery time distributions: time to supplier recovery, time to plant recovery, time to line recovery. The specific data on recovery times were unavailable. As a proxy, we used the distributions of shortage durations and adjusted them to account for reporting delays (UUDIS, 2016).

For the supplier recovery distribution, we fit the distribution of shortage durations for all resolved shortages 2001-2016 in which the reported cause was due to raw material issues. For the plant recovery distribution, we fit the distribution of sole-source injectable shortage durations for which the cause was a manufacturing-related issue. We did not have data for the time to line recovery and assumed it was equal to 0.1 of the time to plant recovery. We evaluated this in sensitivity analysis. For each of these distributions, we also factored in the time the product is partially available (ASHP, 2018) and evaluated several types of distributions and determined that an exponential distribution fit best (Delignette-Muller and Dutang, 2015; R Core Team, 2018). Because we consider discrete time periods, we discretized the distributions to apply a geometric distribution.

1.2. Disruption of time to disruption

To estimate the distribution of the time to disruption for suppliers, plants, and lines, we fit distributions for the time of FDA approval for the generic drug application to the date the shortage began (FDA, 2018a; UUDIS, 2016).

For suppliers, we considered drugs that were short due to raw material issues, and for plants, we considered shortages where the direct cause was a manufacturing issue. We assumed the time to line disruption was 0.3 times the time to a disruption of a plant. Similarly to the time to recover, we evaluated different types of distributions and fit geometric distributions for each.

1.3. Demand

We estimated the annual demand in the United States for vinblastine and vincristine based on Medicare Part B data for individuals at least 65 years old and the demographic information of the population that the drugs are used to treat.

The amounts of vinblastine and vincristine charged to Medicare Part B were approximately 45,000 mg in 2015 and 2016 (CMS, 2018). These drugs are commonly used to treat certain cancers (vinblastine - Hodgkin's disease, testicular cancer, and AIDS-related Kaposi's sarcoma; vincristine - Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Hodgkin's Disease, and Non-Hodgkin lymphoma; ("Drugs.com," 2018). The average proportion of new cases that are in individuals at least 65 years old are 13% for vinblastine-treated cancers and 51% for vincristine-treated cancers (National Cancer Institute, 2018). Then we produced a rough estimate of the total national demand and converted to liquid volume (ml) based on the strengths provided in the Red Book (IBM Micromedex, 2018).

We note that this process assumes the proportion of drug usage for these conditions by age is consistent with the proportion of new cases under 65 and that individuals under 65 are treated at the same rate as individuals on Medicare. We evaluate the sensitivity of our results to the demand estimates in scenario analyses (Appendix Section 2).

1.4. Costs

GDUFA program fees:

Companies pay an annual fee to the FDA based on the number of approved Abbreviated New Drug Applications (ANDAs) they hold. These represent the number of generic drugs the companies are able to market. We estimated the GDUFA program fee that is allocated to each drug by dividing the appropriate fee by the total number of ANDAs the company holds based on the National Drug Code Directory (FDA, 2018b). The company which produces vinblastine has 139 ANDAs which corresponds to a per drug cost of $11,445. The company which produces vincristine holds 164 ANDAs. This corresponds to a per drug cost of $9,700.

Fixed costs:

We estimated the plant fixed cost as the amortized 30-year cost of a plant based on estimates of costs of fill-and-finish facilities, adjusted to 2018 dollars, and divide by 100 products (GAO, 2014; Rudge, 2012). We assumed the fixed line cost is half of this value, and we assumed the supplier fixed cost is one quarter of the total raw material order (calculated as the variable raw material cost multiplied by annual demand).

Production costs:

The loaded cost to produce an injectable drug is 20-60% of the sales price based on conversations with a pharmaceutical manufacturing executive and estimates in literature (Jia and Zhao, 2017). For our base parameter values, we assumed the loaded cost to be 40% of the sales price. We calculated the total cost to produce the drug annual as the product of 40%, the sales price, and annual demand. To back out the unit production costs, we subtracted the GDUFA and non-GDUFA fixed costs and raw material costs and divided the resulting value by annual demand.

2. Sensitivity and scenario analyses

The one-way sensitivity analysis results for each drug are presented in the tornado diagrams of Figure A-1. In the upper bound (UB) analyses, the parameters were increased by 20% vs. the baseline values, and in the lower bound (LB) analyses, they were decreased by 20%.

In the baseline analysis, the time horizon length is two years. When this is varied to one year, three years, and five years, for vinblastine, the expected annual profit is within 1% of the baseline value, and the optimal solution does not change. Similarly, for vincristine, for one-, three-, and five- year time horizons, the expected annual profit is within 2% of the baseline value, and the optimal solution does not change. The baseline period length is two months. When the period length is decreased from two months to one month, the expected profit for vinblastine does not change and increases 3% vs baseline for vincristine. When the period length is increased to three months, the expected profit decreases 3% vs. baseline for both drugs. Adjusting the period length does not change the optimal solution from baseline for either drug. As the annual demand varies, the optimal solution does not change between 0.7-1.6 times baseline demand for vinblastine and 0.6-2 times baseline for vincristine. As the production capacity of the lines varies to 4 and 8 times the per-period demand, the companies continue to hold no inventory in the optimal solution.

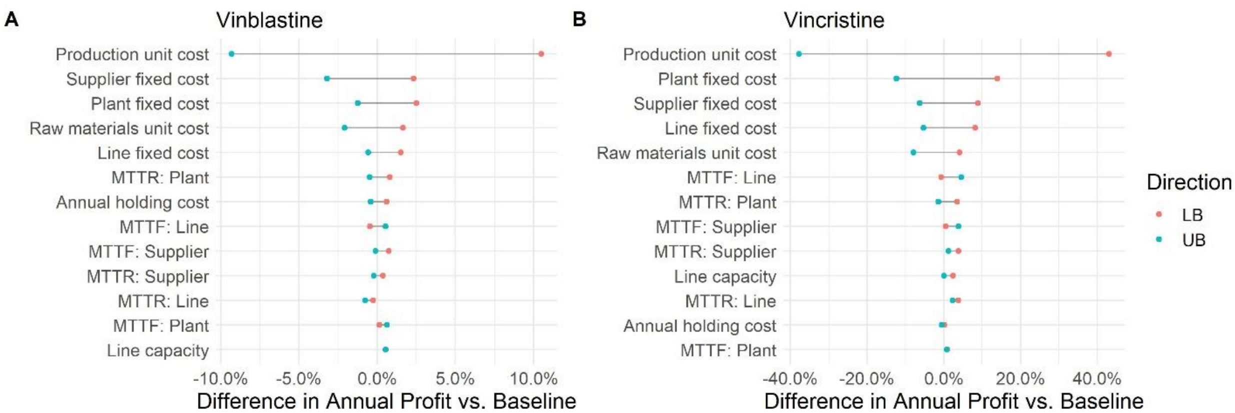

Figure A - 1. One-way sensitivity analysis results

3. Proofs

SCDD Model:

Lemma 1: $\theta_t^\omega \in \{0,1\}$ $\quad \forall t \in T, \omega \in \Omega$

$g^{Line} \in \mathbb{Z}^+$		By definition
$\xi_{nt}^\omega \in \{0,1\}$	$\forall n \in N, t \in T, \omega \in \Omega$	By definition
$\Rightarrow \theta_t^\omega \in \{0,1\}$		Constraints (6-11), Objective function (5) ∎

SCDD-I Model:

Lemma 2: $C_t^\omega \in \{0,1\}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (22) ∎

Lemma 3: $\tilde{C}_t^\omega \in \mathbb{Z}^+$ $\quad \forall t \in T, \omega \in \Omega$

$g^{Line} \in \mathbb{Z}^+$		By definition
$\xi_{nt}^\omega \in \{0,1\}$	$\forall n \in N, t \in T, \omega \in \Omega$	By definition
$\tilde{z}_{jl} \in \{0,1\}$	$\forall j \in J, l \in L$	Constraints (4e)
$\Rightarrow \tilde{C}_t^\omega \in \mathbb{Z}^+$	$\forall t \in T, \omega \in \Omega$	Lemma 2 and Constraints (23)

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Lemma 4: $I_0, I_t^{\omega} \in \mathbb{Z}^{+}$ $\quad \forall t \in \{0\} \cup T, \omega \in \Omega$ $\quad$ Constraints (10, 17, 20, 21, 25, 26, 27c), Objective function (15), Lemma 2

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Lemma 5: $\theta_t^{\omega} \in \{0,1\}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (10, 11, 16, 24), Objective function (15), Lemmas 2-4

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Theorem 1: The following relationships are implied by SCDD-I.

$$C_t^{\omega} = C_t^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28a}$$
$$\tilde{C}_t^{\omega} = \tilde{C}_t^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28b}$$
$$I_t^{\omega} = I_t^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28c}$$
$$\theta_t^{\omega} = \theta_t^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28d}$$
$$\sum_{l \in L} v_{lt}^{\omega} = \sum_{l \in L} v_{lt}^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28e}$$
$$\sum_{j \in J} u_{jt}^{\omega} = \sum_{j \in J} u_{jt}^{\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28f}$$
$$\delta_t^{Avail,\omega} = \delta_t^{Avail,\omega'} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28g}$$
$$\delta_t^{Suffic,\omega} = \delta_t^{Suffic,\omega'} \text{ except case: } \tilde{C}_t^{\omega} = I_0 - I_{t-1}^{\omega} \qquad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega \tag{28h}$$

For (28e-f), we focus on the aggregate used in the objective function (15) because the specific supplier or line used in a given stage are not affected by uncertainty in later stages. For (28h), we exclude the case $\tilde{C}_t^{\omega} = I_0 - I_{t-1}^{\omega}$ because the indicator of sufficient capacity ($\delta_t^{Suffic,\omega}$) can be assigned either the value of 0 or 1 when the excess capacity ($\tilde{C}_t^{\omega}$) is equal to the safety stock deficit ($I_{t-1}^{\omega} - I_0$). The purpose of the indicator is to enforce the minimum operator in constraints (24). The values of the other variables in the constraints (24) are implied to be non-anticipative, and the indicator is not affected by uncertainty revealed in subsequent stages.

Proof of Theorem 1:

Lemma 6: $C_t^{\omega} = C_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

If $\exists (j,k,l)$ s.t. $\xi_{jt}^{\omega}\xi_{kt}^{\omega}\xi_{lt}^{\omega}\tilde{z}_{jl} = 1$, then $C_t^{\omega} = 1$, else $C_t^{\omega} = 0$
$\forall j \in J, k \in K, l \in L_k, t \in T, \omega' \in S_t^{\omega}, \omega \in \Omega$
Constraints (22)

$\xi_{jt}^{\omega} = \xi_{jt}^{\omega'}; \xi_{kt}^{\omega} = \xi_{kt}^{\omega'}; \xi_{lt}^{\omega} = \xi_{lt}^{\omega'}$ $\quad \forall j \in J, k \in K, l \in L, t \in T, \omega' \in S_t^{\omega}, \omega \in \Omega$
Definition of S_t^{ω}

$\Rightarrow C_t^{\omega} = C_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ ■

Lemma 7: $\tilde{C}_t^{\omega} = \tilde{C}_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ $\quad$ Lemma 6 and Constraints (23)

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Lemma 8: $\sum_{j \in J} u_{jt}^{\omega} = \sum_{l \in L} v_{lt}^{\omega}$ $\quad \forall t \in T, \omega \in \Omega$

$\sum_{l \in L} v_{lt}^{\omega} \leq \sum_{j \in J} u_{jt}^{\omega}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (8)
$\Rightarrow \sum_{l \in L} v_{lt}^{\omega} = \sum_{j \in J} u_{jt}^{\omega}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Objective function (15)

$\blacksquare$

Lemma 9: If $C_t^{\omega} = 0$, then $\theta_t^{\omega} = \begin{cases} 1, & \delta_t^{Avail,\omega} = 1 \\ 0, & \delta_t^{Avail,\omega} = 0 \end{cases}$ $\quad \forall t \in T, \omega \in \Omega$

$\delta_t^{Avail,\omega} \in \{0,1\}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (27c)

If $\delta_t^{Avail,\omega} = 1$, then $\theta_t^{\omega} = 1$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (10, 20)
If $\delta_t^{Avail,\omega} = 0$:
$\xi_{jt}^{\omega} \xi_{kt}^{\omega} \xi_{lt}^{\omega} \tilde{z}_{jl} = 0$ $\quad \forall t \in T, \omega \in \Omega, j \in J, k \in K, l \in L_k$ $\quad$ Constraints (22a)
$\sum_{l \in L} v_{lt}^{\omega} = 0$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (6-8, 14)
$\theta_t^{\omega} = 0$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (16, 24)

$\blacksquare$

Lemma 10: If $I_{t-1}^{\omega} = I_{t-1}^{\omega'}$, then $\delta_t^{Avail,\omega} = \delta_t^{Avail,\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

$\nexists I_{t-1}^{\omega} \in (0,1)$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Lemma 4
$\delta_t^{Avail,\omega} = \begin{cases} 1, & I_{t-1}^{\omega} \geq 1 \\ 0, & I_{t-1}^{\omega} = 0 \end{cases}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (25, 27c)

$\blacksquare$

Lemma 11: If $\delta_t^{Avail,\omega} = \delta_t^{Avail,\omega'}$, then $\theta_t^{\omega} = \theta_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

$C_t^{\omega} \in \{0,1\}$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Lemma 2

Case 1: $C_t^{\omega} = 1 \Rightarrow \theta_t^{\omega} = 1$ $\quad \forall t \in T, \omega \in \Omega$ $\quad$ Constraints (10, 19)
Case 2: $C_t^{\omega} = 0 \Rightarrow \theta_t^{\omega} = \theta_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ $\quad$ Lemma 9

$\blacksquare$

Lemma 12: $I_t^{\omega} = I_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

By induction:
$I_0^{\omega} = I_0^{\omega'}$ $\quad \forall \omega' \in S_0^{\omega}, \omega \in \Omega$ $\quad$ Constraints (26)
$I_{t-1}^{\omega} = I_{t-1}^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ $\quad$ Induction hypothesis
$\Rightarrow \sum_{l \in L} v_{lt}^{\omega} = \sum_{l \in L} v_{lt}^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ $\quad$ Constraints (24) and Lemma 6 and 7
$\theta_t^{\omega} = \theta_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ $\quad$ Lemmas 10 and 11

$\Rightarrow I_{t-1}^{\omega} + \sum_{l \in L} v_{lt}^{\omega} - \theta_t^{\omega} = I_{t-1}^{\omega'} + \sum_{l \in L} v_{lt}^{\omega'} - \theta_t^{\omega'}$
$\forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

$\Rightarrow I_t^{\omega} = I_t^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ Constraints (17)

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Lemma 13: $\sum_{l \in L} v_{lt}^{\omega} = \sum_{l \in L} v_{lt}^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ Constraints (24) and Lemmas 6, 7, and 12

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Lemma 14: $\sum_{i \in I} u_{it}^{\omega} = \sum_{i \in I} u_{it}^{\omega'}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ Lemmas 8 and 13

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Lemma 15: $\delta_t^{Suffic,\omega} = \delta_t^{Suffic,\omega'}$ except case: $\tilde{C}_t^{\omega} = I_0 - I_{t-1}^{\omega}$
$\forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$

$\delta_t^{\omega,Suffic} = \begin{cases} 1, & \tilde{C}_t^{\omega} > I_0 - I_{t-1}^{\omega} \\ 0, & \tilde{C}_t^{\omega} < I_0 - I_{t-1}^{\omega} \end{cases}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$ Constraints (10, 17, 18, 24, 27c)

$\Rightarrow \delta_t^{Suffic,\omega} = \delta_t^{Suffic,\omega'}$, except case: $\tilde{C}_t^{\omega} = I_0 - I_{t-1}^{\omega}$ $\quad \forall \omega' \in S_t^{\omega}, t \in T, \omega \in \Omega$
Lemmas 6, 7, 12, and 13

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Thus, Theorem 1 follows from Lemmas 6-15.

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