The International Pharmaceutical Excipients Council

Certificate of Analysis Guide

For Pharmaceutical Excipients

Version 2.1
2024

This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this guide may be used to achieve an equivalent level of assurance for excipient quality.

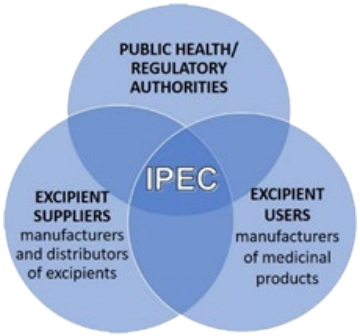
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient development.

IPEC has three major stakeholder groups:

1. Excipient manufacturers and distributors, defined as suppliers in this document,
2. Medicinal (drug) product manufacturers, defined as users in this document, and
3. Public health and regulatory authorities.



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of the reader to review the latest version of the applicable regulatory guidance; however, the version referenced in the guide will be based on the version available at the time the guide was published.

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In this guide, pharmaceutical excipient(s) will be referred as excipient(s). This guide may be applied to veterinary medicines, as appropriate with reference to specific veterinary guidance and regulations.

Throughout the guide, justification implies that a decision is made based on a scientific, quality and/or regulatory considerations.

This guide offers best practice and guidance for an excipient certificate of analysis (CoA).

*Note: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms [1]" for definitions. The first use of a term found in the glossary will be in **BOLD**.*

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This guide was developed by representatives from International Pharmaceutical Excipients Council (IPEC) member companies. IPEC is an industry association whose members consist of excipient manufacturers, distributors, and users.

IPEC greatly appreciate the many hours devoted by the core team of individuals and other contributors listed below, to make this guide available to IPEC members and the broader excipient community. Equally, IPEC extend their thanks to the employers of those same contributors who provide the necessary time and resources, without which, this guide would not be possible.

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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** (excipients). 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 demonstrate that the excipient conforms to its **specification**s and is suitable for use in medicinal products.

1.2 Scope

This guide is applicable to excipients used in the manufacture of medicinal products. Information in the guide may also apply to excipients used in veterinary medicines.

1.3 Principles Adopted

This is an international guide. As such it cannot specify all national legal requirements nor 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 term "should" indicate recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of quality assurance. Note that "should" does not mean "must" or "shall".*

This guide includes notes that offer common examples for interpretation and implementation without adding further requirements. Notes are not intended to contain an exhaustive list. They are presented as indented, italicized text.

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 medicinal products. 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 excipient user for each batch. An additional COA is issued when additional testing is performed by a distributor.

Although identification (ID) tests are typically part of a compendial **monograph**, identification testing by the excipient manufacturer is not a regulatory requirement in some countries. In such instances, identity testing may be waived for dedicated processes or if the excipient manufacturer has process controls in place that together with testing assure the identity of the excipient.

Note: In most countries, identification testing is a regulatory requirement for the medicinal product manufacturer to perform on each receipt of an excipient.

There are multiple ways of including ID testing on the COA. If tested routinely, ID should be listed on the COA (in the test table) with reference to the specific test performed. If the ID test is not performed on the batch, this should be clearly indicated on the COA.

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 (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[1]. It is essential that the manufacturer be known to the user.

The identity of the excipient should be definitively established by stating compendial name and designation, where applicable. If not compendial, the chemical name, trade name and **grade** of the material should be listed.

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[2] 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.

[1] Note that a Confidentiality Agreement or **Quality Agreement** may be required. (refer to IPEC QA Guide [24])

[2] 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.

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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 clearly on the analysis section of the COA (section 7.2 for a detailed discussion of such considerations). In such cases alternative options for the origin of test results other than Quality Control laboratory testing sometimes includes for example [3]:

- In-process testing, or
- Periodic monitoring according to defined plans or continuous monitoring of an attribute or variable with Statistical Process Control (SPC).

When the test attribute cannot be present or cannot fail to meet acceptance criteria, it may be acceptable not to perform a test, for example, limited by upstream controls that involve measurement for an **impurity** to assure it does not enter or form in the process. If a specific test is not performed it should be supported by a documented rationale based on a risk assessment such as referencing historical data.

The Certification and Compliance Statements Section (section 4.3) is used to list various types of statements that may be required depending on the excipient and agreed user requirements. Any declaration by the supplier as to compliance to compendial and/or other regulatory requirements is typically included in this section or provided as a standalone document.

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 Annex 1 for a model COA.

4.1 Body

- Titled “Certificate of Analysis”
- Identity name and address of original manufacturing site
- 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
- Date of manufacture
- Unique identifier to the excipient specification (e.g., USP, NF, Ph. Eur., JP, ChP)
- Expiration or retest date (as applicable) or stability statement
- Where applicable, storage conditions may be mentioned, e.g., for moisture or temperature sensitive materials
- Specification
    - Attribute name
    - Reference to the test method
    - Acceptance criteria or reference to alternative document (e.g., customer-specific criteria included in the **Quality Agreement** [11])
- Analysis
    - Test results based on finished excipient sample, or
    - Alternative test results, as appropriate (section 7.3)
    - **Date retested** and retest interval (if appropriate)

4.2 Certification of Compliance (COC) Statements

- Standard of GMP applied (e.g., IPEC-PQG Excipient GMP, EXCiPACT®)
- Additional compliance statements and applicable references to standards
- Potential to meet additional Compendial Standards (i.e., would comply with another pharmacopoeia, if tested)
- Content listing and grade of ingredients (if a **mixture**)
- Customer specified information

Note: COC statements may be provided in other documents, e.g., Excipient Information Package [4]

4.3 Authorization

- Identity of authorized individual for approval or electronic signature statement with traceability to signatory
- Date of manufacture
- Page Number (i.e., 1 of X pages)

The excipient supplier and user may agree upon special Certificate of Analysis requirements, as required in a Quality Agreement [11].

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 under appropriate **good manufacturing practices** (**GMPs**) [5]. 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.

USP General Notices 3.20 [6] states

> *A drug product, drug substance, or excipient may use the designation "USP" or "NF" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the identity prescribed in the specified compendium.*
>
> *The designation "USP–NF" may be used on the label of an article provided that the label also bears a statement such as Meets NF standards as published by USP", indicating the particular compendium to which the article purports to apply*.
>
> *When the letters "USP," "NF," or "USP–NF" are used on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article.*

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**" [7,8]. Data derived from in-process testing or continuous monitoring of an attribute with statistical process control may be used. On the basis of appropriate justification, analytical methods (including acceptance criteria) that are equivalent or better (i.e., accurate, 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 (section 7). Organoleptic properties, such as appearance, colour and odour are not required to be listed on a COA, unless these attributes are part of a compendial monograph.

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, 2022, or 1 Jan. 2022, 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 that while **re-packaging** operations are to conform to GMP requirements, to provide full **traceability** for a specific excipient batch, both the original Date of Manufacture and date of additional steps, such as re-packaging, are required.

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]. The expiration date and/or the retest date assigned by the excipient supplier applies to the original, unopened package stored at the conditions recommended for storage. 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 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 provided that the Recommended Retest Date is not the same as and does not exceed the Expiration Date. 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.

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6.4 Date Retested

If retesting is performed by an excipient supplier (as noted in section 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 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, 11, 12] 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 (section 7.3). Unless otherwise justified, periodic testing of all parameters should be performed, at an appropriate frequency, to confirm continuing compliance. All the parameters should be checked at an appropriate frequency. When a parameter is tested on a monitoring basis, this should be indicated on the COA.

The USP, Ph. Eur.[3] ChP and JP allow the use of alternate methods of testing provided the alternate methods have been validated and shown to be as effective or better than the monograph methods.

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 excipient manufacturing process and inherent properties. Specification methods should be demonstrated to provide accurate, reproducible and repeatable results for the characteristic being tested.

[3] Ph. Eur. only allows for this when the competent authority allows for it.

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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 [3].” 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.
4. Periodic monitoring of an attribute according to a defined plan,

Where 2, 3 or 4 apply, the technique for how the test result was obtained should be described.

Some attributes e.g., Residual Solvent *USP General Chapter* <467> and Elemental impurities *Ph. Eur. General Chapter 5.20*, due to the excipient’s method of manufacture, may not be reported on a COA but evidence of compliance may be provided in a separate correspondence.

7.3 Alternatives to Excipient Testing

For excipients used in medicinal products, if an excipient attribute “has required criteria”, there must be some measurement or test of the material in each batch 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. Periodic or **skip-lot testing** is acceptable for certain tests [3, 13], with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. Since this would represent a less than full schedule of testing, periodic and/or skip-lot testing should be justified. Appropriate determination to ensure that each batch conforms to appropriate specifications could involve some combination of the following approaches to support that testing is not applicable:

- End-product testing
- In-process testing
- Continuous monitoring of an attribute with statistical process controls
- Documented rationale why a certain test is not required (e.g., residual solvent cannot be present based on method of manufacture).

Results from in-process testing can also be used to replace testing on the finished excipient. “To ensure that a batch of excipient material complies with its required properties, it is acceptable to

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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 [7, 8]."

7.4 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 final excipient testing. This documentation should also include procedures for handling the impact of **significant changes** on the testing program [14].

Unless specified by local regulations, best practice is for an excipient manufacturer to maintain a copy of the CoA for at least one year after the established **shelf life**.

7.5 Example

See Annex 1.

8 ELECTRONICALLY GENERATED CERTIFICATE OF ANALYSIS

Certificates of Analysis issued from computer systems without a handwritten signature are common practice and are acceptable provided the appropriate controls are in-place. Data integrity principles, i.e., ALCOA +, should be incorporated in the procedures and systems used to generate COAs, including the following considerations:

- Access to the computer system for COA management, through username and password, to enter or edit data should be limited to authorized personnel. The system should require periodic changes at an appropriate frequency of each individual password
- Confirmation of the integrity and accuracy of the information stored in the system and transferred to the printed record should be completed during computer system 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

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- 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 GDP Guide [15], section 6.3.

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 [5] or the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients [15]).

10 COA VERIFICATION BY THE MEDICINAL PRODUCT MANUFACTURER

Medicinal product manufacturers should review and verify the COA during the excipient manufacturer qualification process, as described in the IPEC Qualification of Excipient Guide [2]. Data from the COA can only be used to support a release of an excipient batch (under a reduced testing program) if the excipient manufacturer is fully qualified [5]. The medicinal product manufacturer needs to review the COA for every batch received.

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11 REFERENCES

IPEC documents referenced below can be accessed at the following website links:
IPEC-Americas page: https://ipecamericas.org/
IPEC Europe page: https://www.ipec-europe.org/guidelines.html

1. IPEC *General Glossary of Terms and Acronyms*
2. IPEC *Qualification of Excipients for Use in Pharmaceuticals*.
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4. IPEC *Standardized Excipient Information Protocol User Guide*
5. The Joint IPEC – PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients*
6. United States Pharmacopoeia (USP) General Notices 3.20
7. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902)
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9. IPEC *Excipient Stability Guide*
10. United States Pharmacopeia/ National Formulary (USP-NF) General Notices
11. European Pharmacopoeia General Notices
12. US FDA Code of Federal Regulations, 21 CFR 211.84(d)(2)
13. ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.
14. IPEC *Significant Change Guide for Bulk Pharmaceutical Excipients*
15. IPEC *Good Distribution Practices Guide for Pharmaceutical Excipients*
16. 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
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20. Japanese Pharmacopoeia (JP)
21. Japanese Pharmaceutical Excipients (JPE)
22. Chinese Pharmacopoeia (ChP)
23. US FDA 21 CFR Part 11 Electronic Records; Electronic Signatures; Final Rule
24. IPEC *Quality Agreement Guide and Template(s)*

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ANNEX 1
MODEL COA

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 **Phone:** xxx-xxx-xxxx

Name of Manufacturer (if different from Supplier) Email: xxx-xxx-xxxx

Manufacturing Site Address

Product: **Trade Name and Descriptor or Common Name**

Grade: **Grade Designation**

Batch Number: **xxxxxx** Date of Manufacture: **dd/mmm/yyyy**

Recommended Retest Date: <***time from date of manufacture***>

Storage conditions, if applicable[4]

Name (compendial or chemical) and Compendial Designation, as applicable: **XXX** (e.g., USP, NF, Ph. Eur., JP, JPE, ChP)
(List multiple names and designations if nomenclature is different in each compendium)

TEST RESULTS (sample tests & limits for demonstration purposes)

Attribute	Test Method	Specification	Results
Identification[5]	NF, Ph. Eur.	Pass	Complies
Clarity and Colour	JPE	Clear and colourless	Complies
pH (x% solution)	NF	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.	NF	NMT 0.1%	#.# %
Loss on Drying (110C)	NF	NMT 5.0%	#.# %
Loss on Drying (105C)	JPE	NMT 6.0%	#.# %
Particle Size	Supplier Method #	99.5% <150 Microns	####

[4] For USP-NF materials, refer to USP General Chapter <659>
[5] Refer to section 2 for details

Certificate of Analysis

Supplier Company Name
Supplier Company Address

Product: **Trade Name and Descriptor or Common Name**

Grade: **Grade Designation**

Batch Number: **xxxxxx** Date of Manufacture: **dd/mm/yyyy**

ADDITIONAL INFORMATION (sample tests & limits for demonstration purposes)

Nickel	NF	NMT 5 ppm	NMT 5 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.

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 National Formulary (NF), 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) status, 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 or electronic signature statement traceable to Signatory: **xxxxxxxxxxxxxxxxxxxxxx**

Date of approval: **dd/mm/yyyy**

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ANNEX 2
ALTERNATIVES TO EXCIPIENT TESTING EXAMPLE

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) on the relevant parameter is high and based on 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.

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