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CriticalPoint Pearls of Knowledge

API Certificates of Analysis

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Introduction

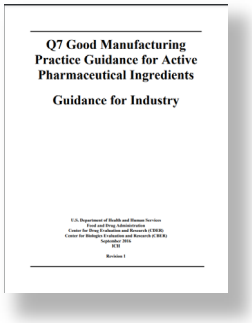
A certificate of analysis (COA) is a critical tool in helping pharmacists ensure the active pharmaceutical ingredient (API) being used to compound preparations meets regulatory requirements. It is issued by the quality department of the API supplier and addresses the identity, quality, and purity of the starting material. According to USP <797>, APIs "must have a COA that includes the specifications (e.g., compendial requirements for quality) and that test results for the component show that the API meets expected quality."[1] A review of the COA is the all-important first step in the compounding process. If you do not know the exact specifications of the API, you cannot be certain you are giving your patients the exact compound their physicians intended to prescribe. A change in lot numbers or differences in suppliers can result in significant disparity in API characteristics and change key specifications in your final compounded sterile preparation (CSP).

Defining API

Before we get into what needs to be on the COA, we want to review the definition of API. As you look through different FDA documents, you may find slightly varied definitions.

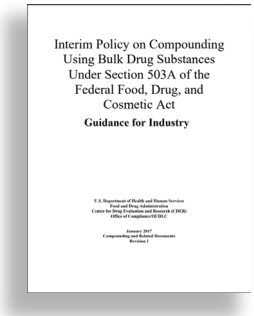
The FDA's "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients—Guidance for Industry" provides a definition for API, which is also known as a drug substance:

> Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.[2]


Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Guidance for Industry

You can also find a definition in the FDA's "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act—Guidance for Industry." This document states that the term bulk drug substance has the same definition as API as defined in 21 CFR 207.1.[3]


Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

> Active pharmaceutical ingredient means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance.[4]

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Based on these definitions, you can see why the quality of the API utilized is so important.

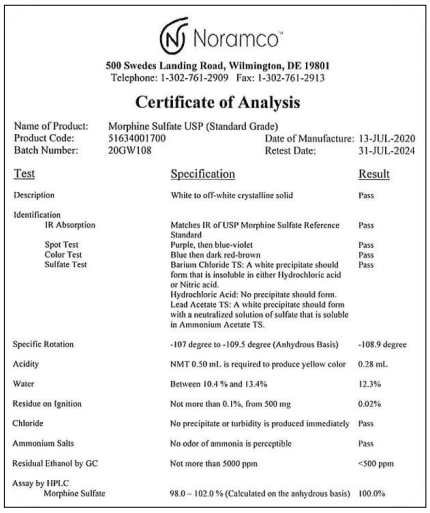
Reviewing the COA

There are a number of key data elements to evaluate in a COA. In the next few sections, we will cover many of the components that could appear on a COA. While not all of these will appear on every COA, for each of these items that does appear, the COA should include the name of the specification/test, the acceptance criteria/tolerances for the test, and the results of those tests.

Remember, the COA tells the story of the API. Missing information, especially specific test results, is a cause for concern, and the manufacturer should be contacted.

General information

Let's look at some general information that needs to be on the COA.



Noramco™

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Certificate of Analysis

Name of Product: Morphine Sulfate USP (Standard Grade)
Product Code: 51634001700 Date of Manufacture: 13-JUL-2020
Batch Number: 20GW108 Retest Date: 31-JUL-2024

Test	Specification	Result
Description	White to off-white crystalline solid	Pass
Identification		
IR Absorption	Matches IR of USP Morphine Sulfate Reference Standard	Pass
Spot Test	Purple, then blue-violet	Pass
Color Test	Blue then dark red-brown	Pass
Sulfate Test	Barium Chloride TS: A white precipitate should form that is insoluble in either Hydrochloric acid or Nitric acid. Hydrochloric Acid: No precipitate should form. Lead Acetate TS: A white precipitate should form with a neutralized solution of sulfate that is soluble in Ammonium Acetate TS.	Pass
Specific Rotation	-107 degree to -109.5 degree (Anhydrous Basis)	-108.9 degree
Acidity	NMT 0.50 mL is required to produce yellow color	0.28 mL
Water	Between 10.4 % and 13.4%	12.3%
Residue on Ignition	Not more than 0.1%, from 500 mg	0.02%
Chloride	No precipitate or turbidity is produced immediately	Pass
Ammonium Salts	No odor of ammonia is perceptible	Pass
Residual Ethanol by GC	Not more than 5000 ppm	<500 ppm
Assay by HPLC		
Morphine Sulfate	98.0 – 102.0 % (Calculated on the anhydrous basis)	100.0%

- Name of the manufacturer: This seems simple, but it should not be overlooked. If they are not able to provide the manufacturer, this is a red flag and needs to be further investigated.
- Name and address of the supplier: Inspectors and regulators will look for this.
- Name of the API: The grade (e.g., USP or NF) must also be included. USP <797> states that the API "must comply with the criteria in the *USP–NF* monograph, if one exists."[1] If one does not exist, some homework is required to determine the quality attributes of the API. Refer to the FDA guidance regarding Bulk Drug Substances Used in Compounding Under Section 503A of the FD&C Act for more information.
- Lot number: This is essential for tracking purposes in case of a recall. Sometimes an API supplier will create multiple batches from one API lot number. The batch number can be expressed as a prefix or suffix of the lot number.
- Catalog number: This number can help ensure you are ordering and receiving the proper API.

Chemical-specific information

There are a few chemical-specific items that should be on the COA. This information is fundamental to ensuring the right drug is used for the CSP.

- Chemical Abstracts Service (CAS) number: The CAS number and the name of the chemical correspond to each other. This is crucial to matching up the proper salt form or base, or when chemicals have different waters of hydration.
- Molecular weight (MW): The MW can be affected by the salt form and waters of hydration, and these factors must be considered when calculating the amount of API for a formula.
- Description of the API: What are the characteristics of the API? What color should it be? Is it granular or a fine powder? Does it have an odor? It is important to know what to look for when examining an incoming API.

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- Assay: This is the percentage of pure API in the bulk powder, which can be represented as the dry or anhydrous basis (after water is removed). The value is almost always less than 100%. You must decide whether the purity and water content are significant enough to warrant adjusting the formula calculations. For example, if an API has a purity of 96% and water content of 4%, the material contains 92 mg/g of pure API.
- Water content: This can also be referenced as loss of drying. This value is the waters of hydration that are chemically bound to the API. For example, if the water content or loss on drying is 5%, 100 mg of your API material will contain 5 mg of water.
- pH: If the CSP is pH sensitive, this can be key information as you consider buffers for the CSP.

Dates

The last two items that should be on your COA are a couple of dates. Make sure you review these carefully. It is not uncommon to find errors associated with these dates, such as the month and year of expiration being before the manufacture date.

- Date of manufacture as well as the date of the last assay: If an API was manufactured over two years ago and that was when the assay was taken, there is a chance the material could have degraded, especially if it was not stored properly. This degradation could have an effect on the stability of the API or how hygroscopic (tendency to absorb moisture) the chemical is, both of which can affect the potency of the CSP. Some API suppliers retest their materials on a regular basis.
- Expiration date of the API: a date that must always be checked before an API is used.

Trust but verify

Be aware there have been cases where the API COA or labeling is wrong. Some examples include:

- The API COA states the material is USP grade when, in fact, the API is not.
- There are variations in the assay results from what is listed on the COA.
- The API is mixed with contaminants, such as the heparin contaminant that was discovered in API going back to 2008.
- The API is labeled as one drug and was later identified as another.

A COA does not provide complete assurance. For this reason, we recommend 503A pharmacies be familiar with the FDA guidance regarding Bulk Drug Substances Used in Compounding Under Section 503A of the FD&C Act. The FDA has issued warning letters to API repackagers for significant violations of current good manufacturing practice (CGMP), and as a result, the FDA recommends that you "Know Your Bulks Supplier."

Although not required for 503A pharmacies, the best assurance can be provided through identity testing of the API, which is performed by a contract lab. You can refer to the USP monograph for the specific identity tests required.

Summary

There are many data elements to consider when receiving API. The COA is more than just a piece of paper that comes with your chemicals. Do not assume that because it comes from an FDA-registered supplier it is acceptable. Not all APIs or API suppliers are created equal. The integrity of CSPs and the compounding process starts with a properly vetted API. It's what we owe our patients.

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References

[1] United States Pharmacopeial Convention, Inc. <797> Pharmaceutical Compounding—Sterile Preparations. 2024.

[2] Food and Drug Administration. Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients—Guidance for Industry. p. 48. September 2016. (accessed March 7, 2025)

[3] Food and Drug Administration. Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act—Guidance for Industry. p. 3. January 2025. (accessed March 7, 2025)

[4] Code of Federal Regulations. Title 21 - Food and Drugs. Chapter I – Food and Drug Administration Department of Health and Human Services. Subchapter C – Drugs: General. Sec. 207.1, (paragraph 2) April 1, 2020. (accessed March 7, 2025)

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