The International Pharmaceutical Excipients Council

Certificate of Analysis Guide for Pharmaceutical Excipients

2013

The IPEC Certificate of Analysis Guide for Pharmaceutical Excipients

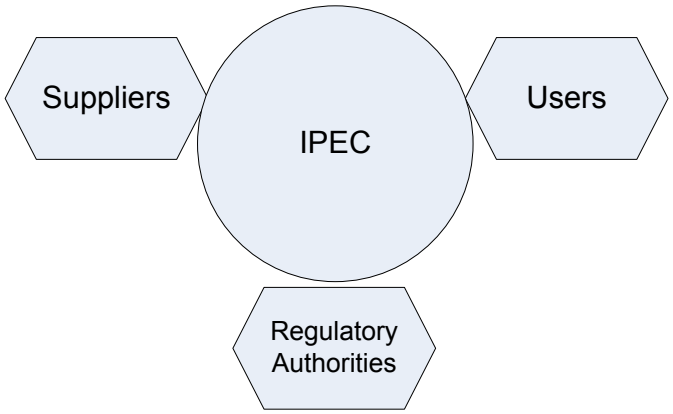
This document represents voluntary guidance for the pharmaceutical excipient industry and the contents should not be interpreted as regulatory requirements. Alternative approaches to those described in this guide may be implemented**.**

FOREWORD

International Pharmaceutical Excipients Council (IPEC) is an international industry association formed in 1991 by manufacturers, distributors and end-users of excipients. At the time of writing there are regional pharmaceutical excipient industry associations including the Americas, Europe, China, and Japan. IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of best practice and guidance concerning excipients.

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, who are considered suppliers in this document,
2. Pharmaceutical manufacturers, who are called users, and
3. Regulatory authorities who regulate medicines.



This document offers best practice and guidance on the content of an excipient **Certificate of Analysis** (COA). It is important that the reader confirm this is the latest version of the guide as found on ipecamericas.org or ipec-europe.org.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS
This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council, an industry association whose members consist of excipient manufacturers, distributors, and users. The company representatives who worked on this Guide are listed below:

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1 INTRODUCTION

1.1 Purpose

This document is meant to serve as a guide for the preparation and appropriate use of a **Certificate of Analysis (COA)** for pharmaceutical **excipients**. [Note that the first time a term is used, it is denoted in bold typeface and is defined in the IPEC Glossary[1].] The goal is 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.

1.2 Scope

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

1.3 Principles Adopted

This is an international guide. As such it cannot specify all national legal requirements or cover in detail the particular characteristics of every excipient.

When considering the use of this guide, manufacturers and distributors should consider how it may apply to that specific organization's product. The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The terminology "should" and "it is recommended" do not necessarily mean "must" and common sense should be used in the application of this guide.

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 excipient GMP, and is suitable for use in pharmaceuticals. It should not be used in lieu of appropriate qualification of the supplier.[2]

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

[1] IPEC Glossary www.ipecamericas.org/glossary
[2] IPEC *Qualification of Excipients for Use in Pharmaceuticals*, 2008

excipient manufacturer is not required to perform identity tests if they have process controls in place that together with testing assure the identity of the excipient.

3 DESIGN AND REQUIRED ELEMENTS OF A CERTIFICATE OF ANALYSIS

The elements of a COA listed below are included in the COA Content section of the guide (see section 4). The excipient supplier (manufacturer or distributor) may organize the elements on the COA at their discretion; however, the sections 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 assure that a change in manufacturing location has not occurred without their knowledge[3]. 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 compendial and trade name, the grade of the material, and applicable compendial designations.

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. Unique identification of the excipient links the COA to the relevant specification[4] 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 Section 6). 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 an Analysis Section. The acceptance criteria and test results are preferably 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 non-specific “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 Section 7.2 for a detailed discussion of such considerations). In such cases alternative options for the origin of test results other than

[3] Note that a Confidentiality Agreement or Quality Agreement may be required.
[4] Best practice is to include a reference to the User’s current specification, i.e., specification number and version or issue date on the COA.

Quality Control laboratory testing include for example[5]:

- In-process testing, or
- 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 for an impurity to assure 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 Certification and Compliance Statements Section (4.3) is used to list various statements that may be required depending on the excipient and agreed 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 (Section 8).

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 and to assure the customer that all pages of the COA are present. See Appendix 3 for a model COA.

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 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

[5] Brian Carlin, Dale Carter, Moira Griffiths, Gregory Larner, Kevin Moore, Barry Rothman, David Schoneker, Catherine Sheehan, Rajendra Uppoor, Phyllis Walsh, and Robert Wiens, *Joint Position Paper on Pharmaceutical Excipient Testing and Control Strategies*, Pharm. Technol. **31** (9) 2007 pages 1-19

- Specification
  - Test Name
  - Reference to the Test Method
  - Acceptance Criteria
- Analysis
  - Test Results based on finished excipient sample, or
  - Alternative test results, as appropriate (Section 7.3)
  - Date Retested (if appropriate)

4.3 Certification and Compliance Statements (may be provided in other documents, e.g. Excipient Information Package[6])

- Standard of GMP applied (e.g., IPEC-PQG Excipient, ICH Q7)
- 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[7]. The first requirement is that the excipient is manufactured according to recognized principles of good manufacturing practices. The second requirement is that the excipient meets all of the acceptance criteria contained in the appropriate compendial monograph. These expectations remain in effect until its expiration or recommended retest date when stored according to manufacturers' recommendations in the manufacturer's original unopened container.

Every compendial article shall 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."[8] Data derived from in-process testing or continuous monitoring of an attribute

[6] International Pharmaceutical Excipients Council of the Americas Standardized Excipient Information Protocol User Guide 2005

[7] Joint IPEC-PQG Good Manufacturing Practice Guide for Pharmaceutical Excipients, 2006 and General Notices to the USP and Ph.Eur.

[8] WHO Technical Report Series, No. 902 and 908

with statistical process control 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 Section 7).

6 ESTABLISHING DATES ON A CERTIFICATE OF ANALYSIS

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 an alphabetic designation be used for the month (it may be abbreviated), rather than a numerical representation. It is also recommended that the year include all 4-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 **re-packaging** 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 re-packaging.

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[9]. Where the excipient is re-packed, 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 re-evaluated to ensure continued compliance with appropriate specifications. An excipient retest date

[9] IPEC Excipient Stability Program Guide 2009

may be extended based upon appropriate testing. The re-evaluation 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. Expiration and Recommended Retest Dates should not be reported by a supplier without sufficient stability data or product history to support the assigned dates.

If stability data in accordance with the IPEC Stability Guide is 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) 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.

7 REPORTING OF DATA

7.1 General Guidance

Many excipients are listed in pharmacopeias and other standard reference works. The excipient specifications are set by the supplier to include all necessary parameters. Some pharmacopeias do not require that analysis of all specification parameters be made on each batch[10] prior to release. However, sufficient analysis and evidence of process stability should exist to assure that the batch meets all specifications before it is released (see 7.3). Periodic testing of all parameters should be performed to confirm continuing compliance. All the parameters should be checked at an appropriate frequency.

The USP-NF and Ph.Eur. allow the use of alternate methods of testing provided the alternate methods have been shown to be as effective or better than the monograph methods.

[10] See current USP-NF, *General Notices*; Ph.Eur., *General Notices*; 21 CFR 211.84 (d) (2)

For excipients that are not included in any pharmacopeia, 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 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."[5] When a compendial or specification test is not performed on the excipient batch, in-process, bulk or packaged, this should be indicated on the COA. Typical statements in lieu of data are "conforms", "if tested will meet compendial requirements", use of 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 statistical process controls.

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

Some attributes e.g., BSE/TSE, Residual Solvent <467>, may not be reported on the COA, but may be provided separately, e.g., in an Excipient Information Package.

7.3 Alternatives to Excipient Testing

For excipients used in drugs sold in the U.S., 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 batch. 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."[5]

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

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."[8]

7.3.1 **Documentation**

The supplier of an excipient should develop and maintain documentation which outlines the process control systems and validation data which 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[11].

7.3.2 Examples

See Appendix 2

8 USE OF ELECTRONICALLY GENERATED CERTIFICATES OF ANALYSIS

Certificates of Analysis issued from computer systems without a handwritten signature are common place 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 checked 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:

- Provide excipient in the manufacturers unopened original package (pass through)
- Repackage from bulk quantities
- Purchase of excipients for re-packaging under a different label.

The nature of the associated services may impact the COA provided as discussed in the IPEC *Good Distribution Practices Guide for Pharmaceutical Excipients* section 6.3.

[11] IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients (2009).

It is expected that the distributor will have the appropriate level of good manufacturing practice in place (for example the Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients* or the IPEC *Good Distribution Practices Guide for Pharmaceutical Excipients)*.

APPENDIX 1

REFERENCES

The Joint IPEC – PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients*, 2006

IPEC *Qualification of Excipients for Use in Pharmaceuticals*, 2008

IPEC *Good Distribution Practices Guide for Pharmaceutical Excipients*, 2006

International Pharmaceutical Excipients Council of the Americas *Standardized Excipient Information Protocol User Guide* 2005

International Pharmaceutical Excipients Council of the Americas *Significant Change Guide for Bulk Pharmaceutical Excipients*, 2009

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ANSI/ASQC A1-1978, Definitions, Symbols, Formulas and Tables for Control Charts, ASQC, (1978), Milwaukee, WI

APPENDIX 1

Quality Assurance for the Chemical and Process Industries: A Manual of Good Practices, Chemical Interest Committee, Chemical and Process Industries Division, American Society for Quality Control, (1987), ASQC Quality Press, Milwaukee, WI

21 CFR Part 11 Electronic Records; Electronic Signatures; Final Rule

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, by-product 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 parameter 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 which 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 parameters have been stabilized.
- For a continuous process, the in-process analyses show that the property which is determined at reduced frequency is stable and within specification. Repeating the test on each batch would be redundant
- An analysis of a parameter 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.

APPENDIX 3

The following example 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)
Manufacturing Site Address

Phone: **xxx-xxx-xxxx**
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 –550C)	#.# %
Viscosity (x% solution)	Ph.Eur.	4.0 – 7.0 mPa-s (@20c)	#.# mPa-s
Water Insoluble Sub.	USP	NMT 0.1%	#.# %
Loss on Drying (110C)	USP	NMT 5.0%	#.# %
Loss on Drying (105C)	JPE	NMT 6.0%	#.# %
Particle Size	Supplier Method #	99.5% <150 Microns	####

ADDITIONAL INFORMATION (sample tests & limits for demonstration purposes)

Heavy Metals	JPE	NMT 10 ppm (as Pb)	NMT 10 ppm*
Arsenic	JPE	NMT 2 ppm	NMT 2 ppm[+]

* This test is performed in-process on each batch and the material has been shown not to change in the finished excipient sample.

[+] This test is performed quarterly based on process validation.

Certificate of Analysis

APPENDIX 3

The following example 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 Good Manufacturing Practice*s*.

Compendial Standards: This batch of ***<Trade Name>*** complies with all of the current requirements listed in the United States Pharmacopeia (USP), the European Pharmacopeia (Ph.Eur.) and the Japanese Pharmaceutical Excipients (JPE).

Other Certification Statements: Any other type of certification, e.g., Residual Solvents, Genetically Modified Organism (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.