Uniworld Consulting, Inc.

Six Sigma Lean

Pharmaceuticals

Chemical Formulation

Background

- A leading pharmaceutical company has increased the efficiency of part of its production facility using Six-sigma. The operation that has been the subject of this improvement manufactures a pharmaceutical intermediate and the company confidently expects a saving in excess of £100,000 p.a. as a direct result. This pharmaceutical intermediate is produced at one stage of a multi-stage synthesis and was identified as the area that would potentially yield the greatest cost savings. The process involved two competing chemical reactions:
  - A + B + C = PRODUCT; A + B = IMPURITY

Background

- Reagent B is very expensive and the objective of the project was to reduce the quantity of B used without allowing the amount of un-reacted C to rise above 1.5%. It was decided to study this process using 16 experiments. In these experiments the two variables were the level of reagent C and the overall amount of solvent in the system.

Development Strategy

The improvement team took action by studying the problem using The Six Sigma Lean Process Improvement Roadmap of

- Define
- Measure
- Analyze
- Improve
- Control

Key Tools Applied

Lean DMAIC methodology

- Process Mapping
- Prioritization (Cause and Effect Matrix)
- FMEA
- Measurements Systems Analysis
- Design of experiments *
- Multiple Response Optimization *

* Described in this case study.

Improve

- Figure 1 is the Designed Experiment.

Figure 1 Experimental Design

Expt	Solvent	Reagent C
1	7000	1
2	8000	1
3	7000	2
4	8000	2
5	8207	1.5
6	8793	1.5
7	7500	2.207
8	7500	0.793
9	7500	1.5

Experiment 1 was performed 5 times.
Experiment 9 was performed 4 times.

Improve

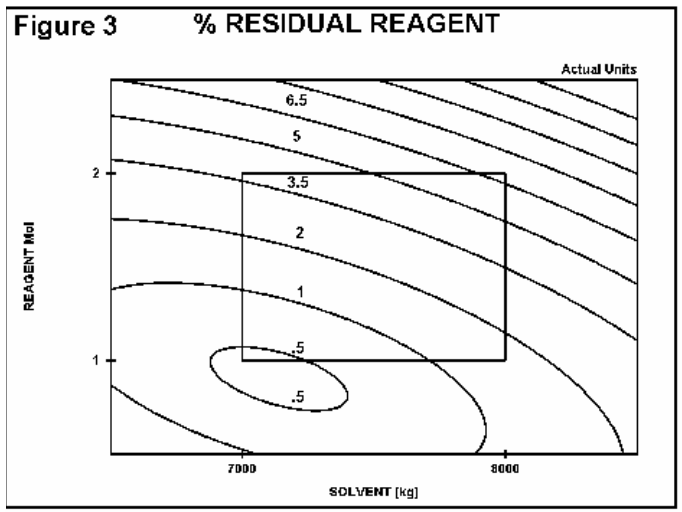
- Each experiment was carried out in the laboratory with the properties of interest being:
  - Residual amount of un-reacted reagent C and
  - Material cost (derived from A + B + C – un-reacted C).
  - The measured values of these two properties are given in Figure 2.

Figure 2

OBS	Residual C	Cost
1	0.41	3.078
2	1.65	3.161
3	3.56	3.099
4	7.01	3.314
5	4.19	3.233
6	1.46	3.056
7	6.46	3.26
8	0.61	3.132
9	1.69	3.07
10(9R)	1.86	3.08
11(9R)	2.42	3.114
12(9R)	2.53	3.124
13(1R)	0.39	3.076
14(1R)	0.39	3.076
15(1R)	0.44	3.081
16(1R)	0.51	3.084

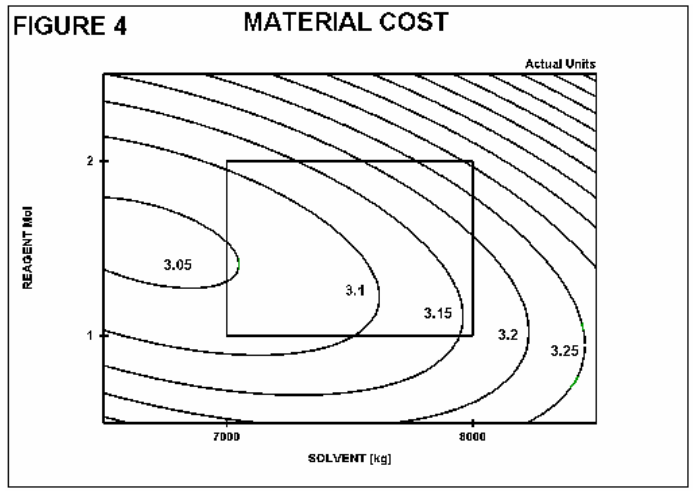
Improve -Findings

- The residual amount of reagent C and the overall material cost were both strongly influenced by the amounts of reagent C and solvent in the original mix
- Mathematical models were generated to explain this relationship. These models can be presented as contour plots as shown in Figure 3 and 4.
  - The contour plot Figure 3 shows how quantity of un-reacted C changes with the amounts of C and solvent added. It shows the area where un-reacted C is below 1.5% and that it reaches a minimum at around 7000 kg solvent and 1 mol reagent.



Improved - Findings

- The contour plot Figure 4 shows how material cost is affected by the variables. Minimum cost is achieved at solvent levels below 7000 kg, reagent C approximately 1.5 mol



- Currently operating conditions were described as:
  - Solvent = 7500 kg, Reagent C = 1 mol
- This produced 0.8% of un-reacted C at a cost of £3.10/kg. The two properties were optimized using multi-response optimization and a new set of operating conditions were suggested at: Solvent = 6800 kg, Reagent = 1.4 mol.

Improve - Findings

- Next confirmatory experiments were carried out in this region. Results are in Figure 5.
- It was finally decided to change production to:
- Solvent = 6750 kg.
  Reagent = 1.5 mol.
- Since these operating conditions have been adopted the amount of un-reacted C has consistently been around 1.3% at a cost of £3.04/kg, a saving of 6p/kg.

Figure 5 CONFIRMATORY EXPTS

SOL (kg)	C (mol)	% RESIDUAL C Predicted	Actual
7000	1.75	2.37	1.99
7000	1.75	2.37	2.1
7000	1.25	0.72	0.69
6750	2.21	4.25	5.81
6750	1.75	2.12	2.29
6750	1.75	2.12	2.15

Control

The controls implemented included:

- Best set of operating conditions as defined from the DOE and Multiple Response Optimization work
- SOPs revised to include new operation conditions

Conclusions

- Followed the roadmap. Concentrated DOE activities on the key input variables from the map, prioritization matrix, and FMEA
- Executed 16 experimental runs
- Reduced amount of chemical required
  - £ 100,000 / year savings