Material Substitution and Process Improvement in Pharmaceutical Tablet Manufacturing Operations

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ABSTRACT

At the Allergan Brazil Operations located in Guarulhos, Brazil, tablet production operations are conducted. The tablet granulation and coating operations required the use of significant amounts of methylene chloride, acetone, ethanol, and isopropyl alcohol.

Allergan targeted methylene chloride primarily due to its toxic profile.[1] Also, methylene chloride accounted for approximately half of the total emissions. The process engineers began testing alternative solvents and processes including water, ethanol, isopropanol, and acetone in order to determine a replacement for the methylene chloride. The result of the two-year evaluation process was that methylene chloride was replaced in all process steps by water, ethanol, isopropanol, or was totally eliminated due to process changes. Validation of the process changes was successful. The consumption of the other solvents was also decreased during the process modifications.

The alternative to eliminating these materials would be to install control devices at an estimated cost of $600K to $1000K. The substitution expenses have been far less significant and there are no ongoing operational costs involved for controlling the emissions of these materials. Finally, the quantity of materials required to conduct the operations has decreased overall when the total solvents used prior to the substitutions versus current practice are compared. The benefit to the employees who conduct the operations is also substantial.

INTRODUCTION

Allergan is an eye and skin disease management health care company with specialty areas including neuro-muscular disorders and retinoid therapies. The company produces both prescription and "over the counter" products on a worldwide basis.

This paper is a follow up to a project begun in 1997 and first reported in 1998.[1] The Allergan Brazil Operations, located in Guarulhos, Brazil, had identified several solvents which through process changes and materials substitution could be eliminated or consumption reduced significantly. The main target for elimination or material substitution was methylene chloride, which was the highest quantity solvent consumed in the tablet manufacturing process.

MATERIALS AND METHODS

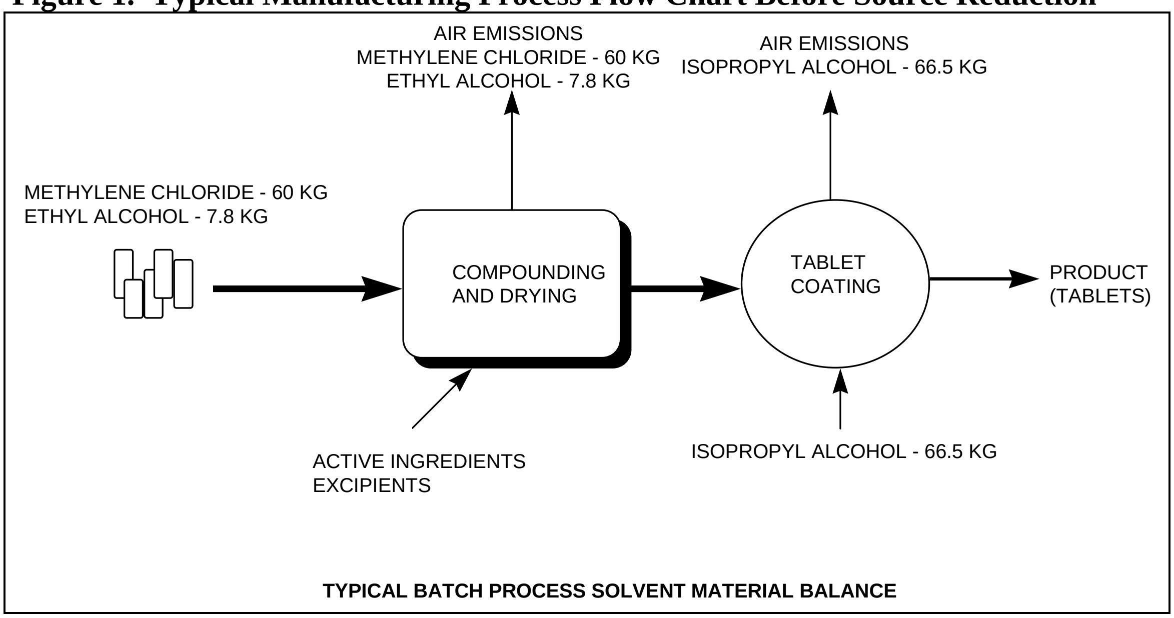
Previously, a methylene chloride consumption history was conducted for the site along with a review of the batch records for each tablet process. A summary of the methylene chloride consumed and the batch quantities were tabulated (Table 1).

Table 1. Summary of Solvent and Quantity Consumed per Batch for Product 1 before Substitution based on 1999 Data.

Operation	Hazardous Material	Product 1
Tablet Compounding	Methylene Chloride	60.0 kg
	Isopropyl Alcohol	66.5 kg

For each batch process, the process flow was identified along with emission points for each step of the process (Figure 1). Each step in the batch processes was analyzed as to whether it was needed to make the final product. The analysis was conducted with a team of personnel representing production, quality assurance, environmental health and safety, manufacturing support engineering, and facility engineering. The team identified the process steps, which were not required as well as the steps that could be upgraded for efficiency purposes.

Figure 1. Typical Manufacturing Process Flow Chart Before Source Reduction



The regulatory process for changes in pharmaceutical manufacturing was commenced with certain steps either being eliminated or improved. This process can take anywhere from three months to two years in Brazil depending on a number of factors.

After the elimination or modifications of steps in the production process were analyzed, then the analysis of material substitutions was begun. The substitutions were targeted based on the emissions identified in Table 1 and Figure 1 as well as the toxicity of the materials being emitted to employees and the community. Table 2 lists the product and the substitutions identified during this final phase of the elimination/substitution project.

Table 2. Summary Source Reduction Alternatives by Product

Product	Existing Compounding Solvent Type Consumed	New Compounding Solvent Type Consumed
1	Methylene Chloride	None required, change process
	Isopropyl Alcohol	Water

Once the priorities were established, laboratory and test batch work was conducted to determine which process steps or substitutes performed the best. After the new process steps or substitutions were determined then full-scale batch tests were conducted. Upon successful completion of several batches, the process step changes or substitutions were made an official part of the manufacturing process. The regulatory approvals were filed. Finally, the revised manufacturing process was implemented on a full-time basis.

RESULTS AND DISCUSSION

The results of the component/step elimination and substitution process with the remaining product are presented in Table 3.

Table 3. Solvent Type and Quantity Eliminated by Product based on June 1997 Data

Product	Manufacturing Phase	Solvent Type Eliminated	Quantity Eliminated (kg/year)	Material Cost Savings (US$/year)
1	Granulation	Methylene Chloride	66,000	$8,118
	Coating	Isopropyl Alcohol	73,150	~$4,000

Methylene chloride was a component used in the wet granulation process. It was determined that changing the process step to a direct granulation process versus a wet granulation process was feasible and more efficient. Methylene chloride was eliminated from the manufacturing processes altogether with this process change. Coating tablets with water was found to be as effective as using isopropyl alcohol, so the isopropyl alcohol was substituted with water. This final substitution resulted in 66,000 kg/year of methylene chloride emissions and 73,150 kg/year of isopropyl alcohol emissions being eliminated.

Total emissions eliminated by this project since 1998 through material substitution and process changes are approximately 224,146 kg/year.

Control systems were quoted and found to range from $600,000 to $1,000,000 in capital cost with operations and maintenance costs estimated to be greater than $100,000/year. The limitations on space and the proximity of the general public to the site would have made the operation of these types of control systems difficult to manage.

CONCLUSION

The benefits of pollution prevention versus "end of pipe controls" are well demonstrated by this project. Economically, eliminating the use of a hazardous material makes much more sense than trying to control the use and emission of the material. The reduction in the cost of goods also makes economic sense. Finally, the liability risks of using hazardous materials are reduced when the materials are no longer required. These liabilities can include spills, releases, community complaints, regulatory oversight, employee exposures, and waste management. There are also no ongoing maintenance requirements for this type of project once the project is completed. Pollution prevention approaches tend to also be faster to implement and return the benefits immediately. The response to this project has been consistent with Allergan EHS Policy.

REFERENCES

1. Whaley, M.B.; Gomes, P., "Material Substitutions in Pharmaceutical Tablet Manufacturing Operations", presented at the Air & Waste Management Association's 91st Annual Meeting & Exhibition, June 14-19, 1998, San Diego, California.

KEY WORDS

Emissions Reductions
Material Substitution
Process Change
Methylene Chloride
Isopropyl Alcohol
Pollution Prevention
Tablet Manufacturing
Pharmaceutical