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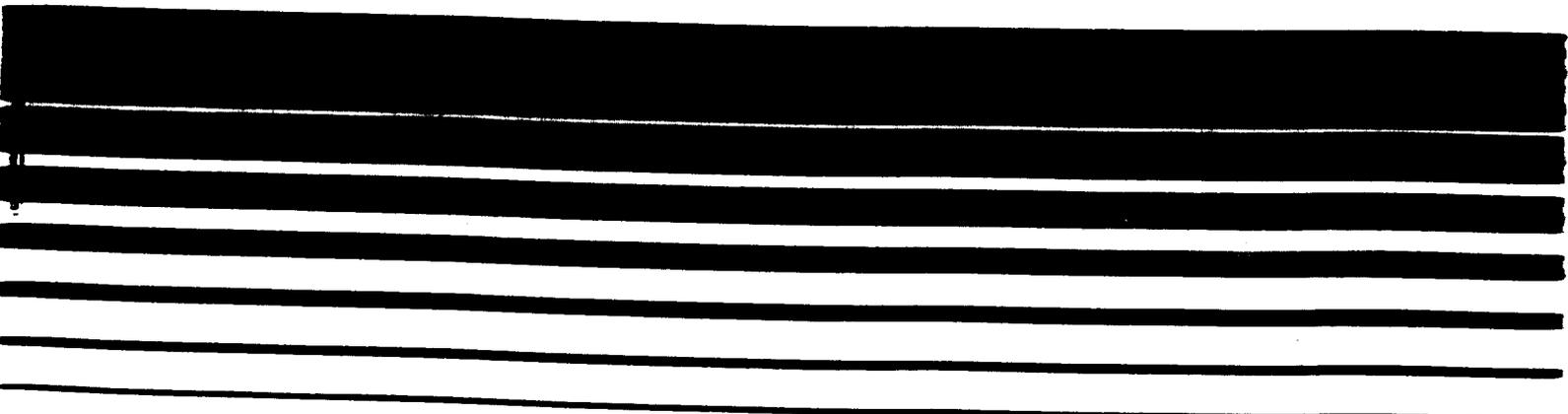
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PHARMACEUTICALS
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Control of Volatile Organic Emissions from Manufacture of Synthesized Pharmaceutical Products



2.0 PLANT CHARACTERIZATION AND REGULATORY APPROACH

2.1 SYNTHESIZED PHARMACEUTICAL MANUFACTURING PLANTS

The synthesis of medicinal chemicals may be done in a very small facility producing only one chemical or in a large integrated facility producing many chemicals by various processes. Most of the estimated 1200 plants are relatively small. Organic chemicals are used as raw materials and as solvents, and solvents constitute the predominant VOC emission from production. Plants differ in the amount of organics used; this results in widely varying VOC emission rates. Therefore, some plants may be negligible VOC sources while others are highly significant.

Nearly all products are made using batch operations. (In addition, several different products or intermediates are likely to be made in the same equipment at different times during the year; these products, then, are made in "campaigned" equipment. Equipment dedicated to the manufacture of a single product is rare, unless the product is made in large volume.)

Basically, production of a synthesized drug consists of one or more chemical reactions followed by a series of purifying operations. Production lines may contain reactors, filters, centrifuges, stills, dryers, process tanks, and crystallizers piped together in a specific arrangement. Arrangements can be varied in some instances to accommodate production of several compounds. A very small plant may have only a few pieces of process equipment but a large plant can contain literally hundreds of pieces, many of which are potential VOC emission sources.

Figure 2-1 shows a typical flow diagram for a batch synthesis operation. To begin a production cycle, the reactor may be water washed and perhaps dried with a solvent. Air or nitrogen is usually used to purge the tank after it is cleaned. In this example, solid reactants and solvent are charged to a 3,785 liter glass batch reactor equipped with a condenser (which is usually water-cooled). Still other volatile compounds may be produced as product or by-products. Any remaining unreacted VOC is distilled off. After the reaction and solvent removal are complete, the pharmaceutical product is transferred to a holding tank. After each batch is placed in the holding tank, three to four washes of water or solvent may be used to remove any remaining reactants and by-products. The solvent used to wash may also be evaporated from the reaction product. The crude product may then be dissolved in another solvent and transferred to a crystallizer for purification. After crystallization, the solid material is separated from the remaining solvent by centrifugation. While in the centrifuge, the product cake may be washed several times with water or solvent. Tray, rotary, or fluid-bed dryers may then be employed for final product finishing.)

2.2 REGULATORY APPROACH

The plant characterization in the preceding section reveals the complexities of synthesized pharmaceutical manufacture. Each plant is unique, differing from other plants in size, types of products manufactured, amounts and types of VOC used, and air pollution control problems encountered. The dissimilarities make it impossible to define typical emission levels or emission factors for an average plant. This in turn prevents identifying in this document which sources definitely need to be controlled and how much overall emission reduction can be effected.

With this in mind, it appears that a reasonable approach to regulation is to investigate emission levels and control options for a given plant on a plant by plant basis. The individual investigations would be begun by first determining which plants are significant VOC emitters and within such plants which process emission points are largest.

Emission data for pharmaceutical plants are scarce. Therefore, emission estimates will have to be obtained through other means. One way is to have plants submit solvent purchase and use information similar to that tabulated in Appendix A. The information in the Appendix resulted from a survey of 26 pharmaceutical manufacturers concerning amounts and types of VOC used and the ultimate disposition for each. As shown in the tables, estimates for air emissions were provided. It is acknowledged that these are only material balance estimates; nonetheless, they should be of sufficient accuracy to answer the question of whether or not the plant is a significant source.

Plants concluded to be significant VOC emitters would be candidates for a control program. The next step is to account for the bulk of total plant emissions by determining emissions from individual pieces of process equipment. Common methods are sampling and analysis of vent streams, material balance, and theoretical calculation. Many vents are neither easily nor inexpensively sampled, and in some instances material balances will not be satisfactory. Therefore, theoretical evaluations may have to be conducted. Equations are presented in Appendix B that will aid in calculating potential emissions from process operations. Because of the assumptions underlying the equations, calculated values will tend to represent maximum possible emissions from an operation.

Especially in larger plants, attempts to sample, perform material balances, or calculate emissions from all plant vents would be an expensive and time consuming task. It would be better to concentrate on the larger vents, which are

3.0 EMISSION SOURCES AND APPLICABLE SYSTEMS OF EMISSION REDUCTION

Compounds typically emitted during pharmaceutical manufacture are listed in the tables in Appendix A. The list is not exhaustive but does account for the great majority of VOC emissions from plants reporting. These compounds are commonly used as solvents, although at times they may be used as raw materials. Emissions of VOC's formed during reaction are estimated to contribute only a small fraction to total emissions.

Volatile organic compounds may be emitted from a variety of sources within plants synthesizing pharmaceutical products. Because of the number of sources, the discussion of emissions and applicable controls is organized by process component. (The following process components have been identified as VOC sources and are discussed in this chapter: reactors, distillation units, dryers, crystallizers, filters, centrifuges, extractors, and tanks.)

3.1 REACTORS

3.1.1 Reactor Description and Operation

The typical batch reactor is glass lined or stainless steel and has a capacity of 2,000 to 11,000 liters (500-3000 gallons). For maximum flexibility, the tanks are usually jacketed to permit temperature control of reactions. Generally, each is equipped with a vent which may discharge through a condenser. They can be operated at atmospheric pressure, elevated pressure, or under vacuum. Because of their flexibility, reactors may be used in a variety of ways. Besides hosting chemical reactions, they can act as mixers, heaters, holding tanks, crystallizers, and evaporators.

put on a condenser. To handle this situation most modern reactors or distillation units have condenser/receiver systems which are manifolded to permit using alternate coolants.⁴

4.1.1 Condenser Performance

Any component of any vapor mixture can be condensed if brought to equilibrium at a low enough temperature. The temperature necessary to achieve a given solvent vapor concentration is dependent on the vapor pressure of the compound.

When cooling a two-component vapor where one component can be considered noncondensable, for example, a solvent-air mixture, condensation will begin when the temperature is reached where the vapor pressure of the volatile component is equal to its partial pressure. The point where condensation first occurs is called the dew point. As the vapor is cooled further, condensation continues and the partial pressure stays equal to the vapor pressure. The less volatile a compound, that is, the higher the normal boiling point, the lower will be the amount that can remain vapor at a given temperature.)

In cases where the solvent vapor concentration is high, for example, from the desorption cycle of a carbon adsorber, condensation is relatively easy. However, for sources where concentrations are typically below 25 percent of the lower explosive limit (LEL), condensation is economically infeasible.

If the relationship between VOC vapor pressure and temperature is known, the removal efficiency of a condenser can be estimated. The following method may be used to estimate removal efficiency. This method is applicable to gas streams containing a single condensable VOC component.)

Emission Reduction Calculation Method

1. Make up a Cox chart for the VOC using vapor pressure and temperature data from a suitable reference book and specially designed graph paper.⁵ An example

It is sometimes simpler to calculate the vapor pressure of a VOC at one temperature, rather than plotting a Cox chart. This can be done by the use of Antoine's equation:

$$\text{Log}_{10} P_i = a - \left(\frac{b}{c + T_i} \right)$$

where P_i = vapor pressure of the VOC;
 T_i = temperature of the system, °C;
a, b, c = Antoine equation constant from Lange's Handbook of Chemistry.⁶

The calculation methods for gases containing more than one condensable component are complex, particularly if there are significant departures from ideal behavior of the gases and liquids. As a simplification, the temperature necessary for control by condensation can be roughly approximated by the weighted average of the temperatures necessary for condensation of each VOC considered separately but at concentrations equal to the total organic concentration.

4.1.2 Applicability

Condensers work best on gas streams that are or nearly are saturated with the condensable VOC. Many streams in synthesized pharmaceutical manufacturing facilities fit this description. Condensers are less attractive control options when the gas stream is dilute or far from saturation. In this case considerable cooling would be required just to bring the stream to the saturation point, and additional cooling would be required to actually condense the VOC. In these situations, other control techniques may be better choices.

Sometimes condenser performance may be limited by characteristics of condensable components. For example, the lower temperature limit for condenser operation will be the point where one of the condensables first freezes. Operating below that point would result in freezing water or VOC (as the case may be) to condenser tubes or walls rendering them ineffective as heat transfer surfaces.

Section 5
COST ANALYSIS

5.1 INTRODUCTION

5.1.1 Purpose

This chapter presents capital and annualized cost estimates for equipment to control VOC emissions from plants manufacturing synthesized pharmaceutical products. Because the amount and type of emissions vary widely from plant to plant, each control application will be unique. Therefore, in some situations, control system construction materials, operating conditions, installation expenses, etc. will be different from those assumed in calculating costs for this chapter. In instances where regulatory decisions hinge on the cost of control, it would be proper to consider additional information that may more accurately reflect control costs for the plant in question.

5.1.2. Scope

The preceding section described systems for controlling emissions from the following sources in this industry: storage and transfer operations, reactors, crystallizers, centrifuges, filters, dryers, and distillation condensers. Table 5-1 lists the 14 techniques for controlling these sources that are analyzed in terms of capital and operating costs in this section. The table presents the emission sources and appropriate control techniques and their expected VOC control efficiencies.

The control costs are developed for typical pharmaceutical operations within typical size ranges. In practice, however, it may be possible for one device to control more than one emission source.

Annualized emissions and their reductions cannot presently be quantified because of the variety of pharmaceutical manufacturing operations, the many kinds and concentrations of organic compounds, and the frequent use of batch