⟨1080⟩ BULK PHARMACEUTICAL EXCIPIENTS—CERTIFICATE OF ANALYSIS

1. INTRODUCTION

1.1 Purpose

This general information chapter is derived from the *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*, prepared by the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) and is meant to serve as a guide for the preparation and appropriate use of a Certificate of Analysis (COA) for pharmaceutical excipients. The goals are to standardize the content and suggest a format for COAs for excipients, and to clearly define the roles and responsibilities for the excipient manufacturer and distributor. The detailed definitions and discussions are intended to establish a uniform approach. By providing this foundation for mutual understanding, the COA will serve as an important element of the overall supply chain controls needed to provide the user with assurance of excipient conformance to specification and its suitability for use in pharmaceuticals.

The chapter is divided into several parts. The first part provides background discussion necessary for the design and required elements of a COA. The section *4. COA Content* is provided to show the format and placement of information in the COA. This is followed by a detailed discussion to ensure that the purpose and meaning of the specific information contained in the COA is understood. For a list of terms used in this informational chapter and their definitions, see the *Glossary*.

1.2 Scope

This chapter is applicable to excipients used in the manufacture of pharmaceutical products.

1.3 Principles Adopted

As an international guide, this informational chapter cannot specify all national legal requirements or cover in detail the particular characteristics of every excipient. When considering the use of this chapter, manufacturers, distributors, and users should consider how it may apply to that specific organization's product. The diversity of excipients means that some principles

of the chapter may not be applicable to certain products and processes. The terminology "should" and "it is recommended" do not necessarily mean "must" in the application of this chapter.

2. GENERAL GUIDANCE

The COA is a legal document that certifies the quality of the excipient and demonstrates that the batch conforms to the defined specifications, has been manufactured under recognized principles of good manufacturing practices (GMPs), and is suitable for use in pharmaceuticals. It should not be used in lieu of appropriate qualification of the supplier (*1*).

A COA for excipients should be prepared and issued by the company responsible for the material, following the general guidelines discussed below. It is expected that a complete and accurate COA is provided to the user for each batch and/or delivery of excipient. When analysis is performed by a distributor, the distributor should issue a COA to the user for any analysis that was performed by or on behalf of the distributor. In such cases, industry best practice is for the distributor to provide the user with the original manufacturer's COA and the distributor's COA.

Identification testing by the excipient manufacturer is not a regulatory requirement. The excipient manufacturer is not required to perform identity tests if they have process controls in place that together with testing ensure the identity of the excipient.

3. DESIGN AND REQUIRED ELEMENTS OF A COA

The elements of a COA listed below are included in *4. COA Content*. The excipient supplier may organize the elements on the COA at their discretion; however, the sections in this chapter have been designed to present the required and optional information in a logical manner.

The original manufacturer and manufacturing site should be identified if different from the supplier and supplier location. The intent is to enable the user to ensure that a change in manufacturing location has not occurred without their knowledge. It is essential that the manufacturer be known to the user. To protect confidentiality through the supply chain, the use of codes for manufacturers and manufacturing sites on the COA is acceptable as long as the user can link the code to the manufacturer and site of manufacture. The identity of the excipient should be definitively established by stating the compendial name and trade name (if any), the grade of the material, and the applicable compendial designations on the COA.

A batch number or other means of uniquely identifying the material quantity covered by the COA, and information relating specifically to it, are typically included in a body section (see *4.2 Body*). Unique identification of the excipient links the COA to the relevant specification and is traceable to a specified batch. The date of manufacture and, if applicable, the expiration date, recommended retest date, or other relevant statement regarding the stability of the excipient is typically included in this section (a detailed discussion of dates on the COA is contained in *6. Establishing Dates on a COA*). User-required information could also be included here.

The actual test results applicable to the quantity of material covered by the COA are included in *Appendix 1: Model COA*. Preferably, the acceptance criteria and test results are included for each characteristic listed. Test method designation and acceptance criteria may be communicated to the customer by reference to other controlled documents, e.g., sales specifications. Reporting of actual data and observations is recommended rather than nonspecific "passes" or "conforms" statements, unless the test is qualitative or this is the acceptance criteria as listed in a compendium or other specification.

If the reported results are not derived from sampling the finished excipient batch, it should be noted on the analysis section of the COA (see *7.2 Data versus Conformance* for a detailed discussion of such considerations). In such cases, alternative options for the origin of test results other than quality control laboratory testing include, for example (*2*):

- In-process testing
- Continuous monitoring of an attribute or variable and application of appropriate statistical process control (SPC) methods

It may be acceptable not to perform a test when the test attribute cannot be present or cannot fail to meet acceptance criteria, e.g., limited by upstream controls that involve measurement of an impurity to ensure it does not enter or form in the process. Not performing a specified test should be supported by a suitable documented rationale based on a documented risk assessment.

The section *4.3 Certification and Compliance Statements* is used to list various statements that may be required, depending on the excipient and agreed to user requirements. Any declaration by the supplier as to compliance with compendial and/or other regulatory requirements is typically included in this section.

The basis for COA approval should appear on the COA (see *8. Use of Electronically Generated COAs*).

4. COA CONTENT

The following information should appear on the COA or by reference. It is important that all pages of the COA are numbered and include the total number of pages for document control, to assure the customer that all pages of the COA are present. See *Appendix 1: Model COA* for an example.

4.1 Identifying Information

- Title "Certificate of Analysis"
- Identity and address of original manufacturing site: name or other suitable identifier that is unique to the manufacturer and site (e.g., code)

- Responsible organization that issues the COA, address, and contact information (if different from the original manufacturer)
- Name (compendial or chemical) and compendial designation, as applicable
- Grade
- Trade name
- Batch number

4.2 Body

- Date of manufacture
- Unique identifier to the excipient specification
- Expiration or retest date (as applicable) or stability statement
- Specification
  - Test name
  - Reference to the test method
  - Acceptance criteria
- Analysis
  - Test results based on the finished excipient sample, or
  - Alternative test results, as appropriate (see *7.3 Alternatives to Excipient Testing*)
  - Date retested (if appropriate)

4.3 Certification and Compliance Statements

- Standard of GMP applied (e.g., IPEC-PQG Excipient, ICH Q7, NSF/IPEC/ANSI 363, EXCiPACT™)
- Additional compliance statements and applicable references to standards
- Potential to meet additional compendial standards
- Content listing and grade of ingredients (if a mixture)
- Customer specified information

4.4 Authorization

- Identity of authorized individual for approval or electronic signature statement
- Date of approval or suitable alternative
- Page number (i.e., 1 of X pages)

5. REQUIREMENTS FOR COMPENDIAL DESIGNATION

For a supplier to claim a compendial grade on the COA for an excipient, there are two requirements to be met. The first requirement is that the excipient is manufactured according to recognized principles of GMPs (see *General Notices, 3.10 Applicability of Standards*). The second requirement is that the excipient meets all of the acceptance criteria contained in the appropriate compendial monograph, unless its difference is stated on its label, as defined under *General Notices, 3.20 Indicating Conformance*. These expectations remain in effect until its expiration or recommended retest date, when stored according to the manufacturer's recommendations in the manufacturer's original unopened container.

Every compendial article must be so constituted that when examined in accordance with these assay and test procedures, it meets all the requirements in the monograph defining it, as well as meeting any provisions of the *General Notices*, general chapters, or rules, as applicable. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with compendial standards before the batch is released for distribution. Data derived from in-process testing or continuous monitoring of an attribute with SPC may be used. With appropriate scientific justification, analytical methods that are equivalent or better (i.e., more accurate, more precise, etc.) to that which appears in the monograph may be substituted by the supplier when judging compliance of the batch with the compendial standards (see *7. Reporting of Data*).

6. ESTABLISHING DATES ON A COA

6.1 General Guidance

In reporting dates on COAs for excipients, it is important that a clear and unambiguous format be used to prevent possible misinterpretation. To accomplish this, it is recommended that the name of the month be used to designate the month (it may be abbreviated), rather than a numerical representation. It is also recommended that the year include all four digits (i.e., Jan. 1, 2010, or 1 Jan. 2010, etc.).

6.2 Date of Manufacture

The date of manufacture should be clearly defined by the original manufacturer and consistently applied for the particular excipient and process based on established policies and procedures.

It is important to note that while repackaging operations are to conform to GMP requirements, repackaging alone is not considered a processing step that can be used in determining the date of manufacture. To provide traceability for a specific excipient batch, other dates may be required in addition to the date of manufacture, to reflect additional steps such as repackaging.

6.3 Expiration Date and Recommended Retest Date

The stability of excipients may be an important factor in the stability of the finished pharmaceutical dosage forms that contain them. Therefore, it is important that the COA indicates stability of the excipient either by reporting the expiration date and/or the recommended retest date. This provides users with key information concerning the usability of the excipient in the period between the date of manufacture and the use of the excipient by the user.

Appropriate expiration and/or recommended retest dates for excipients should be established from the results of a documented stability-testing program or from documented historical data. Expiration and recommended retest dates should not be reported by a supplier without sufficient stability data or product history to support the assigned dates. Where the excipient is repackaged, the effect of this operation and the new packaging materials on the expiry or retest date should be evaluated to determine if such dates need to be changed.

The expiration date of an excipient cannot be extended. The retest date for an excipient is the date indicated by the supplier after which the excipient should be reevaluated to ensure continued compliance with appropriate specifications. An excipient retest date may be extended based upon appropriate testing. The reevaluation of the excipient may include physical inspection and/or appropriate chemical, physical, or microbiological testing.

It is acceptable to report both an expiration date and a recommended retest date on the COA for excipients, if applicable.

If stability data (*3*) are not available for an excipient, then an appropriate statement should be included on or with the COA to indicate what is known about the stability of the material, and/or whether stability studies are in progress.

6.4 Date Retested

If retesting is performed by an excipient supplier (as noted in *6.3 Expiration Date and Recommended Retest Date*), and the results are used by the supplier to extend the length of time that the material may be used, then the date retested should also be reported, preferably on the COA, but alternative communication means are acceptable. The specific tests that were subject to retesting should be clearly identified, and the results obtained upon retesting should be reported. After retesting, a new recommended retest date should be reported on the COA.

6.5 Additional Dates

Other dates may appear on a COA, if desired by the excipient supplier or requested by the user. Examples include the release date, shipping date, date of testing, and date the COA was printed or approved. Any additional dates that appear on a COA for excipients should include a clear indication of what the date represents.

Change to read:

7. REPORTING OF DATA

7.1 General Guidance

For the excipients listed in *USP–NF*, the product specifications are set by the supplier to include all attributes listed in the monograph. It is not required that analysis of all specification attributes be made on each lot. However, sufficient analysis and evidence of process stability should exist to ensure that the batch meets all specifications before it is released (see *7.3 Alternatives to Excipient Testing*). Periodic testing of all attributes should be performed to confirm continuing compliance. All the attributes should be verified at an appropriate frequency.

General Notices, 6.30. Alternative and Harmonized Methods and Procedures allows the use of alternative methods and/or procedures if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, and in some other aspects of the procedure performance and handling, and give equivalent or better results.

For excipients that are not included in *USP–NF*, specifications should be set by the supplier to ensure that the quality of the material is maintained on a continuing basis and reflects both the inherent properties of the excipient and its manufacturing process. Specification methods should be demonstrated to provide accurate, reproducible, and repeatable results for the characteristic(s) being tested.

7.2 Data versus Conformance

Finished excipient tests are often performed on bulk excipient after all manufacturing processes are complete but prior to packaging. “Where an in-process or bulk excipient test result is traceable to the finished excipient material, such a test result can be reported on the COA” (*2*). When a compendial or specification test is not performed on the excipient batch, in-process,

bulk, or package, this should be indicated on the COA. Typical statements or information in lieu of data may include the following:

- "Conforms"
- "If tested will meet compendial requirements"
- A footnote to indicate the last measurement or other suitable practice

Measurements reported on a COA can be derived from:

1. Testing a representative sample from the finished excipient batch
2. In-process testing of a representative sample where the attribute remains unaffected by further routine processing
3. Continuous monitoring of an attribute in combination with SPCs

Where number 2 or number 3 apply, the technique for how the test result was obtained should be described.

Some attributes [e.g., bovine spongiform encephalopathy (BSE)/transmissible spongiform encephalopathy (TSE)], *Residual Solvents* ⟨467⟩, *Elemental Impurities—Limits* ⟨232⟩, and/or genetically modified organism (GMO) statements may not be reported on the COA and may be provided separately.

7.3 Alternatives to Excipient Testing

For excipients used in drugs sold in the United States, if an excipient attribute "has required criteria, there must be some measurement or test of the material in each lot to ensure that the criteria are met. This may be a measurement from a surrogate test, from in-process control data, or from testing or measurement of the finished material in each lot. Conversely, FDA representatives believe that an approach, which allows for skip testing based on a satisfactory product quality history alone is not acceptable from a cGMP standpoint because such an approach does not adequately verify that each lot meets all of its specifications" (*2*).

It is noted that ICH Q6A allows for periodic/skip lot testing of the drug product and drug substance (*4*).

Results from in-process testing can also be used to replace testing on the finished excipient. "To ensure that a lot of excipient material complies with its required properties, it is acceptable to rely on tests or measurements conducted on samples of material taken at an in-process stage of production, provided that the in-process material will not be affected by subsequent processing or holding with respect to the attributes being verified. There should be justification that test results or measurements, or product performance characteristics, do not change from the in-process stage to the finished product" (*2*).

7.3.1 DOCUMENTATION

The supplier of an excipient should develop and maintain documentation that outlines the process control systems and validation data that justify the use of alternatives to finished excipient testing. This documentation should also include procedures for handling the impact of significant changes on the testing program (see ▲*Significant Change for Bulk Pharmaceutical Excipients* ⟨1195⟩▲ (CN 1-May-2021)).

7.3.2 EXAMPLES

See *Appendix 2: Alternatives to Excipient Testing—Examples*.

8. USE OF ELECTRONICALLY GENERATED COAs

COAs issued from computer systems without a handwritten signature are commonplace and are acceptable, provided the appropriate controls are in place. The following considerations should be met:

- Access to the computer system for COA management; entering and editing of data should be limited to authorized personnel
- Authentication by username and password as well as the change of each individual password at an appropriate frequency should be required
- Confirmation of the integrity and accuracy of the information stored in the system and transferred to the printed record should be completed during implementation and then periodically verified thereafter
- Data entered into a computer system from which information is extracted for a COA and changes made thereafter should be accompanied by time- and date-stamped audit trails

With these criteria met, the issuance of electronically generated COAs is acceptable, provided the COA includes contact information.

9. DISTRIBUTOR INFORMATION

Distributors provide excipients and associated services such as:

- Make excipient available in the manufacturer's unopened original package (pass through)
- Repackage excipients from bulk quantities
- Purchase excipients for repackaging under a different label

A distributor should not change the original title and data of the COA or other quality documents. Whenever possible, the original manufacturer's documentation should be used, or transcription of data should be verified.

It is expected that the distributor will have the appropriate level of GMP in place (see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩).

GLOSSARY

Acceptance criteria: Numerical limits, ranges, or other suitable measures of acceptance for test results.

Batch (lot): A specific quantity of material produced in a process or series of processes so that batch can be expected to have uniform character and quality within specified limits. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch (lot) number: A unique combination of numbers, letters, and/or symbols that identifies a batch and from which the production and distribution history can be determined.

Batch process: A manufacturing process or processing step that produces the excipient from a discrete supply of raw material that is present before the completion of the reaction.

Certificate of analysis (COA): A document listing the test methods, specification, and results of testing a representative sample from the batch to be delivered.

Chemical property: A quality attribute that is measured by chemical or physicochemical test methods.

Continuous process or processing: A process that continually produces the excipient from a continuing supply of raw material.

Contract facility: An internal or external facility that provides services to the manufacturer or distributor of an excipient. These can include, but are not limited to, the following: manufacturing facilities, laboratories, repackaging facilities (including labeling), and warehouses.

Date of manufacture: A date indicating the completion of the final manufacturing process (as defined by the supplier for the particular excipient and process).

Date retested: The date when retesting is performed by an excipient supplier to extend the length of time that the material may be used.

Distributor: All parties in the distribution/supply chain starting from the point at which an excipient is transferred outside the control of the original manufacturer's material management system including parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.

Excipient: Substances other than the drug substance that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Expiry (expiration) date: The date designating the time during which the excipient is expected to remain within specifications and after which it should not be used.

Impurity: Any component of an excipient that is not the intended chemical entity but is present as a consequence of the raw materials, excipient manufacturing process, or excipient degradation.

Original manufacturer or manufacturer: Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material.

Packaging: The container and its components that hold the excipient for storage and transport to the customer.

Physical property: A quality attribute that can be measured solely by physical means.

Process: The combination of operating steps (including synthesis, isolation, purification, packaging, etc.) that produce the finished excipient.

Process capability index (C_p): A statistical measurement that can be used to assess whether or not the process is adequate to meet specifications. A state of statistical control can be said to exist if the random variation in test results for a process attribute is such that the calculated process capability is >1.33 (see *Appendix 2: Alternatives to Excipient Testing—Examples* for further definition).

Process step: A documented instruction to the pharmaceutical excipient manufacturing personnel directing that an operation be done.

Processing: Operations to change product characteristics by mainly physical treatment through, e.g., milling, sieving, distilling, filtration, blending.

Repackaging: The action of changing the packaging of the material.

Retest date: The date when a specific batch of material must be reexamined to ensure that it is still suitable for use.

Skip lot (periodic) testing: The performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis, with the understanding that those batches not tested still must meet all the acceptance criteria established for that product. This represents a less than full schedule of testing and therefore should be justified, presented to, and approved by the regulatory authority before implementation. When tested, any failure of the starting material to meet the acceptance criteria established for the skip lot (periodic) test should be handled by proper notification of the appropriate regulatory authority or authorities. If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

Significant change: Any change that has the potential to alter an excipient's physical, chemical, or microbiological property from the norm, and/or that may alter the excipient's performance in the dosage form.

Site: A defined location of the equipment in which the excipient is manufactured. It may be within a larger facility. A change in site may be to a different part of the existing facility, but in a different operational area, or to a remote facility including a contract manufacturer.

Specification: A list of tests; references to analytical procedures; and pre-established numerical limits, ranges, or other criteria for the tests described for a material, that the material is required to meet.

Stable process: A process is considered stable when the output of the process, regardless of the nature of the processing (batch or continuous), can be demonstrated by appropriate means to show a level of variability that consistently meets all aspects of the stated specification (both USP specific and customer specific) and is thus acceptable for its intended use.

Stability: Continued conformance of the excipient to its specifications.

Supplier: Person or company providing pharmaceutical starting materials on request. Suppliers may be distributors, manufacturers, traders, etc.

Supply chain: All steps in the entire chain of distribution starting from the point at which an excipient is transferred outside the control of the original manufacturer's material, to a management system downstream, to the final user of the excipient.

User: A party who utilizes an excipient in the manufacture of a drug product or another excipient.

APPENDICES

Appendix 1: Model COA

The following sample COA is provided to illustrate the principles discussed in the guide and is not meant to be prescriptive.

Certificate of Analysis (sample tests, limits, and statements are for demonstration purposes)

Supplier Company Name			
Supplier Company Address			
Manufacturing Location			
Name of Manufacturer (if different from Supplier)		Phone: **xxx-xxx-xxxx**	
Manufacturing Site Address		Fax: **xxx-xxx-xxxx**	
Product: **Trade Name and Descriptor or Common Name**			
Grade: **Grade Designation**		Customer Code: **xxxxxx** (if applicable)	
Batch Number: **xxxxxx**		Date of Manufacture: **dd/mmm/yyyy**	
Recommended Retest Date: *<time from date of manufacture>*			
Compendial Name and Listing: *USP–NF*, *Ph.Eur.*, *JP*, or *JPE* (List multiple names and designations if nomenclature is different in each compendium)			
Test Results (sample tests & limits for demonstration purposes)			
Test	**Test Method**	**Specification**	**Results**
Appearance	Visual examination	White granular powder	Complies
Foreign matter	Visual examination	Free from visible contamination	Complies
Identification—JPE	Tests A–C	Pass	Complies
Clarity and color	*JPE*	Clear and colorless	Complies
pH (x% solution)	*USP*	5.0–7.0	#.#
Residue on ignition	*JPE*	NMT 1.0% (450°–550°C)	#.# %
Viscosity (x% solution)	*Ph.Eur.*	4.0–7.0 mPa-s (@20°C)	#.# mPa-s
Water insoluble sub.	*USP*	NMT 0.1%	#.# %
Loss on drying (110°C)	*USP*	NMT 5.0%	#.# %
Loss on drying (105°C)	*JPE*	NMT 6.0%	#.# %
Particle size	Supplier method #	99.5% <150 µm	####
Additional Information (sample tests & limits for demonstration purposes)			
Heavy metals	*JPE*	NMT 10 ppm (as Pb)	NMT 10 ppm[a]
Arsenic	*JPE*	NMT 2 ppm	NMT 2 ppm[b]

[a] This test is performed in-process on each batch and the material has been shown not to change in the finished excipient sample.
[b] This test is performed quarterly based on process validation.

The following sample COA is provided to illustrate the principles discussed in the guide and is not meant to be prescriptive.

Supplier Company Name
Supplier Company Address
Product: **Trade Name and Descriptor or Common Name**
Grade: **Grade Designation**
Batch Number: **xxxxxxx**
Certification and Compliance Statements
GMP compliance: This batch of *<**Trade Name**>* has been manufactured using excipient GMP.

Compendial standards: This batch of <***Trade Name***> complies with all of the current requirements listed in the *United States Pharmacopeia* (*USP*), the *European Pharmacopoeia* (*Ph.Eur.*), and the *Japanese Pharmaceutical Excipients* (*JPE*).
Other certification statements: Any other type of certification e.g., Residual Solvents, GMO derived, or customer-specific information, should be listed here. These may vary depending on regional regulatory requirements, specific GMP issues, and customer desired information, based on their use of the excipient.
Identity of authorized individual for approval: xxxxxxxxxxxxxxxxxxxxxxxx
Title
Date of approval: dd/mmm/yyyy
This COA was released from a controlled electronic document management system.

Appendix 2: Alternatives to Excipient Testing—Examples

The following are examples of situations where alternatives to finished excipient testing might be justified. These are not the only situations where a sound technical basis can be demonstrated, neither are they examples of situations where alternatives to finished excipient testing will always be appropriate.

- An impurity, byproduct, or unreacted raw material could not be present in the product because the raw materials and chemical reactions used could not contain or generate it above the specified limits.
- The process capability index (*Cp*) for the relevant attribute is high and thus indicates a stable process. Statistical analysis of the reduced frequency data should show that the property remains stable and within specifications. A process is considered stable when the output of the process, regardless of the nature of the processing (batch or continuous), can be demonstrated, by appropriate means, to show a level of variability that consistently meets all aspects of the stated specification (both pharmacopeia and user specific) and is thus acceptable for its intended use. For continuous processing, it is also important to demonstrate that the material has been produced under conditions where the process has achieved a form of "steady state", i.e., minimal operator intervention and the in-process attributes have been stabilized.
- For a continuous process, the in-process analyses show that the property that is determined at a reduced frequency is stable and within specification. Repeating the test on each batch would be redundant.
- An analysis of an attribute that is determined on every batch in process has been shown to provide assurance that the final test requirement can be met. Such data can be used to support testing the finished excipient at reduced frequency.

REFERENCES

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