

## Certificates of Analysis, Material Safety Data Sheets and Pharmaceutical Compounding

**Goal:** To provide information for pharmacy practitioners and students on the purpose, content and use of a Certificate of Analysis (C of A).

**Objectives:** After reading and studying the article, the reader will be able to:

1. Differentiate between a Certificate of Analysis and a Material Safety Data Sheet.
2. Describe the content and characteristics of the Certificate of Analysis.
3. Identify the difference between a Certificate of Analysis and a USP monograph.
4. Identify who is responsible for establishing the standards and content of the official USP/NF.

### INTRODUCTION

USP Chapter <795> Pharmacy Compounding-Nonsterile Preparations states "The Pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and relevant scientific data and information." The compounding of quality preparations must involve the use of quality chemicals.<sup>1</sup>

Ingredients used in compounding official compounded preparations must meet the requirements of compendial monographs, if the substance is official. If not an official substance, reasonable standards can be applied for acceptance to be used in compounding. If a USP or NF grade is not available, or when food, cosmetics, or other substances are or must be used, the use of another high quality source, such as analytical reagent (AR), certified American Chemical Society (ACS), or Food Chemicals Codex (FCC) grade, is an option for professional judgment. For any substance used in compounding not purchased from a registered drug manufacturer, the pharmacist should establish purity and safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source.

USP Chapter <795> also states that "The bulk drug

substances must be accompanied by a valid certificate of analysis." For ingredients other than bulk drug substances, pharmacists should use ingredients that comply with an applicable USP-NF monograph or the USP Chapter <795>.

It has been stated that "without the certificate of analysis, the material is valueless". The question of what tests should be evaluated for ingredient quality and what tests are most important in evaluating Certificates of Analysis often arise among compounding pharmacists. The purpose of this article is to present the use of Certificates of Analysis for assessing ingredient quality, standards and their use. These tests are based on the U.S. Pharmacopeia 35-National Formulary 30.

There are standards for active pharmaceutical ingredients (APIs) and excipients developed by the USP Council of Experts, which is responsible for the content of USP's official and authorized publications. USP-NF standards are recognized widely because they are authoritative, science-based and are established by a transparent and credible process. A drug or excipient monograph contains tests and acceptance criteria to comply with compendial standards for strength, quality, and purity of the substance.

Loyd V. Allen, Jr., Ph.D., R.Ph.

- Professor Emeritus, University of Oklahoma College of Pharmacy
- Editor in Chief, International Journal of Pharmaceutical Compounding
- Dr. Allen is not affiliated with Perrigo Pharmaceuticals



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ACPE Number 0748-0000-13-002-H04-P (0.1CEU)  
The initial release for this lesson is 12/01/13.  
**This lesson is no longer valid for CE credit after 12/01/16.**

## DEFINITIONS

Certificate of Analysis - An authenticated document, issued by an appropriate authority, that certifies the quality and purity of pharmaceuticals, as well as animal and plant products being exported. Also, a “certificate” is an official document attesting the truth of the facts stated.

It is documentation that provides all the required information about a particular material, giving the end user confidence that the reference material is fit for its intended purposes. The C of As accompanying materials are generally designed to be as clear and concise as possible, while complying with the appropriate ISO guide requirements.

## MONOGRAPH STANDARDS

A USP/NF monograph provides the article’s name, definition, specifications, and other requirements related to packaging, storage, and labeling. The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality and purity of the article. Table 1 provides an example list of specifications in monographs; not every substance will have all the specifications listed but will list those that are appropriate.

A monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of articles from different manufacturers. These alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases.

Manufactured product monographs (tablets, capsules, solutions, injections, suppositories, etc.) generally include percentage strength requirements for the API, which vary depending upon the drug, etc. Also included in a product monograph are performance standards and specific tests for the dosage forms, e.g. disintegration and dissolution for tablets; dissolution for capsules; pH for solutions; sterility and endotoxin limits for sterile injections.

Compounded preparation monographs include formulas, specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH, beyond-use dates based on stability studies, and detailed assays (majority of monographs).

Table 1: Example Monograph Specification Components for APIs or Excipients

Assay	Numeric value
Completeness of solution	Passes Y/N
Congearing temperature	Numeric value
Crystallinity	Passes Y/N
Density of solids	Numeric value
Description and Solubility (Physical appearance)	Narrative
Distilling range	Numeric value
Identity	Passes Y/N
Impurities and Foreign Substances	Passes Y/N and/or Numeric values
Loss on drying	Numeric value
Loss on ignition	Numeric value
Melting range or temperature	Numeric value
Odor	Passes Y/N
Performance Tests	Varies
pH	Numeric value
Powder fineness	Passes Y/N
Refractive index	Numeric value
Residual Solvents	Passes Y/N
Specific gravity	Numeric value
Specific surface area	Numeric value
Viscosity	Numeric value
Water	Numeric value

## CERTIFICATES OF ANALYSIS

Information on the name of the API or excipient including, where appropriate, its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For APIs or excipients with an expiry date, the expiry date should be provided on the label and certificate of analysis. For APIs or excipients with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical), as listed in Table 1. Physical descriptions/appearance are described in the "Description and Relative Solubility of USP and NF Articles" section of the USP/NF.

Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repackager or reprocessor, the certificate of analysis should show the name, address, and telephone number of the repackager/reprocessor and reference the name of the original manufacturer.

If new certificates are issued by or on behalf of repackagers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

The primary responsibility for the preparation of the C of A belongs to the manufacturer. The user of a bulk substance should always receive a C of A for the material being used. To utilize test results from a C of A, the user should establish the reliability of the supplier's C of A test results. There are currently few standardized requirements for the content or format of C of As for excipients. The C of A template generally consists of a (1) header, (2) body, (3) analysis, (4) certification and compliance statements and a (5) footer. Dates on the C of A generally consist of the (1) date of manufacture, (2) expiration date and recommended re-evaluation/retest dates, (3) date retested, and others as appropriate.

### Example

If the bulk drug substance is a USP/NF item, then the specific tests listed in the compendia should be addressed. For example, Hydrocortisone USP includes a purity rubric (...not less than 97.0% and not more than 102.0% of  $C_{21}H_{30}O_5$ , calculated on the dried basis). The individual tests may have an official USP chapter associated with them. If so, the method detailed should be followed unless another method has been validated to be at least as good, if not better, than the method listed in the USP. The USP General Chapters associated with the tests below are provided in parentheses. Hydrocortisone USP has specific tests for which information should be provided, including the following:

Identification (chapter <181>, <191>, <193>, <197>, <201>, <563>)

Specific rotation (chapter <781>)

Loss on drying (chapter <731>)

Residue on ignition (chapter <281>)

Chromatographic purity (chapter <621>)

Assay (chapter <621>)

Therefore, the Certificate of Analysis should address the tests/requirements listed for the specific substance/article. If a bulk drug substance is listed as "USP" or "NF", the inference is that the substance meets the standards and passes the tests required for the USP or NF designation. It should be noted that some of the responses to the various tests on the Certificates of Analysis may be numerical and some may be simply "Passes", as in the following example:

TEST	REQUIREMENT	RESULT
Specific rotation (chapter <781>)	Between +150° and +156°	+152°
Organic Volatile Impurities	Meets the requirements	Passes

If a substance is not available as a USP or NF item, then appropriate tests can be used that are similar to those required for related substances but in all cases should include a purity rubric and an assay result. An example USP monograph for Morphine Sulfate is shown in Figure 1 and it can be compared with an example Morphine Sulfate Certificate of Analysis in Figure 2.

Figure 1: Example Morphine Sulfate Monograph from the USP

## Morphine Sulfate (mor' feen sul' fate).

(C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>·5H<sub>2</sub>O 758.83

Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 $\alpha$ ,6 $\alpha$ )-, sulfate (2:1) (salt), pentahydrate. 7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate (2:1) (salt) pentahydrate [6211-15-0].

Anhydrous 668.77 [64-31-3].

» Morphine Sulfate contains not less than 98.0 percent and not more than 102.0 percent of (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>, calculated on the anhydrous basis.

**Packaging and storage** – Preserve in tight, light-resistant containers. Store up to 40° as permitted by the manufacturer.

**USP REFERENCE STANDARDS** <11> –

### USP Morphine Sulfate RS

#### Identification –

**A:** *Infrared Absorption* <197K> : dried at 145° for 1 hour.

**B:** To 1 mg in a porcelain crucible or small dish add 0.5 mL of sulfuric acid containing, in each mL, 1 drop of formaldehyde TS: an intense purple color is produced at once, and quickly changes to deep blue-violet (*distinction from codeine, which gives at once an intense violet-blue color, and from hydromorphone, which gives at first a yellow to brown color, changing to pink and then to purplish red.*)

**C:** To a solution of 5 mg in 5 mL of sulfuric acid in a test tube add 1 drop of ferric chloride TS, mix, and heat in boiling water for 2 minutes: a blue color is produced, and when 1 drop of nitric acid is added, it changes to dark red-brown (codeine and ethylmorphine give the same color reactions, but hydromorphone and papaverine do not produce this color change).

**D:** A solution (1 in 50) responds to the tests for *Sulfate* <191>.

**SPECIFIC ROTATION** <781S> : between -107° and -109.5°.

*Test solution:* the equivalent of 20 mg per mL, in water.

**Acidity** – Dissolve 500 mg in 15 mL of water, add 1 drop of methyl red TS, and titrate with 0.020 N sodium hydroxide: not more than 0.50 mL is required to produce a yellow color.

**WATER, Method I** <921> : between 10.4% and 13.4% is found.

**RESIDUE ON IGNITION** <281> : not more than 0.1%, from 500 mg.

**Chloride** – To 10 mL of a solution (1 in 100) add 1 mL of 2 N nitric acid and 1 mL of silver nitrate TS: no precipitate or turbidity is produced immediately.

**Ammonium salts** – Heat 200 mg with 5 mL of 1 N sodium hydroxide on a steam bath for 1 minute: no odor of ammonia is perceptible.

**Limit of foreign alkaloids** – Dissolve 1.00 g in 10 mL of 1 N sodium hydroxide in a separator, and shake the solution with three successive portions of 15, 10, and 10 mL of chloroform, passing the chloroform solutions through a small filter previously moistened with chloroform. Shake the combined chloroform solutions with 5 mL of water, separate the chloroform layer, and carefully evaporate on a steam bath to dryness. To the residue add 10.0 mL of 0.020 N sulfuric acid, and heat gently until dissolved. Cool, add 2 drops of methyl red TS, and titrate the excess acid with 0.020 N sodium hydroxide: not less than 7.5 mL is required (1.5%).

#### Assay –

**Mobile phase** – Dissolve 0.73 g of sodium 1-heptanesulfonate in 720 mL of water, add 280 mL of methanol and 10 mL of glacial acetic acid, mix, filter, and degas. Make adjustments if necessary (see System Suitability under *Chromatography* <621>).

**Standard preparation** – Dissolve an accurately weighed quantity of USP Morphine Sulfate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.24 mg per mL. Prepare a fresh solution daily.

**System suitability preparation** – Dissolve suitable quantities of USP Morphine Sulfate RS and phenol in Mobile phase to obtain a solution containing about 0.24 and 0.15 mg per mL, respectively.

**Assay preparation** – Transfer about 24 mg of Morphine Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

**Chromatographic system** (see *CHROMATOGRAPHY* <621>) – The liquid chromatograph is equipped with a 284-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation and the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for phenol and 1.0 for morphine sulfate; the resolution, R, between phenol and morphine sulfate is not less than 2.0; the tailing factor for the morphine sulfate peak is not more than 2.0; and the relative standard deviation for replicate injections of the Standard preparation is not more than 2.0%.

**Procedure** – Separately inject equal volumes (about 25  $\mu$ L) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of (C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub> in the portion of Morphine Sulfate taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of anhydrous morphine sulfate in the *Standard preparation*, as determined from the concentration of USP Morphine Sulfate RS corrected for moisture content by a titrimetric water determination; and r<sub>U</sub> and r<sub>S</sub> are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

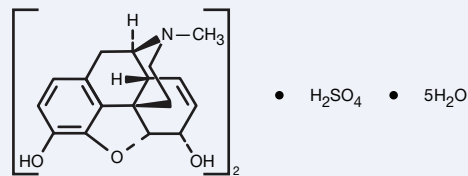


Figure 2: Example Morphine Sulfate Certificate of Analysis

CERTIFICATE OF ANALYSIS

Morphine Sulfate, USP CAS 62111-15-0  
 $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$  Lot No. \_\_\_\_\_  
 MW 758.83

TEST	SPECIFICATION		RESULTS
	Min.	Max	
Assay	98.0	102.0%	100.5%
	(anhydrous basis)		
Identification	To pass test		Passes test
Specific rotation	-107°	-109.5°	-108.1°
Acidity	To pass test		Passes test
Water	10.4%	13.4%	12.5%
Residue on ignition	nmt 0.1%		0.06%
Chloride	To pass test		Passes test
Ammonium salts	To pass test		Passes test
Limit of foreign alkaloids	To pass test		Passes test
Physical appearance:			
	White, feathery, silky crystals, cubical masses of crystals, or white crystalline powder.		
	To pass test		Passes test
Manufacturer name, address, telephone			
Signature of Certificate of Analysis Coordinator _____			

specification of “not less than” or “nlt” or “not more than” or “nmt”, “passes” or “does not pass”, narrative descriptions, etc.

Certificates of Analysis are lot-specific and must match the current lot of bulk drug substance or excipient being used for compounding. When comparing a Certificate of Analysis for an official ingredient, product or preparation, it is required that all the specifications are within the allowable tolerances. For APIs for which there is not an official monograph, one can usually select a monograph of an API in a similar class for a guideline for individual specifications.

**MANUFACTURED DRUG PRODUCTS USED IN COMPOUNDING**

When manufactured drug products are used in compounding, they will not be accompanied by a Certificate of Analysis but will be accompanied by a Product Information Package Insert. This information along with the product’s specific lot number should be maintained on file to document the specific product that was used in compounding. However, there can be difficulties in compounding with commercial products, as follows.

The USP standards for pharmaceutical compounding require the active pharmaceutical ingredient (API) in a compounded preparation to be present in an amount equal to 90.0 to 110.0% of the label. This can pose a problem when compounding using commercially manufactured products due to the variation in allowable strengths by USP dosage form monographs or from the standards set in the individual New Drug Application. To see what can occur, let’s look at the following example.

Example:

A stability study was recently published.<sup>2</sup> The authors conducted an appropriate study but there are some items of interest to consider. The investigators utilized 500 mg vials of doripenem and reconstituted them with 10 mL of 0.9% sodium chloride injection as recommended by the manufacturer. Then, the contents of one or two vials was added to either 100 mL PVC containers or 100 mL elastomeric infusion pumps containing either 90 or 80 mL of either 0.9% sodium chloride injection or 5% dextrose injection to produce solutions with doripenem concentrations of 5 mg and 10 mg per mL respectively. Six replicate bags were made for each combination of doripenem concentration, diluent and infusion container.

**ACCEPTANCE CRITERIA**

The acceptance criteria for the individual tests allow for analytical error, unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. The numerical standards of rounding numerical values are explained in the USP/NF with examples that should be followed; this is important for any test result on the low or the high end of the range. An article that has been prepared to tighter criteria than those specified in the monograph does not constitute a basis for a claim that the article “exceeds” the compendial requirements. In some cases, an allowable range is provided, in others it may be a

An acceptable range for the 5 mg/mL concentration would be between 4.5 and 5.5 mg/mL; for the 10 mg/mL concentration would be between 9 and 11 mg/mL. At 25° C, 4 of the 8 solutions were outside of the acceptable range; at 5° C, 3 of the 8 solutions were outside of the acceptable range and at 25° after being frozen and thawed, 8 solutions were outside of the acceptable range. In other words, 9 of the 24 solutions (37.5%) do not meet the standards of the USP requirement of 90 – 110%.

One can readily see that compounding using manufactured products can place the pharmacist in a situation where their final preparations are not in compliance with the USP standards. The pharmacist has no way of knowing the actual analyzed strength of the API in the commercial product. It may be anywhere in the range of 90.0-110.0% or it may be 80.0-120.0% or even a broader or different range. If the pharmacist does not know what the strength of the API is in the commercial product, then there is a possibility that the compounded preparation will be outside the allowable USP standards that have been adopted by most states in their laws and regulations. Obviously, in many clinical situations, this variation will not be significant. It does become significant, however, when samples are selected and analyzed by regulatory agencies and found to be outside of expected specifications. This situation is not encountered when using bulk substances accompanied by Certificates of Analysis and actually reinforces their importance.

## CERTIFICATE OF ANALYSIS MANAGEMENT

Certificates of Analysis should be obtained and kept on record as documentation of the quality of chemicals used in compounding preparations. Most Certificates of Analysis are provided in a standard 8.5 X 11 inch format and are reasonably similar in appearance between manufacturers of bulk substances. These certificates can be alphabetically arranged and maintained in standard three ring notebooks.

## RECORD MAINTENANCE

There is no specific length of time stated in Chapter <795> for maintaining the Certificates of Analysis, which are lot-specific. Pharmaceutical judgment would suggest that the Certificates be maintained on file for a designated time period after the last of the specific lot of the substance was used that would include the projected time of patient administration. In referring to the recommended Beyond-Use Dates, the maximum time would generally be 6 months.

## MATERIAL SAFETY DATA SHEETS

Material Safety Data Sheets (MSDSs) differ from C of As. A MSDS is a written document that outlines information and procedures for handling and working with chemicals. The material safety data sheet (MSDS), safety data sheet (SDS), or product safety data sheet (PSDS) is an important component of compounding or manufacturing records. It is intended to provide workers and emergency personnel with procedures for handling or working with a specific substance in a safe manner. A MSDS includes information such as physical data (melting point, boiling point, flash point, etc.), toxicity, health effects, first aid, reactivity, storage, disposal, protective equipment, and spill-handling procedures. MSDS formats can vary from source to source within a country depending on national requirements. It identifies the manufacturer of the material (with name, address, phone, and fax number) and usually includes (1) chemical identity, (2) hazardous ingredients, (3) physical and chemical properties, (4) fire and explosion data, (5) reactivity data, (6) health hazards data, (7) exposure limits data, (8) precautions for safe storage and handling, (9) need for protective gear, and (10) spill control, cleanup, and disposal procedures. MSDSs are generally not lot specific.

## SUMMARY

Certificates of Analysis are a vital component of quality pharmaceutical compounding. In addition, Material Safety Data Sheets should also be obtained and kept on file for personnel safety and protection.

## REFERENCES

1. United States Pharmacopeia 35/National Formulary 30. US Pharmacopeial Convention, Inc., Rockville, MD 2012, 344-386.
2. Crandon JL, Sutherland C, Nicolau DP. Stability of doripenem in polyvinyl chloride bags and elasomeric pumps. *AJHP* 2010;67(18):1539-1544.