

heavy metals such as copper and zinc to precipitate the product as a metal salt from the aqueous broth, after which the broth is filtered and the product is extracted from the solid residue. Ion exchange or adsorption involves removal of the product from the broth using solid materials such as ion exchange resin, adsorptive resin or activated carbon to bond with the product. The product is extracted from the solid phase material using solvent extraction followed by solvent evaporation.

2. Biological and Natural Extraction

Biological and natural extraction is used to manufacture pharmaceutically active ingredients whose molecular structure is too complex for chemical synthesis or fermentation methods. Extraction involves the collection and processing of large volumes of plant or animal matter to produce small quantities of product. Initially, this large volume material is subject to a large, usually organic solvent-based, extraction procedure to obtain a first product cut or extraction. This cut is purified in many successive extraction operations. At each stage of the extraction process, the volume of material used becomes smaller. In the end, the volume of product may be only a few thousandths of the mass of material handled in the earlier procedures. Generally, the yield from extraction procedures is very small and pharmaceutical companies use extraction only when they have no other alternative.

Recently, pharmaceutical manufacturers have been developing bioengineered microorganisms that can produce pharmaceutically active ingredients. Pharmaceutical manufacturers sometimes use extraction procedures to obtain and purify these ingredients, but EPA understands generally that the amounts of water and solvents used in these procedures at this time are minimal. Nonetheless, EPA is soliciting information and data to better characterize wastewaters from these operations (see Section XIV at solicitation number 11.0).

3. Chemical Synthesis

Chemical synthesis involves the use of a series of chemical reactions to produce pharmaceutically active ingredients, usually starting with common feedstock chemicals as raw materials. The product of each successive chemical reaction then becomes the reactant in the next chemical reaction until the final reaction step of the synthesis is reached when the pharmaceutically active

ingredient product is generated. More pharmaceutically active ingredients are manufactured by chemical synthesis than by any other process.

4. Mixing/Compounding/Formulating

Before active ingredients can be used as pharmaceuticals, they must be prepared in dosage forms. The primary dosage forms utilized by the industry include tablets, capsules, liquids and ointments. For example, in tablet-making, manufacturers blend pharmaceutically inactive materials filler (e.g., starch) and binder (e.g., corn starch) with the active ingredient(s) and form tablets using a tablet press machine. Mixing, compounding, and formulating operations are utilized by more plants than any other process operation.

VIII. Summary of Data Gathering Efforts

A. Technical and Economic Data

1. 1989 Screener Survey of the Pharmaceutical Industry

In 1988, the Agency developed a short questionnaire for distribution to all known or suspected pharmaceutical manufacturers. The purpose of the questionnaire was to identify facilities that could be affected by future effluent limitations guidelines and standards applicable to the pharmaceutical manufacturing industry. The Information Collection Review (ICR) package for this questionnaire was sent to OMB in May 1989 and approved in June 1989. The questionnaire was sent to 1163 facilities in July of 1989. The Agency received 962 responses.

2. 1990 Pharmaceutical Manufacturing Industry Survey

In early 1989, EPA began to develop a questionnaire to gather the technical and financial information necessary for this rulemaking. EPA met with industry representatives during the questionnaire development process in an effort to keep the industry informed of the Agency's plans and to solicit informed comments on questionnaire design. Before pretesting the questionnaire, EPA sent a preliminary version of the questionnaire to the Pharmaceutical Manufacturers Association (now known as the Pharmaceutical Research and Manufacturers of America) for distribution and review by representatives of member companies. The Agency then incorporated all appropriate comments of the industry representatives into a pretest version of the questionnaire. In 1990, EPA sent pretest versions of the questionnaire to eight facilities for response and

comment. Along with their responses, the pretest candidates provided information on the amount of time required to complete the questionnaire and suggestions for improving the questionnaire as an information gathering instrument.

The pretest suggestions were used to develop a final version of the questionnaire, which was part of an ICR package that was sent to OMB for approval in May 1990. In August of that year, OMB cleared part A (technical section) of the questionnaire and some questions in part B (economic and financial) but denied clearance for most of the part B plant-specific financial and economic questions. In order to accommodate OMB's and industry's concerns about the need for responses to plant-specific economic and financial questions, the Agency developed a certification procedure. This procedure allowed industry respondents to certify that future pharmaceutical category regulations would not impact their facility above a certain dollar amount. A respondent making the certification was not required to respond to most of the part B questions.

In May 1991, the Agency submitted a revised ICR package to OMB, including the certification option discussed above. OMB approved the questionnaire and EPA sent the final questionnaire to 280 facilities in September 1991. EPA received responses from 244 of the 304 facilities still engaged in pharmaceutical manufacturing with solvent use.

3. Sampling and Analytical Program

Between 1986 and 1991, EPA conducted a sampling program at 13 pharmaceutical manufacturing facilities to: (1) Characterize the pollutants in the wastewater being discharged directly to surface waters and indirectly to POTWs; (2) generate pollutant treatment system performance data from facilities with well-operated advanced biological treatment systems (those systems attaining better than BPT annual average effluent quality); and (3) obtain treatability data from steam stripping units.

Prior to 1986, the Agency had focused on five conventional pollutants and 126 priority pollutants in the pharmaceutical manufacturing industry's wastewater. Beginning in 1986, the Agency expanded the analysis of pharmaceutical wastewater and wastewater treatment plant sludges to determine the presence and levels of all the pollutants on the "Industrial Technology Division (ITD) List of Analytes" (hereinafter, the "List of Analytes").