1. Introduction

On September 21, 1998, the U.S. Environmental Protection Agency (EPA) promulgated final effluent limitations guidelines and standards under the Clean Water Act (CWA). These regulations amended existing effluent limitations guidelines and standards codified at 40 Code of Federal Regulations (CFR) Part 439.

2. Overview of NPDES Program and National Pretreatment Program

This section presents a brief overview of the NPDES Permit program and the National Pretreatment Program. For more background information regarding EPA's programs to develop national standards for point source categories, refer to the U.S. EPA NPDES Permit Writer's Manual (EPA-833-B-96-003). In addition, a permit writer should also consult the Industrial User Permitting Guidance Manual (EPA-833/R-89-001).

3. Scope of 40 CFR Part 439

The revisions to the effluent limitations guidelines and standards promulgated on September 21, 1998 apply only to subparts A through D of the pharmaceutical manufacturing industry. Subpart E (Research) was not revised by the September 21, 1998 final regulations. Subpart E operations at stand-alone facilities or at manufacturing facilities with subpart A, B, C, and/or D operations continue to be subject to the existing BPT effluent limitations guidelines for subpart E, revised October 27, 1983 (40 CFR 439.52).

1. Introduction

On September 21, 1998, the U.S. Environmental Protection Agency (EPA) promulgated final effluent limitations guidelines and standards under the Clean Water Act (CWA). These regulations amended existing effluent limitations guidelines and standards codified at 40 Code of Federal Regulations (CFR) Part 439.

EPA had first promulgated regulations for the pharmaceutical manufacturing point source category in 1976 (41 Federal Register (FR) 50676) for the following five subcategories of the industry:

- Subpart A - Fermentation Products Subcategory
- Subpart B - Extraction Products Subcategory
- Subpart C - Chemical Synthesis Subcategory
- Subpart D - Mixing, Compounding, and Formulating Subcategory
- Subpart E - Research Subcategory

The 1976 regulations established monthly best practicable control technology currently available (BPT) limitations for biochemical oxygen demand (BOD_5) and chemical oxygen demand (COD) for all subcategories. EPA did not establish daily maximum effluent limitations for these parameters. EPA established a pH limitation within the range of 6.0 to 9.0 standard units. The regulations also set maximum 30 day average concentration-based limitations for total suspended solids (TSS) for subparts B, D and E. EPA established no TSS limitations for subparts A and C.

On October 27, 1983, at 48 FR 49808, EPA revised the subcategory names to those used currently and promulgated revised BPT limitations as well as best available technology economically achievable (BAT) limitations and pretreatment standards for new sources (PSNS) and pretreatment standards for existing sources (PSES) for subparts A thru D to cover the toxic pollutant cyanide, conventional pollutants, BOD_5, TSS and pH and the nonconventional pollutant COD. The 1983 regulations retained the regulations for BOD_5 and COD established in 1976 but added concentration-based limitations for these parameters applicable to subparts B, D and E. EPA also promulgated BPT, BAT, PSES and PSNS for pH (6.0-9.0) and BAT concentration-based limitations controlling the discharge of cyanide for subpart A through D. While the Agency also had proposed new source performance standards (NSPS) for BOD_5, TSS and pH in the October 1983 notice, it did not adopt NSPS for these parameters. On December 16, 1986, at 51 FR 45094, EPA promulgated best conventional pollutant control technology (BCT) effluent limitations guidelines for BOD_5, TSS and pH for subparts A thru D. That final rule set BCT effluent limitations equal to the existing BPT effluent limitations guidelines for BOD_5, TSS, and pH.

The 1998 regulations amended the effluent limitations guidelines for subparts A through D. Facilities or operations involved in research continue to be subject to the regulations in subpart E.

Direct discharging facilities with operations in the four manufacturing subcategories were required to comply with the 1998 regulations by November 20, 1998. The compliance date for existing source indirect discharging facilities was as soon as possible, but no later than September 21, 2001. Permit writers and control authorities are required to issue permits (or other control mechanisms) to ensure that affected facilities are complying with the new regulations. **This document is specifically written to provide guidance to permitting and pretreatment control authorities in issuing National Pollutant Discharge Elimination System (NPDES) permits and permits (or other control mechanisms) to pharmaceutical facilities with manufacturing operations in the four subcategories discussed above.**
Permitting or pretreatment control authorities will need to determine which facilities fall under 40 CFR Part 439 and how to write the permits or pretreatment agreements for these facilities to ensure their

compliance under the new regulations. EPA has provided information in Sections 2 - 10 to help permit writers and pretreatment control authorities in this process.

- **Section 2** presents a brief overview of the NPDES Program and the National Pretreatment Program;
- **Section 3** presents the scope of the promulgated final effluent limitations guidelines and standards and describes which facilities are subject to the rule;
- **Section 4** discusses the pollutants regulated under 40 CFR Part 439 for facilities with operations in subparts A, B, C, D and E;
- **Section 5** discusses the technology bases for the effluent limitations guidelines and standards promulgated for facilities with operations in subparts A, B, C, D, and E;
- **Section 6** discusses the in-process and end-of-pipe points where affected facilities must demonstrate compliance with the rule;
- **Section 7** presents the effluent limitations guidelines and standards promulgated for facilities with operations in subparts A, B, C, D, and E;
- **Section 8** walks through the process of establishing permit limits for facilities with operations in subparts A, B, C, D, and E;
- **Section 9** presents five case studies as examples for establishing permits for facilities with operations in subparts A, B, C, D, and E; and
- **Section 10** contains a list of resources for additional guidance in establishing permits for affected facilities.

EPA's objective here is to provide guidance on issuing permits and pretreatment control mechanisms to facilities with operations in the above subcategories in an easy-to-read format. While this manual attempts to address many permitting issues and situations that may be covered by the regulation, there are other sources that may be helpful in developing permits/pretreatment control mechanism for facilities with operations in subparts A, B, C, D, and E. The manual identifies and references other sources throughout the text that can be accessed to get additional guidance. Also included in Section 10 is a list of these and other sources and how to order them, as well as a list of EPA and other authorities to contact for more guidance.

2. Overview of NPDES Program and National Pretreatment Program

This section presents a brief overview of the NPDES Permit program and the National Pretreatment Program. For more background information regarding EPA's programs to develop national standards for point source categories, refer to the *U.S. EPA NPDES Permit Writer's Manual* (EPA-833-B-96-003). In addition, a permit writer should also consult the *Industrial User Permitting Guidance Manual* (EPA-833/R-89-001).

2.1 What is the NPDES Permit Program?

Section 301(a) of the CWA prohibits the discharge of pollutants except in compliance with CWA Section 402, among other sections. Section 402 authorizes the issuance of NPDES permits for direct dischargers (i.e., existing or new industrial facilities that discharge process wastewaters from any point source into receiving waters). Permit writers must develop NPDES permits to control these discharges, using effluent limitations guidelines and standards and water-quality based effluent limitations.

2.1.1 What Are Effluent Limitations Guidelines and Standards?

EPA establishes effluent limitations guidelines and standards to require a minimum level of treatment for industrial point sources. EPA bases its effluent limitations guidelines and standards on the demonstrated performance of model process and treatment technologies that are found to be economically achievable by an industrial category or subcategory. Although effluent limitations guidelines and standards are based on the performance of model process and treatment technologies, EPA does not mandate the use of specific technologies. Dischargers are free to use any available control technique to meet the limitations.

2.1.2 What Are Water-Quality-Based Effluent Limitations?

All receiving waters have ambient water quality standards that are established by the states or EPA to maintain and protect designated uses of the receiving water (e.g., aquatic life-warm water habitat, public water supply, primary contact recreation). Permit writers may find that the application of the effluent limitations guidelines result in pollutant discharges that exceed the water quality standards in particular receiving waters. In such cases, permit writers are required by the CWA and federal guidelines to develop more stringent water-quality-based effluent limitations (WQBELs) for the pollutant to ensure that the water quality standards are met. States can use the total maximum daily load (TMDL) process as one way of quantifying the allowable pollutant loadings in receiving waters, based on the relationship between pollution sources and in-stream water quality standards.

Because EPA and state permitting authorities are familiar with their respective water quality standards and knowledgeable in waste load allocations and other procedures to maintain water quality standards these issues are not addressed in this document. To learn more about how TMDLs are developed, refer to *Guidance for Water-Quality-Based Decisions: The TMDL Process* (EPA 440/4-91-001). To learn how to apply water quality standards in NPDES permits, refer to the *Technical Support Document for Water Quality-Based Toxics Control* (EPA/505/2-90-001).

2.2 What Is the National Pretreatment Program?

The CWA requires EPA to promulgate nationally applicable pretreatment standards that restrict pollutant discharges from facilities that discharge wastewater indirectly through sewers flowing to publicly-owned treatment works (POTWs). (See Section 307(b) and (c), 33 U.S.C. 1317(b) & (c)). National pretreatment standards are established for those pollutants in wastewater from indirect dischargers that may pass

through, interfere with, or are otherwise incompatible with POTW operations. Generally, pretreatment standards are designed to ensure that wastewaters from direct and indirect industrial dischargers are subject to similar levels of treatment. In addition, all POTWs that must develop local pretreatment programs are required to implement specific local treatment limits applicable to their industrial indirect dischargers to prevent pass through and interference and to prevent the introduction into POTWs of certain pollutants (e.g., pollutants that create a fire or explosion hazard, corrosion or pollutants that result in toxic gases that may cause acute worker health or safety problems). All other POTWs must establish local limits to prevent pass through or interference to ensure compliance with the POTW's NPDES permit or sewage sludge uses. (See 40 CFR 403.5). CWA Section 402(b)(8) requires that permits for certain POTWs receiving pollutants from significant industrial sources subject to pretreatment standards under CWA Section 307(b) must establish a pretreatment program to ensure compliance with these standards. EPA has published regulations to define the requirements of this POTW pretreatment control program.

2.2.1 What Are National Pretreatment Standards?

40 CFR Part 403 presents the general pretreatment regulations for existing and new sources of pollution. The following table presents the content of each section of 40 CFR Part 403.

Table 2-1: Contents of 40 CFR Part 403

40 CFR Section	Content
403.1	Purpose and applicability
403.2	Objective of general pretreatment regulations
403.3	Definitions
403.4	State or local law
403.5	National pretreatment standards: prohibited discharges
403.6	National pretreatment standards: categorical standards
403.7	Removal credits
403.8	Pretreatment program requirements: development and implementation by POTW
403.9	POTW pretreatment programs and/or authorization to revise pretreatment standards: submission for approval
403.10	Development and submission of NPDES state pretreatment programs
403.11	Approval procedures for POTW pretreatment programs and POTW granting of removal credits.
403.12	Reporting requirements for POTWs and industrial users
403.13	Variances from categorical pretreatment standards for fundamentally different factors
403.14	Confidentiality
403.15	Net/gross calculation
403.16	Upset provision
403.17	Bypass
403.18	Modification of POTW pretreatment programs

40 CFR 403.5(a)(1) generally prohibits users of a POTW (indirect dischargers) from discharging pollutants to the POTW that cause pass-through or interference. Pass-through is defined as a discharge that exits the POTW into waters of the United States in quantities or concentrations that, alone or in conjunction with a discharge or discharges from other sources, causes a violation of any requirement of the POTW's NPDES permit. Interference is defined as a discharge that, alone or in conjunction with a discharge or discharges from other sources, both: (1) inhibits or disrupts the POTW, its treatment processes, or its operations; or its sludge processes, use, or disposal; and (2) causes the POTW to violate any requirement of its NPDES permit, or prevents sewage sludge use or disposal (40 CFR 403.3).

40 CFR 403.5(c) and 40 CFR 403.8 specify that POTWs that have flows greater than 5.0 million gallons per day (mgd) and that receive pollutants that pass through or interfere with their operations or are otherwise subject to categorical pretreatment standards must develop and enforce local limits to comply with the National Pretreatment Standards.

2.3 Applicability of Effluent Limitations Guidelines and Standards

Pharmaceutical facilities that discharge waters to receiving streams or POTWs are required to meet one (or more) of the following effluent limitations guidelines and standards established by the CWA.

Table 2-2: Description of Effluent Limitations Guidelines and Standards

Acronym	Guideline or Standard	Applicable pollutants and discharge type [a]
BPT	Best practicable control technology currently available	Conventional pollutants at an existing direct discharger [b]
BCT	Best conventional pollutant control technology	Conventional pollutants at an existing direct discharger
BAT	Best available technology economically achievable	Toxic and nonconventional pollutants at an existing direct discharger
NSPS	New source performance standards	Conventional, toxic, and nonconventional pollutants at a new source, direct discharger
PSES	Pretreatment standards for existing sources	Toxic and nonconventional pollutants at an existing indirect discharger
PSNS	Pretreatment standards for new sources	Toxic and nonconventional pollutants at a new source, indirect discharger

[a] These terms are defined in the glossary.
[b] Nonconventional and priority pollutants can also be controlled by BPT regulations.

With the September 21, 1998 promulgation of the regulation, EPA has revised BPT, BAT, NSPS, PSES, and PSNS for the pharmaceutical manufacturing point source category. **Note that although this document focuses on these new effluent limitations guidelines and standards, those limitations and standards that were not revised remain in effect unless otherwise stated in the September 21, 1998 promulgated rule.** Table 2-3 summarizes the applicability of these effluent limitations guidelines and standards.

Table 2-3: Effluent Limitations Guidelines and Standards Applicable to Each Program

Program	Type of Discharger	Existing or New Source?	Applicable Guidelines and Standards Previously Established	Additional Guidelines and Standards (from 9/21/98 Rule)
NPDES Permit Program	Direct Discharger	Existing Source	BCT BPT BAT	 BPT BAT
		New Source	NSPS	NSPS
National Pretreatment Program	Indirect Discharger	Existing Source	PSES	PSES
		New Source	PSNS	PSNS

3. Scope of 40 CFR Part 439

The revisions to the effluent limitations guidelines and standards promulgated on September 21, 1998 apply only to subparts A through D of the pharmaceutical manufacturing industry. Subpart E (Research) was not revised by the September 21, 1998 final regulations. Subpart E operations at stand-alone facilities or at manufacturing facilities with subpart A, B, C, and/or D operations continue to be subject to the existing BPT effluent limitations guidelines for subpart E, revised October 27, 1983 (40 CFR 439.52).

Pharmaceutical manufacturers use many different raw materials and manufacturing processes to create a wide range of products with therapeutic value. Pharmaceutical products are produced by a number of processes. These include the following: chemical synthesis, fermentation, extraction from naturally occurring plant or animal substances, mixing, compounding, and formulating operations, or by refining a technical grade product.

The regulations establish different requirements depending on whether a manufacturing operation is an existing source or a new source. The pharmaceutical manufacturing industry regularly may make equipment and process changes to existing manufacturing processes. Consequently, permitting authorities should carefully review EPA regulations before deciding whether a particular source of discharge is an *existing source* or a *new source*.

The definition of new source for direct dischargers is at 40 CFR 122.2 and the new source definition for indirect dischargers is at 40 CFR 403.3. Direct discharging pharmaceutical new sources have to meet more stringent BOD_5 and TSS standards than existing sources. In the case of indirect facilities, PSES and PSNS are identical.

The pharmaceutical guidelines and standards regulation applies generally, but not exclusively, to process wastewater discharges resulting from the manufacture of pharmaceutical products and from pharmaceutical research reported within three specified U.S. Department of Commerce Bureau of the Census Standard Industrial Classification system (SIC) groups and to the manufacture of certain pharmaceutical products not reported under the three SIC codes. The regulation does not apply to dischargers from the manufacture of pharmaceutical products included in eight other SIC subgroups and three other identified pharmaceutical products. Which pharmaceutical product process wastewaters are, and are not, subject to this regulation is explained in further detail at 40 CFR 439.0. The currently applicable regulations may be found in any edition of the CFR dated July, 1999 or later.

A logic chart presenting the applicability of the September 21, 1998 pharmaceutical effluent limitations guidelines and standards is presented in Figure 3-1.

The pharmaceutical products, processes, and activities covered by this regulation include:

- Products covered by the U.S. Department of Commerce, Bureau of the Census Standard Industrial Classification (SIC) Code No. 2836, with the exception of diagnostic substances. (Products covered by SIC Code No. 2836 were formerly covered under the 1977 SIC Code No. 2831.)

- Medicinal chemicals and botanical products covered by SIC Code No. 2833.

- Pharmaceutical products covered by SIC Code No. 2834.

- All fermentation, natural extraction, chemical synthesis and formulation products considered to be pharmaceutically active ingredients by the Food and Drug Administration (21 CFR 210.3(b)(7)) that are not covered by SIC Code Nos. 2833, 2834, or 2836.

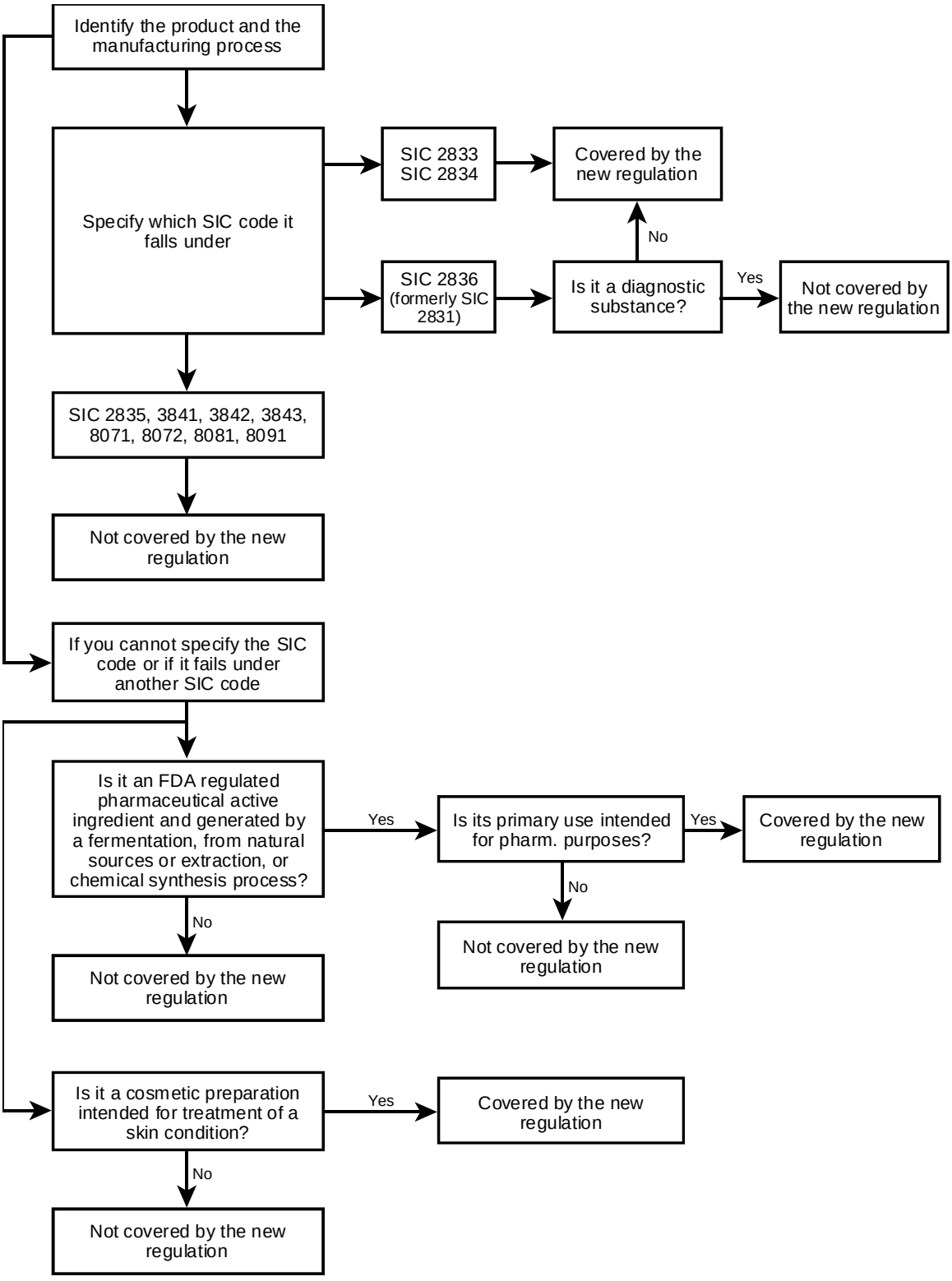

Figure 3-1: Product Applicability Basis of the September 21, 1998 Pharmaceutical Manufacturing Effluent Limitations Guidelines

- Multiple end-use products derived from pharmaceutical manufacturing operations (e.g., components of formulations, intermediates, or final products, provided that the primary use of the product is intended for pharmaceutical purposes).

- Products not covered by SIC Code Nos. 2833, 2834, and 2836 or other categorical limitations and standards if they are manufactured by a pharmaceutical manufacturer by processes that generate wastewaters that in turn closely correspond to those of pharmaceutical products. (An example of such a product is citric acid.)

- Cosmetic preparations covered by SIC Code No. 2844 that contain pharmaceutically active ingredients or ingredients intended for treatment of some skin condition. (This group of preparations does not include products such as lipsticks or perfumes that serve to enhance appearance or to provide a pleasing odor, but do not provide skin care. In general, this also excludes deodorants, manicure preparations, shaving preparations and non-medicated shampoos that do not function primarily as a skin treatment.)

Products or activities specifically excluded from the pharmaceutical manufacturing category are:

- Surgical and medical instruments and apparatus reported under SIC Code No. 3841.

- Orthopedic, prosthetic, and surgical appliances and supplies reported under SIC Code No. 3842.

- Dental equipment and supplies reported under SIC Code No. 3843.

- Medical laboratories services reported under SIC Code No. 8071.

- Dental laboratories services reported under SIC Code No. 8072.

- Outpatient care facility services reported under SIC Code No. 8081.

- Health and allied services reported under SIC Code No. 8091, and not classified elsewhere.

- Diagnostic devices other than those reported under SIC Code No. 3841.

- Animal feeds that include pharmaceutical active ingredients such as vitamins and antibiotics, where the major portion of the product is non-pharmaceutical, and the resulting process wastewater is not characteristic of process wastewater from the manufacture of pharmaceutical products.

- Foods and beverage products fortified with vitamins or other pharmaceutical active ingredients, where the major portion of the product is non-pharmaceutical, and the resulting process wastewater is not characteristic of process wastewater from the manufacture of pharmaceutical products.

Since the final pharmaceutical manufacturing regulations were promulgated on Sept. 21, 1998, many pharmaceutical and other manufacturers have begun producing bioengineered products using bioengineering techniques developed from bench scale research operations. While these operations are generally similar to those of Part 439, the provisions of these subparts do not apply to these bioengineering operations. Thus, permit writers should develop applicable limitations and standards for these operations based on best professional judgment. The limitations and standards in Part 439 may be a useful resource to the permit writer in determining appropriate limitations and standards when the character of the wastewater from the bioengineering operations is similar to that of the Part 439 wastewater from like operations.

QA/QC laboratory wastewaters which do not come in contact with pharmaceutical manufacturing operations and are discharged separately (i.e., are not commingled with other regulated waste streams upstream of the compliance monitoring point) are excluded from the subpart A, B, C, and D limitations.

In addition, facilities regulated by the organic chemicals, plastics and synthetic fibers (OCPSF) effluent limitations guidelines and standards (40 CFR Part 414) that manufacture pharmaceutical products and intermediates will be subject to the OCPSF effluent limitations guidelines and standards provided that the wastewater generated as a result of the manufacture of pharmaceutical products and intermediates is less than 50% of the total process wastewater flow at the facility.

Example 1: A facility manufactures medicated shampoo that treats dandruff and is classified in SIC Code 2844. Is this facility covered under the pharmaceutical September 21, 1998 regulation?

This facility would be subject to the pharmaceutical regulation since it manufactures products which contain a pharmaceutically active ingredient generated by a fermentation, natural source (plant and animal), extraction, chemical synthesis, or formulation process.

Example 2: A facility manufactures herbal medicines that do not contain an FDA regulated pharmaceutically active ingredient (as defined in 21 CFR 210.3(b)(7)). Is this facility subject to the pharmaceutical September 21, 1998 regulation?

This facility would not be subject to the pharmaceutical regulation since it does not manufacture or process a pharmaceutically active ingredient.