United States
Environmental Protection
Agency

Office of Water
Mail Code 4303

EPA 821-B-99-003
August 1999

Analytical Method Guidance for the
Pharmaceutical Manufacturing
Point Source Category

Contents

Contents (Continued)

Tables

Disclaimer

This *Analytical Methods Guidance* (Guidance) is provided to help implement national policy on effluent limitations guidelines and standards for the pharmaceutical industry. This Guidance does not, however, substitute for the CWA or EPA's regulations, nor is it a regulation itself. Thus, it cannot impose legally binding requirements on EPA, States, or the regulated community and may not apply to a particular situation based upon case-specific circumstances. EPA and State decision makers retain the discretion to adopt approaches on a case-by-case basis that differ from this Guidance where appropriate. EPA may change this Guidance in the future.

Executive Summary

On September 21, 1998, the U.S. Environmental Protection Agency (EPA) promulgated revised regulations for the pharmaceutical industry to control both effluent discharges and air emissions. The purpose of this Guidance is to assist dischargers in the selection of appropriate methods for determination of pollutants in wastewater from pharmaceutical facilities with operations in fermentation; extraction; chemical synthesis; mixing, compounding, and formulating; and research. The material presented is intended solely for guidance and does not alter any statutory requirements.

1 Introduction

On September 21, 1998, the U.S. Environmental Protection Agency (EPA) promulgated final effluent limitations guidelines and standards at 40 CFR 439 under the Clean Water Act (CWA) for the following four subcategories of the pharmaceutical industry:

Subcategory A Fermentation
Subcategory B Extraction
Subcategory C Chemical Synthesis
Subcategory D Mixing, Compounding, and Formulating

EPA also reformatted and clarified language without revision to certain specified provisions in the Subcategory E - Research subcategory. This Guidance is specifically written to help in selecting appropriate methods to measure pollutants in wastewater from pharmaceutical facilities that fall within the purview of the subcategories listed above. To help in this process, EPA has addressed the following topics:

- **Section 2** presents an overview of the parameters regulated in the final effluent limitations guidelines and standards and approved methods to analyze for these parameters;
- **Section 3** discusses flexibility in performing the approved analytical methods and equivalence among methods;
- **Section 4** discusses how to solve matrix problems;
- **Section 5** walks through the process of choosing the most appropriate analytical method to use in analyzing for regulated parameters; and
- **Section 6** presents responses to specific concerns from industry regarding analytical methods.

EPA hopes that this Guidance provides help on the use of analytical methods when measuring for parameters from facilities with operations in the above mentioned subcategories in an easy-to-read format. While this Guidance attempts to address issues and situations that may be covered by the regulation, there are other sources that one may wish to consult in selection of an analytical method for facilities that conduct Subcategory A, B, C, D and E operations. Therefore, this Guidance identifies and references other sources throughout the text that provide additional guidance. Also included in Section 7 is a list of these and other sources, and a list of EPA and other authorities to contact for more guidance.

2 Overview of Approved Analytical Methods for Complying with the Pharmaceutical Regulation

This section provides a brief overview of the parameters (analytes) regulated under the pharmaceutical effluent limitations guidelines and standards. It also provides a description of approved analytical methods, and where these methods can be located. For more background information on the parameters regulated or the approved analytical methods, refer to the Pharmaceutical Manufacturing Category Effluent Limitations Guidelines, Pretreatment Standards, and New Source Performance Standards; Final Rule at 40 CFR Parts 136 and 439.

What parameters are being regulated?

In the September 21, 1998 rule, EPA established effluent limitations guidelines and standards for conventional, toxic, and nonconventional pollutants found in wastewater from pharmaceutical facilities in Subcategories A, B, C, and D. Table 2-1 presents a comprehensive list of pollutants regulated for these facilities; however, not all pollutants listed are regulated at each regulatory level. These pollutants are also listed in 40 CFR 439.

What are the approved analytical methods for the regulated parameters?

Dischargers are required to use the test methods promulgated in tables at 40 CFR 136.3 or incorporated by reference in those tables, when available, to monitor pollutant discharges from the pharmaceutical manufacturing industry, unless specified otherwise by the permitting authority. The full list of approved test methods for the conventional, toxic, and non-conventional pollutants regulated under the effluent limitations guidelines and standards for the pharmaceutical industry are presented in Table 2-2. Applicable drinking water methods that have been promulgated at 40 CFR Part 141 and American Society for Testing Materials (ASTM) Methods D3371, D3695, and D4763 have been incorporated by reference in 40 CFR 136.3. Also, EPA Methods 1666, 1667, and 1671 have been promulgated with the final

pharmaceutical effluent limitations guidelines and standards and may be used to monitor discharges from the pharmaceutical industry.

In addition EPA expects to promulgate a performance-based measurement system (PBMS) for water programs in the Federal Register during 1999. PBMS is designed to increase the flexibility to select suitable analytical methods for compliance monitoring, and would reduce the need for prior EPA approval of methods. Under PBMS, EPA would specify "performance criteria" for methods, which the Agency would derive from the existing approved methods. For additional information on PBMS, see the proposed rule published March 28, 1997 (62 FR 14976) and the notice of intent to adopt PBMS Agency-wide, published October 6, 1997 (62 FR 52098).

Where can these approved analytical methods be found?

Some EPA test methods are published at 40 CFR 136, Appendix A, while other methods are available in compendia. Test methods for pharmaceutical pollutants of concern published at 40 CFR 136, Appendix A are methods 601, 602, 604, 612, 624, 625, 1624, and 1625. Compendia of pharmaceutical methods are available from the National Technical Information Services (NTIS) PB91-231480 and PB92-207703, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, Virginia 22161. The NTIS toll free number is 1-800-553-6847. These EPA methods are published in the following compendia:

- EPA Methods 1666, 1667, and 1671 - *Analytical Methods for the Determination of Pollutants in Pharmaceutical Manufacturing Industry Wastewater* (EPA 821-B-98-016). This compendium is also available from the pharmaceutical rulemaking action homepage on the World Wide Web.

- EPA Method 502.2 - *Methods for the Determination of Organic Compounds in Drinking Water* (EPA-600/4-88-039)

- EPA Method 524.2 - *Methods for the Determination of Organic Compounds in Drinking Water-Supplement II* (EPA-600/R-92-129)

ASTM test methods D3371, D3695, and D4763 are available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, Pennsylvania 19428-2959 (610-832-9500).

Table 2-1: Pollutants Regulated Under Effluent Limitations Guidelines and Standards[1]

Pollutants	Subcategory A	Subcategory B	Subcategory C	Subcategory D	Subcategory E
BOD_5	✓	✓	✓	✓	✓
Chemical oxygen demand (COD)	✓	✓	✓	✓	✓
pH	✓	✓	✓	✓	✓
TSS	✓	✓	✓	✓	✓
Acetone	✓	✓	✓	✓	
Acetonitrile	✓		✓		
Ammonia	✓		✓		
n-Amyl acetate	✓	✓	✓	✓	
Amyl alcohol	✓		✓		
Benzene	✓		✓		
n-Butyl acetate	✓		✓		
Chlorobenzne	✓		✓		
Chloroform	✓		✓		
Cyanide	✓		✓		
o-Dichlorobenzene	✓		✓		
1,2-Dichloroethane	✓		✓		
Diethylamine	✓		✓		
Dimethyl sulfoxide	✓		✓		
Ethanol	✓		✓		
Ethyl acetate	✓	✓	✓	✓	
n-Heptane	✓		✓		
n-Hexane	✓		✓		
Isobutyraldehyde	✓		✓		
Isopropanol	✓		✓		
Isopropyl acetate	✓	✓	✓	✓	
Isopropyl ether	✓		✓		
Methanol	✓		✓		
Methyl cellosolve	✓		✓		
Methyl formate	✓		✓		
Methyl isobutyl ketone (MIBK)	✓		✓		
Methylene chloride	✓	✓	✓	✓	
Phenol	✓		✓		

Table 2-1 (Continued)

Pollutants	Subcategory A	Subcategory B	Subcategory C	Subcategory D	Subcategory E
Tetrahydrofuran	✓		✓		
Toluene	✓		✓		
Triethylamine	✓		✓		
Xylenes	✓		✓		

[1]Not all pollutants are regulated at each regulatory level.

Table 2-2: Approved Test Methods

Pharmaceutical Pollutants	CAS Registry No.	Analytical Method Number	Minimum Level[1]
BOD_5	C-002	405.1	2 mg/L
COD	C-004	410.1	50 mg/L
		410.2	5 mg/L
		410.3	250 mg/L
		410.4	3 mg/L; 20 mg/L[2]
TSS	C-009	160.2	4 mg/L
pH	C-006	150.1	N/A
acetone (2-propanone)	67-64-1	D3695	**TBD**
		D4763	**TBD**
		524.2	**TBD**
		1624	50 µg/L
acetonitrile	75-05-8	1666	5 mg/L
		1671	50 mg/L
		D3371	**TBD**
		D3695	**TBD**
ammonia (as N)	1336-21-6	350.2	50 µg/L
		350.3	50 µg/L
		350.1	10 µg/L
n-amyl acetate	628-63-7	1666	5 µg/L
		D3695	**TBD**
n-amyl alcohol	71-41-0	1666	500 µg/L
		D3695	**TBD**
benzene	71-43-2	602	0.5 µg/L
		624	10 µg/L
		1624	10 µg/L
		D4763	**TBD**
		D3695	**TBD**
		502.2	**TBD**
		524.2	**TBD**
n-butyl-acetate	123-86-4	1666	5 µg/L
		D3695	**TBD**
tert-butyl alcohol	75-65-0	1666	100 µg/L

Table 2-2 (Continued)

Pharmaceutical Pollutants	CAS Registry No.	Analytical Method Number	Minimum Level[1]
chlorobenzene	108-90-7	601	1 µg/L
		602	0.5 µg/L
		624	20 µg/L
		1624	10 µg/L
		502.2	**TBD**
		524.2	**TBD**
chloroform	67-66-3	601	0.2 µg/L
		624	5.0 µg/L
		1624	10 µg/L
		502.2	**TBD**
		524.2	**TBD**
		551	**TBD**
cyanide(total)		335.2	**TBD**
		335.3	**TBD**
o-dichlorobenzene	95-50-1	601	0.5 µg/L
		602	1.0 µg/L
		612	5.0 µg/L
		624	ND
		625	5.0 µg/L
		1625	10 µg/L
		502.2	**TBD**
		524.2	**TBD**
1,2-dichloroethane	107-06-2	601	0.1 µg/L
		624	10 µg/L
		1624	10 µg/L
		D3695	**TBD**
		502.2	**TBD**
		524.2	**TBD**
diethylamine	109-89-7	1666	200 mg/L
		1671	50 mg/L
dimethyl sulfoxide	67-68-5	1666	100 mg/L
		1671	20 mg/L
ethanol	64-17-5	1666	20 mg/L
		1671	2 mg/L
		D3695	**TBD**

Table 2-2 (Continued)

Pharmaceutical Pollutants	CAS Registry No.	Analytical Method Number	Minimum Level[1]
ethyl acetate	141-78-6	1666	10 µg/L
		D3695	**TBD**
n-heptane	142-82-5	1666	10 µg/L
		D3695	**TBD**
n-hexane	110-54-3	1666	10 µg/L
		D3695	**TBD**
isobutyraldehyde	78-84-2	1666	10 µg/L
		1667	50 µg/L
isopropanol	67-63-0	1666	200 µg/L
		D3695	**TBD**
isopropyl acetate	108-21-4	1666	10 µg/L
		D3695	**TBD**
isopropyl ether	108-20-3	1666	5 µg/L
		D3695	**TBD**
methanol	67-56-1	1666	50 mg/L
		1671	2 mg/L
		D3695	**TBD**
Methyl Cellosolve®	109-86-4	1666	50 mg/L
		1671	20 mg/L
methylene chloride	75-09-2	601	1.0 µg/L
		624	10 µg/L
		1624	10 µg/L
		502.2	**TBD**
		524.2	**TBD**
methyl formate	107-31-3	1666	100 µg/L
4-methyl-2-pentanone (MIBK)	108-10-1	1624C	50 µg/L
		1666	10 µg/L
		D3695	**TBD**
		D4763	**TBD**
		524.2	**TBD**
phenol	108-95-2	604	0.5 µg/L
		625	5.0 µg/L
		1625	10 µg/L
		D4763	**TBD**

Table 2-2 (Continued)

Pharmaceutical Pollutants	CAS Registry No.	Analytical Method Number	Minimum Level[1]
n-propanol	71-23-8	1666	20 mg/L
		1671	50 mg/L
		D3695	**TBD**
tetrahydrofuran	109-99-9	1666	20 µg/L
		524.2	**TBD**
toluene	108-88-3	602	0.5 µg/L
		624	20 µg/L
		1624	10 µg/L
		D3695	**TBD**
		D4763	**TBD**
		502.2	**TBD**
		524.2	**TBD**
triethlyamine	121-44-8	1666	200 mg/L
		1671	50 mg/L
xylenes[3]	N/A	1624C	10 µg/L
		1666	10 µg/L, 5 µg/L

[1]Some analytical methods report a Method Detection Limit (MDL) only. This specifically applies to the 600-series methods. In those cases, EPA calculated a minimum level (ML) from the MDL originally reported in the method. The minimum level value was determined by multiplying the MDL by 3.18 and rounding to the nearest number in the series (1, 2, or 5) x 10^n, where n is an integer. In addition, EPA added MLs for the Method 1624C entries associated with 4-methyl-2-pentanone and xylenes. These Method 1624C MLs correspond to the reporting limits used in EAD's analytical databases.

[2]For Method 410.4, two MLs are listed. The 3 mg/L ML corresponds to the automated procedure, and the 20 mg/L ML corresponds to the manual procedure.

[3]m+p-xylene (CAS No. 136777-61-2) has a ML of 10 µg/L, while o-xylene (CAS No. 95-47-C) has a ML of 5 µg/L in Method 1666.

TBD - To be determined from the analytical method by the laboratory. The laboratory must first use the MDL procedure specified in 40 CFR Part 136, Appendix B, and then calculate the ML from the MDL using the procedure specified in footnote 1 above. The resulting ML must be equal to or less than the ML listed for that analyte in Table 2-2 or must be less than or equal to the regulatory compliance level specified by the control authority.

ND - not determined

N/A - not applicable

3 Flexibility in Performing Analytical Methods

This section discusses flexibility in analytical methods applicable to wastewater from pharmaceutical operations. This section also discusses the process of demonstrating equivalency using a modified analytical method. This discussion is summarized from *Guidance on Evaluation, Resolution, and Documentation of Analytical Problems Associated with Compliance Monitoring* (EPA 821-B-93-001).

Is there flexibility in performing analytical methods?

In promulgating analytical methods for measurement of pollutants, EPA has provided flexibility for dealing with interferences. The major flexibility options are discussed in the preamble to the 40 CFR Part 136 methods (49 FR 43234) and include a mechanism for obtaining approval of an alternative test procedure on a nationwide basis and/or on a site-specific basis (40 CFR 136.4 and 136.5). In addition to the flexibility outlined in 40 CFR Part 136, flexibility is permitted in each analytical method. The analyst is permitted to "improve separations or lower the cost of analyses" provided that the results obtained are not less precise and accurate than the results obtained using the unmodified method."

Why would a method be modified?

The objective in modifying a method is to overcome interferences and to make the method more specific for a given pollutant, more sensitive, more accurate, or in some other way improve the method. Improvements can be made to a method but require the analyst to demonstrate that results by any modification would be equal to or better than results obtained with the unmodified method.

How does someone demonstrate equivalency of a modified method?

The performance of a modified method is measured by precision and bias or recovery, and can be extended to include detection limit, gas chromatographic resolution, mass spectral resolution, and other measures of method performance. A start-up test is required prior to practicing a method. This test is described in detail in Section 8 of the 600-series and 1600-series wastewater methods and is also used in the Office of Drinking Water 500-series methods. Results of the start-up test must meet the precision and recovery requirements of that method. After the requirements are met for the unmodified method the start-up test must be repeated with the modification as a part of the modified method. The modification is permitted if the precision and recovery specified in the unmodified method are achieved.

4 Solutions to Matrix Problems

This section describes some of the available solutions to matrix interference problems. These solutions are summarized from the document, *Guidance on Evaluation, Resolution, and Documentation of Analytical Problems Associated with Compliance Monitoring* (EPA 821-B-93-001).

How to Solve Matrix Problems Involving Volatile Organic Pollutants

Some of the available solutions to matrix problems for volatile organic pollutants are:

Use of selective GC detectors

The specificity provided by the electrolytic conductivity detector allows the detection of halogenated analytes in complex matrices. Likewise the photoionization detector allows the detection of aromatic analytes in complex matrices. For example, if chloroform is being monitored at the daily maximum pretreatment limit of 0.02 mg/L, and the unregulated compounds methanol, ethanol, and/or propanol interfere with EPA Method 624, EPA Method 601 will allow the sample to be diluted by a factor of more than 100 because the MDL in EPA Method 601 (0.00005 mg/L) is 400 times lower than the limit. Similarly, EPA Method 502.2 would allow the sample to be diluted by a factor of more than 300 because the MDL in EPA Method 502.2 is 1,000 times lower than the limit. Further, the electrolytic conductivity detector is specific to halogenated compounds and would respond very strongly to chloroform and very poorly to methanol, ethanol, and/or propanol, thereby providing great specificity for chloroform.

Micro-extraction and gas chromatography with selective detectors

For selective GC detectors that provide sensitivity beyond that required to detect analytes of interest, micro-extraction can be substituted in place of purge-and-trap. Using the micro-extraction technique, the pH of the water can be adjusted to attempt to keep the interferences in the water while the analytes of interest are extracted.

Sample dilution

For selective GC detectors that provide sensitivity beyond that required to detect analytes of interest, the sample can be diluted, by a factor of 10 - 100 to overcome matrix problems.

Isotope dilution

The use of labeled compounds frequently permit the pollutant to be determined in the presence of interferences because the unique spectrum of the labeled compound can be located in the presence of these interferences, and the pollutant can then be located by reference to the labeled compound. Isotope dilution requires mass spectrometry for detection.

How to Solve Matrix Problems Involving Semivolatile Organic Pollutants

Some of the available solutions to matrix problems for semivolatile organic pollutants are:

Use of selective GC detectors

The use of selective detectors allows the detection of a specific class of analytes in complex matrices. In addition, the added sensitivity gained by the use of selective detectors can allow for dilution to overcome matrix problems.

pH change

Allows for the separation of the pollutants of interest from interferences. For example, if the pollutant of interest is neutral and the main interferences are acidic, the pH can be adjusted in the range of 12-13 and the acidic interferences will remain in the water as their salts while the neutral pollutants are extracted using an organic solvent.

Gel-permeation (size-exclusion) chromatography

This technique has been shown to be effective for removing lipids and high-molecular-weight interferences that can degrade GC and mass spectrometer performance. This technique is described in Revision C of Method 1625.

Solid-phase extraction (SPE) cartridge

Although not fully evaluated, SPE has been shown to be effective in removing interferences from extracts containing pesticides and in the extraction of pollutants from drinking water.

Florisil, alumina, and silica gel

These absorbents are effective in separating neutral species from polar interferences.

Isotope dilution

The use of labeled compounds frequently permit the pollutant to be determined in the presence of interferences because the unique spectrum of the labeled compound can be located in the presence of these interferences, and the pollutant can then be located by reference to the labeled compound. Isotope dilution requires mass spectrometry for detection.

5 Choosing the Appropriate Analytical Method

This section walks through the process of establishing the most appropriate analytical method to use for determination of the regulated parameters. This process is not exclusive, but should help in identifying an appropriate method to use in determining particular analytes.

Which parameters should be measured in the wastewater?

As part of the implementation of national policy on effluent limitations guidelines and standards for the pharmaceutical industry, a facility will be issued a National Pollutant Discharge Elimination System (NPDES) permit or pretreatment requirement. This permit or requirement will outline what is necessary for monitoring wastewater discharges for compliance, including which parameters are regulated and their associated discharge standards. This permit will determine which parameters need to be monitored through sample analysis.

What are the approved analytical methods for the wastewater?

The approved analytical methods for compliance monitoring are those promulgated at 40 CFR 136.3 or incorporated by reference in the tables in 40 CFR 136.3. Table 2-2 presents the approved test methods for the conventional, toxic, and non-conventional pollutants regulated under the pharmaceutical effluent limitations guidelines and standards.

How does someone choose between approved methods?

For most analytes, multiple methods have been approved for analysis. To make a determination of which approved methods to use, a facility should consider the following:

- The groups of analytes that need to be monitored for compliance;
- The minimum level for the analyte versus the limitation that needs to be met to show compliance;
- The cost of the analytical method; and
- The wastewater matrix that is being analyzed.

Can the analytes that need to be monitored be grouped?

Depending on the pollutants to be monitored and the limitations for those pollutants, it may be possible to measure for several pollutants with the same method. As an example, a facility that is required to monitor for ammonia, isopropanol, acetonitrile, 1,2-dichloroethene and methyl formate could monitor using the approved methods listed in Table 5-1 (taken from Table 2-2).

Table 5-1: Test Methods for Example Analytes

Analyte	CAS Registry No.	Analytical Method Number	Minimum Level[1]
acetonitrile	75-05-8	1666	5 mg/L
		1671	50 mg/L
		D3371	**TBD**
		D3695	**TBD**
ammonia (as N)		350.2	50 µg/L
		350.3	50 µg/L
		350.1	10 µg/L
1,2-dichloroethane	107-06-2	601	0.1 µg/L
		624	10 µg/L
		1624	10 µg/L
		D3695	**TBD**
		502.2	**TBD**
		524.2	**TBD**
isopropanol	67-63-0	1666	200 µg/L
		D3695	**TBD**
methyl formate	107-31-3	1666	100 µg/L

[1]Some analytical methods report a Method Detection Limit (MDL) only. This specifically applies to the 600-series methods. In those cases, EPA calculated a minimum level (ML) from the MDL originally reported in the method. The minimum level value was determined by multiplying the MDL by 3.18 and rounding this value to the nearest number in the series (1, 2, or 5) x 10^n, where n is an integer.
TBD - To be determined from the analytical method by the laboratory. The laboratory must first use the MDL procedure specified in 40 CFR Part 136, Appendix B, and then calculate the ML from the MDL using the procedure specified in footnote 1 above. The resulting ML must be equal to or less than the ML listed for that analyte in Table 2-2 or must be less than or equal to the regulatory compliance level specified in the permit.

Our example facility has the opportunity to group several analytes under EPA Method 1666 and ASTM Method D3695. Acetonitrile, isopropanol, and methyl formate can all be analyzed using EPA Method 1666. Similarly, acetonitrile, 1,2-dichloroethene, and isopropanol can all be analyzed using ASTM Method D3695. In both cases ammonia can not be grouped under the same analytical method as the other analytes. It is typically

advisable to choose the fewest number of methods that covers all analytes, while considering the other factors such as the minimum level of quantitation (ML) relevant to the permit limit.

Is the analytical method chosen sensitive enough?

To determine if an approved analytical method is sensitive enough to measure for the analyte, the ML for the analyte needs to be compared to the limitation for that analyte. For each analyte there may exist a daily maximum and monthly average concentration limitation in the final effluent limitations guidelines and standards for the pharmaceutical manufacturing industry. These limitations will depend also on the discharging status of the facility. The monthly average limits for the analytes listed above are shown in Table 5-2.

Table 5-2: Limitations for Example Analytes

Analyte	Effluent Monthly Average Limitation	
	Direct Discharger (mg/L)	Indirect Discharger (mg/L)
Acetonitrile	10.2	NR
Ammonia	29.4	29.4
1,2-Dichloroethane	0.1	8.2
Isopropanol	1.6	NR
Methyl formate	0.5	8.2

NR - Not regulated

Presented in Table 5-3 and 5-4 are the effluent limitations for the non-conventional pollutants for the pharmaceutical industry based on discharge type.

Comparing these limits with the MLS for the analytes in the approved analytical methods shows that EPA Method 1671 cannot be used to perform compliance monitoring for acetonitrile because its ML of 50 mg/L is above the monthly average limitation. Any of the approved analytical methods can be used for the remaining pollutants because the MLs for the analytes in these methods are below the monthly average limitation.

Examples of selected methods for both direct and indirect discharging facilities under this case study are provided below. For a direct discharging facility with our example group of pollutants, one possible solution would be to analyze samples by the following methods:

- 350.1, 350.2, or 350.3 for ammonia;
- 601, 624, or 1624 for 1,2-dichloroethene; and
- 1666 for acetonitrile, isopropanol, and methyl formate.

For an indirect discharging facility with our list of pollutants one possible solution would be to analyze samples by the following methods:

- 350.1, 350.2, or 350.3 for ammonia;
- 601, 624, or 1624 for 1,2-dichloroethene; and
- 1666 for methyl formate.

How much does an analysis using the analytical method cost?

Analytical costs by method will vary by laboratory, region of the country, and number of samples submitted for analysis. In general, the simpler the analytical technique, the less expensive the analysis (for example: Methods 601 and 602 are generally less expensive than Methods 624 and 625, which are generally less expensive than Methods 1624 and 1625). A facility should work with its analytical laboratory to determine the least costly method of analysis. By grouping parameters that can be measured by the same method, a cost saving may be possible over using different analytical methods.

How does someone determine if there will be wastewater matrix interference problems?

Determination of wastewater matrix interference problems will be a case-by-case situation. A facility will likely know the most about what substances are in its wastewater. The substances likely to be in a given wastewater may be known from previous wastewater analyses or may be deduced from a knowledge of the chemicals and solvents used in production and the parameters and byproducts likely to be generated in these processes.

A facility will need to work with its analytical laboratory to identify matrix interference problems and to determine if techniques are available to address these problems. ***Matrix interference problems may be indicated by a failure of the laboratory to achieve the ML for an analyte in the method or a failure to meet the QC requirements in the method.

Table 5-3: Pharmaceutical Effluent Limitations for Direct Discharging Facilities

Regulated parameter	Effluent limitations	
	Maximum Daily Discharge (mg/L)	Average Monthly Discharge Must Not Exceed (mg/L)
Ammonia (as N)	84.1	29.4
Acetone	0.5	0.2
4-Methyl-2-pentanone (MIBK)	0.5	0.2
Isobutyraldehyde	1.2	0.5
n-Amyl acetate	1.3	0.5
n-Butyl acetate	1.3	0.5
Ethyl acetate	1.3	0.5
Isopropyl acetate	1.3	0.5
Methyl formate	1.3	0.5
Amyl alcohol	10.0	4.1
Ethanol	10.0	4.1
Isopropanol	3.9	1.6
Methanol	10.0	4.1
Methyl Cellosolve	100.0	40.6
Dimethyl Sulfoxide	91.5	37.5
Triethyl Amine	250.0	102.0
Phenol	0.05	0.02
Benzene	0.05	0.02
Toluene	0.06	0.02
Xylenes	0.03	0.01
n-Hexane	0.03	0.02
n-Heptane	0.05	0.02
Methylene chloride	0.9	0.3
Chloroform	0.02	0.01
1,2-Dichloroethane	0.4	0.1
Chlorobenzene	0.15	0.06
o-Dichlorobenzene	0.15	0.06
Tetrahydrofuran	8.4	2.6
Isopropyl ether	8.4	2.6
Diethyl amine	250.0	102.0
Acetonitrile	25.0	10.2

Table 5-4: Pharmaceutical Effluent Limitations for Indirect Discharging Facilities

Regulated parameter	Pretreatment standards	
	Maximum Daily Discharge (mg/L)	Average Monthly Discharge Must Not Exceed (mg/L)
Ammonia (as N)	84.1	29.4
Acetone	20.7	8.2
4-Methyl-2-pentanone (MIBK)	20.7	8.2
Isobutyraldehyde	20.7	8.2
n-Amyl acetate	20.7	8.2
n-Butyl acetate	20.7	8.2
Ethyl acetate	20.7	8.2
Isopropyl acetate	20.7	8.2
Methyl formate	20.7	8.2
Methyl Cellosolve	275.0	59.7
Isopropyl ether	20.7	8.2
Tetrahydrofuran	9.2	3.4
Benzene	3.0	0.6
Toluene	0.3	0.1
Xylenes	3.0	0.7
n-Hexane	3.0	0.7
n-Heptane	3.0	0.7
Methylene chloride	3.0	0.7
Chloroform	0.1	0.03
1,2-Dichloroethane	20.7	8.2
Chlorobenzene	3.0	0.7
o-Dichlorobenzene	20.7	8.2
Diethyl amine	255.0	100.0
Triethyl amine	255.0	100.0

6 Answers to Specific Concerns from Industry Regarding Analytical Methods

This section provides responses to some of the industry's comments regarding analytical methods. For a complete listing of comment responses see the Pharmaceutical Comment Response Document in the public record for the final pharmaceutical effluent limitations guidelines and standards.

Isotope Dilution Methods

Some industry commenters were concerned that the isotope dilution gas chromatography/mass spectrometry (GC/MS) methods have not been demonstrated to give more accurate or precise results than the equivalent non-isotope dilution methods. EPA has demonstrated that isotope dilution methods are approximately twice as precise (half the relative standard deviation) as non-isotope dilution methods and yield an average recovery of approximately 100 percent vs 80 percent for non-isotope dilution methods. The results of the study are given in reference 10 listed at the end of Method 1625 at 40 CFR Part 136, Appendix A. However, to allow dischargers to use lower cost methods, EPA has approved use of the GC methods and the non-isotope dilution GCMS methods listed at 40 CFR Part 136. The facility has the flexibility to choose any approved method that will provide a result showing compliance.

Office of Solid Waste (OSW) SW-846 Methods

Some industry commenters wanted Office of Solid Waste (OSW) SW-846 Methods to be approved for pharmaceutical wastewater. However, EPA concluded that it should not include OSW SW-846 methods in the list of approved methods because SW-846 methods are published only as "guidance." The Clean Water Act requires EPA to promulgate guidelines establishing test procedures (analytical methods) to support categorical regulations and other activities in the wastewater program. EPA did not feel that the guidance provided by SW-846 met this criteria. During the development of the pharmaceuticals industry final rule, data were submitted by the industry and accepted by EPA. These

data were gathered using a modification of EPA Office of Solid Waste Method 8015. Modifications to this method consisted of the addition of several analytes and increased quality assurance and quality control (QA/QC). The modifications were consistent with the procedures used for determination of these analytes in EPA Method 1671 which was approved for use at 40 CFR Part 136 in the pharmaceutical manufacturing industry final rule. In the future, EPA may allow use of the SW-846 methods, and any other method, when EPA promulgates guidelines establishing test procedures under a performance-based measurement system (PBMS). In the meantime, laboratories may request approval for use of the SW-846 methods, or other methods, under EPA's alternate test procedure (ATP) program at 40 CFR 136.4 and 136.5.

Transfer of an Analyte Between Methods

Some laboratories asked whether a target analyte from one EPA-approved method could be transferred to another EPA-approved method, thereby reducing the number of methods required for monitoring. During development of the Pharmaceuticals Industry final rule, EPA did not evaluate the effect of transferring analytes between methods. On March 28, 1997, when EPA proposed the Streamlining Initiative (now referred to as the performance-based measurement system or "PBMS"), the Agency included a procedure to allow the addition of an analyte to an existing method. This procedure centered around meeting the quality control (QC) acceptance criteria for performance tests for the analyte. As of the date of the issuance of this Guidance, the PBMS rule has not been promulgated.

Using PBMS as the basis for transfer of an analyte from one method to another, EPA recommends allowance of a transfer, provided the following conditions are met: (1) the QC tests in the method from which the analyte is transferred mus be run as an integral part of the method to which the analyte is transferred, (2) the QC acceptance criteria in the method from which the analyte is transferred must be met when the QC tests are run as an integral part of the method to which the analyte is transferred, and (3) the MDL obtained for the analyte in the method to which the analyte is transferred must be equal to or less than MDL in the method from which the analyte is transferred or less than one third the regulatory compliance limit specified in the permit, whichever is greater.

QC tests in the 600- and 1600-series EPA methods include calibration, calibration verification, initial and ongoing precision and recovery, analysis of blanks, and matrix spike/matrix spike duplicates. EPA recommends that these QC tests be performed and the QC acceptance criteria be met, as follows:

1) When the analyte is transferred to a method, the added analyte must be included in the initial calibration and ongoing calibration checks, and the QC acceptance criteria in the method from which the analyte is transferred must be met for both initial calibration and calibration verification.

2) All initial and ongoing performance tests in the method from which the analyte is transferred must be performed as an integral part of the method to which the analyte is transferred, and

the QC acceptance criteria in the method from which the analyte is transferred must be met. The initial and ongoing tests must include a blank with the initial demonstration of performance and with each sample batch.

3) The quality control check or matrix spike/matrix spike duplicate test (whichever is applicable) in the method from which the analyte is transferred must be performed as an integral part of the method to which the analyte is transferred, and the QC acceptance criteria in the method from which the analyte is transferred must be met.

4) An MDL study must be performed for the analyte as an integral part of the method to which the analyte is transferred, and the MDL obtained must be equal to or less than either a) the MDL in the method from which the analyte is transferred or b) one-third the regulatory compliance limit specified in the permit, whichever is greater.

Notes:

1. A possible conflict could arise if the methods are chromatographic (i.e., GC or GC/MS). Some EPA chromatographic methods contain QC tests and QC acceptance criteria for absolute and/or relative retention time. When transferring an analyte between methods, it is unlikely that the two methods would require use of the same chromatographic column and it is therefore unlikely that the retention time criteria in the method from which the analyte is transferred could be met in the method to which the analyte is transferred. To resolve this issue, the absolute and/or relative retention time requirements are waived for the transferred analyte only. If there are absolute and/or relative retention time requirements for the target analytes in the method to which the analyte is transferred, those requirements must continue to be met.

2. Some methods do not contain an MDL but contain a minimum level of quantitation (ML) for each analyte. MLs were created by multiplying the MDL by 3.18 and rounding. Therefore, for the purpose of establishing that the MDL for a transferred analyte is less than or equal to the MDL in the method from which the analyte is transferred, divide the ML by 3.18 to establish the MDL.

Examples:

Example 1: The final rule requires that certain volatile analytes be determined by EPA Method 524.2. These analytes may be added to EPA Method 1666 or any other approved method provided the three conditions specified above are met.

Example 2: The final rule requires that tert-butyl alcohol, diethylamine, dimethyl sulfoxide, isobutyraldehyde, methyl cellosolve, methyl formate, and triethyl amine be analyzed by EPA Method 1666 or 1671. These analytes may be added to EPA Method 624, 625, or any other approved method provided that the three conditions specified above are met.

Is This Guidance Applicable to Other Rules?

This Guidance allows transfer of analytes between methods without prior EPA approval under the Pharmaceuticals Manufacturing Industry final rule only. For industrial categories and subcategories other than for Pharmaceuticals Manufacturing, EPA will handle requests for transfer of analytes between methods on a case-by-case basis until a PBMS final rule is promulgated.

Second Column Confirmation Using Method 1671

Some laboratories have asked if second-column confirmation is required when Method 1671 is used. Method 1671 was developed using a single column and second-column confirmation is not required with this method. However, EPA believes that it is prudent to confirm the identity of any pollutant detected by use of a second column or other confirmatory technique (e.g., GCMS). Confirming pollutant identity will assure that an interferant is not causing a false positive, possibly causing a false violation of a permit limit.

Can Different Labeled Compounds be Used with the Isotope Dilution Methods?

Yes, provided that the same labeled compound is used for calibration on all performance tests.

What Laboratories are Capable of Practicing the Approved Methods?

Many laboratories routinely practice wastewater and drinking water methods. For methods specific to the PMI analytes listed in Table IF at 40 CFR 136.3 (63 FR 50424), EPA has had inquiries from a number of industry representatives to identify laboratories that are either practicing these methods or are considering setting up to practice the methods. For assistance in identifying laboratories, contact those individuals listed in Section 7 of this Guidance.

In What Fraction (Volatiles or Semi-Volatiles) are the Analytes That Are Determined by Direct Aqueous Injection?

Historically, EPA has classified any non-pesticide organic pollutant that can be measured by the purge-and-trap technique as a “volatile” pollutant and any pollutant determined by extraction, concentration, and extract injection as a “semi-volatile” pollutant. Certain Pharmaceutical Industry analytes (e.g., methanol, triethylamine, methyl formate) are not determined using either of these techniques but are determined by direct aqueous injection (DAI).

Samples to be tested for volatiles pollutants are collected into volatile organic analysis (VOA) vials with zero headspace; samples to be tested for semi-volatile pollutants are collected into open containers using continuous sampling techniques. EPA is concerned that certain of the DAI analytes may be lost by volatilization if a sample containing these analytes is collected into an open container

using continuous sampling techniques. To prevent this loss, samples to be tested for the DAI analytes must be collected in the same way as samples for volatiles; i.e., they should be collected as grab samples in VOA vials with zero headspace. If compositing is required, the samples should be composited in the laboratory in the same way as with VOA samples.

7 Where to Get Additional Help

Provided in this section are additional sources of information, and EPA contacts, that may provide additional information related to the final pharmaceutical effluent limitations guidelines and standards. Specifically, this section presents a list of documents and websites either relating to the final pharmaceutical effluent limitations guidelines and standards or compliance monitoring and methods. These lists also include information on how to reach EPA program personnel and how to access these information sources.

Questions specifically related to the effluent limitations guidelines and standards for the pharmaceutical industry should be directed to:

Dr. Frank Hund
Engineering and Analysis Division (4303)
U.S. EPA
401 M Street, SW
Washington, DC 20460
Tel: (202) 260-7182
Fax: (202) 260-7185
E-Mail: hund.frank@epa.gov

Questions specifically related to analytical methods for the pharmaceutical industry should be directed to:

Maria Gomez-Taylor
Engineering and Analysis Division (4303)
U.S. EPA
401 M Street, SW
Washington, DC 20460
Tel: (202) 260-1639
Fax: (202) 260-7185
E-Mail: gomez-taylor.maria@epa.gov

Documents Supporting the 1998 Promulgated Rule

- **Development Document for Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category**, EPA-821-R-98-0005, July 1998.
- **Environmental Assessment of the Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Industry**, EPA-821-B-98-008, July 1998.
- **Statistical Support Document for Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Industry**, EPA-821-B-98-007, July 1998.
- **Background Information Document for the Final Air Rules**
- **Permit Guidance Document for the Pharmaceutical Manufacturing Point Source Category**

Documents on Compliance Monitoring and Methods

- **Guidance on Evaluation, Resolution, and Documentation of Analytical Problems Associated with Compliance Monitoring**, EPA-821-B-93-00" June 1993.
- 40 CFR Part 136, Appendix A (EPA Methods 601, 602, 604, 612, 624, 625, 1624, and 1625).
- **Analytical Methods for the Determination of Pollutants in Pharmaceutical Manufacturing Industry Wastewater**, EPA-821-B-98-016, July 1998.
- **Methods for the Determination of Organic Compounds in Drinking Water**, EPA-600/4-88-039.
- **Methods for the Determination of Organic Compounds in Drinking Water-Supplement II**, EPA-600/R-92-129.
- American Society for Testing and Materials (ASTM Methods D3371, D3695, and D4763).

Websites

- EPA's homepage on the World Wide Web: **http://www.epa.gov**
  EPA's office of science and technology's analytical methods page on the World Wide Web: **http://www.epa.gov/OST/Methods/**
  EPA's Office of Ground Water and Drinking Water's analytical methods page on the World Wide Web: **http://www.epa.gov/OGWDW/Methods/methods.html**
  EPA's pharmaceutical rulemaking actions homepages on the World Wide Web: **http://www.epa.gov/ost/guide/pharm** (water documents)

http://www.epa.gov/ttn/oarpg (air documents)

- ASTM's homepage on the World Wide Web: **http://www.astm.org**