2013 Certificate of Analysis Guide for Pharmaceutical Excipients

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DEFINING QUALITY

Overview

- IPEC Background info
- Why a new CoA guide?
- Access to guide
- Position of guide within the regulatory environment
- Major changes
- General Guidance
- Format, Design and Required Elements
- Further Details on Requirements

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IPEC Offers Excipient Stakeholders a Regional Voice with Global Influence

IPEC Federation
- Established in 2009,
- based in Belgium / made up of regional IPECs

IPEC-Americas
- North, South and Middle Americas
  Partnership with Sindusfarma (Brazil) and SaFybi (Argentina)

IPEC-Europe
- Europe, North Africa, Middle East

IPEC Japan

IPEC China

IPEC India (being formed)

IPEC: Where Industry Standards are Defined by The Excipient Experts

- The IPEC Federation pursues harmonization of Guides across regional IPEC organizations
- IPEC is a non-profit trade association with many diverse member companies
  - Excipient development
  - Excipient manufacturing and distribution
  - Pharma companies that use excipients

This is a subset of the 62 companies that are members of IPEC-Americas

Is your company an IPEC member?

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Learn More About How to Get Involved with IPEC at IPECAmericas.Org

- IPEC Americas' contributions
  - 12 industry standard setting Guides
  - The association has taken leadership positions on impactful topics such as USP's Chapter on Residual Solvents and FDA's Guidance on Melamine
  - Annual regulatory and educational conferences
- Member company benefits
  - Influence industry standards
  - Participate in new developments while they are emerging
  - Network and collaborate with excipient related companies, academics, and regulators

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IPEC GMP Related Guides and Initiatives

- IPEC Excipient Information Package User Guide, 2013
- **IPEC Certificate of Analysis Guide for Pharmaceutical Excipients, 2013**
- IPEC-Americas Good Distribution Practices Audit Guide For North American Distribution of Pharmaceutical Excipients, 2011
- The Joint IPEC – PQG Good Manufacturing Practices Guide, 2006
- The Joint IPEC–PQG Good Manufacturing Practices Audit Guide, 2007
- **IPEC- Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009**
- IPEC-Americas Excipient Master File Guide, 2004
- IPEC Qualification of Excipients for Use in Pharmaceuticals Guide, 2008
- The IPEC Excipient Stability Program Guide, 2010

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Other IPEC Guides and Initiatives

- The IPEC Quality Agreement Guide and Template, 2009
- IPEC Good Distribution Practices Guide, 2006
- The IPEC Excipient Composition Guide, 2009 (new)
- IPEC Americas and Europe Excipient Pedigree Position Paper
- IPEC Excipient Stability Program Guideline, 2010 (new)
- IPEC Validation Guide (being finalized)
- IPEC New Excipient Safety Evaluation Procedure
  - Panel Review of Safety Data by World Class Experts for specific Intended Uses

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2013 Certificate of Analysis Guide for Pharmaceutical Excipients

- Update to original guide
- IPEC Europe and Americas involved in revision
- To be provided to IPEC Japan and IPEC China for possible adoption and publication in their respective regions
- Why update the guide?
  - Last version was from 2000
  - Many regulatory developments in the last 13 years
  - Commitment by IPEC to update guides on a periodic basis going forward

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Access to Guide

- Where can the guide be accessed?

https://ipecamericas.org/ipec-store

- IPEC Store
- Free

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How is this Document Positioned within the Global Regulatory Environment?

- IPEC member company issues were identified and addressed in the revision process
- FDA's comments were also addressed during the revision process
- International excipient GMP certification standards include requirements that are consistent with this guide
  - NSF/IPEC 363: Good Manufacturing Practices (GMP)for Pharmaceutical Excipients (anticipated publication 2013) defines the minimum required CoA content
  - Also EXCiPACT Certification Standards for Pharmaceutical Excipients: Good Manufacturing Practices/Good Distribution Practices includes various CoA related requirements

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What has Changed?

- Major changes were made to address:
  1. Date formats and use of terms other than expiration date or recommended re-evaluation date
  2. Absence of name and address of the original manufacturer
  3. Absence of analytical method reference
  4. Circumstances when the excipient manufacturer does not need to perform identification tests
  5. Frequency of testing
  6. Computer software constraints
  7. Legibility
  8. Supply chain transparency

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2013 CoA Guide - Purpose and Scope -

- To serve as a guide for the preparation and appropriate use of a Certificate of Analysis (CoA) for pharmaceutical **excipients**
- Goals:
  - To standardize the content
  - Suggest a format for CoAs for excipients
  - Clearly define the roles and responsibilities for the excipient manufacturer and distributor
  - Achieve uniform industry approach
- To provide the user with assurance of excipient conformance to specification and suitability for pharmaceutical use

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2013 CoA Guide - Principles and Guidance -

- Diversity of excipients
  - Some principles of the guide may not be applicable to certain products and processes

- Terminology "should" and "it is recommended" do not necessarily mean "must"
- Common sense should be used in the application of this guide

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2013 CoA Guide - Guidance Continued -

- What is a CoA?
  - Legal document that certifies the quality of the excipient
  - Demonstrates that the batch conforms to the defined specifications
  - Indicates that the material has been manufactured under excipient GMP
  - Demonstrates suitability for use in pharmaceuticals

- The CoA should not be used in lieu of appropriate qualification of the supplier

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2013 CoA Guide - Guidance Continued -

- CoA should be issued when analysis is performed by a distributor
- Best practice is for the distributor to provide the user with the original manufacturer's CoA and the distributor's CoA (if testing was performed)
- Identification testing by the excipient manufacturer is not a regulatory requirement
  - Not required to perform identity tests if they have process controls in place that together with testing assure the identity of the excipient

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Major Changes

Date Format Change

- Due to international applicability an unambiguous date format was required
- Dates (e.g., re-evaluation or expiration date) can be clearly communicated
- Example of an unambiguous date format:
  - **DD MMM YYYY** (e.g., 14 JUL 2013)
  - use alpha characters to designate the month and four digits to designate the year
- Best practice ensures that excipients used in the manufacture of drug products meet specification requirements at time of use and that confusion does not lead to use of expired excipients

Original Manufacture Information

- The **name** of manufacturing **site** and address should be clearly indicated
  - Enable user to assure that a change in manufacturing location has not occurred without their knowledge
  - Name and address should appear **directly** or **by reference** (i.e., using a code)

Original Manufacture Information

- To protect confidentiality through the supply chain
  - Use of codes for manufacturers and manufacturing sites is acceptable
  - User must be able to link the code to the manufacturer and site of manufacture
  - Such information may require a confidential disclosure agreement
- Excipient user is responsible for knowing the name of the original manufacturer (OM) and the address of the OM site for every lot received
- Essential that the manufacturer be known to the user
- Identification of OM emphasized in discussions that IPEC-Americas had with FDA

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Analytical Method Reference

- Excipient user must know the analytical methods used by the excipient manufacturer to test each lot when CoA data are used for batch release
- Analytical method references should appear on the CoA
  - Or be linked to a specification document so the analytical method used for each test is clearly communicated to the user
- In the case where the analytical method is included on the linked specification instead of the CoA, the excipient user must be provided with the specification document

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Identity

- The excipient supplier (manufacturer or distributor) may organize the elements on the CoA at their discretion
- Sections have been designed to present the required and optional information in a logical manner
- The **identity** of the excipient established by stating:
  - Compendial and trade name
  - Grade of the material
  - Applicable compendial designations

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Identity and Identification Tests

- To clarify confusion within the industry regarding reporting of identification tests on the CoA for excipients
- Reporting is not required when an excipient manufacturer has other control procedures in place that provide adequate assurance that their product will meet the identification test, if tested
- In addition, the user must perform an identification test on every batch received regardless of whether the supplier has performed the identification test or not
- Supported by:
  - USP General Notices 5.40
  - 21 CFR § 211.84(d)(1)
  - EU legislation

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Frequency of Testing

- Many companies use reduced testing programs and rely on their supplier's CoA data and
  - Supplier statements in the past that the specifications for particular test were certified through the use of in-process or skip-lot testing
- Historically pharmacopeias (USP) have allowed this approach and ICH Q6A has allowed for skip-lot testing of the drug product and drug substance
- However, based on recent comments from FDA
  - Users should not be allowed to rely on in-process measurements to justify a specified test parameter without documented evidence (e.g., site audits) to demonstrate that appropriate procedures are in place to assure compliance

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Frequency of Testing

- According to FDA representatives - appropriate determination to ensure that each lot conforms to appropriate specifications could involve some combination of the following approaches:
  1. End-product testing
  2. In-process testing
  3. Continuous monitoring of an attribute with statistical process controls
  4. Documented rationale that, based on the method of manufacture, the test attribute cannot be present and therefore the test is not applicable (e.g., residual solvents)"
- The CoA Guide refers to bullets 2–4 (above) as "other than finished excipient testing" and results derived from other than finished excipient testing should be clearly indicated in the CoA
- For example, the test name can be footnoted to indicate the test result is obtained from other than finished excipient testing.

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Verification of authenticity

- Excipient user should periodically verify the authenticity and validity of the CoA
- Accomplished during a supplier audit or otherwise by sending the CoA to the issuer to verify that it is authentic
- Frequency of verification based on risk assessment
  - reliability of the excipient manufacturer
  - supply chain
- Should include name and title of the person who authorized

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Verification of authenticity

- Note: A computer generated CoA provides an equivalent or better degree of assurance that the CoA is appropriately authorized than an original hand-signed document
  - Where proper controls are in place
- There is no legal requirement to have a hand-signed CoA in most countries provided that appropriate controls are in place for an alternative computer-generated signature process
- If a distributor issues a CoA on their letterhead, their CoA should be traceable back to the original manufacturer's CoA
- The distributor's CoA should include the original manufacturer's name and location or code (if used)

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Format and Design of the CoA

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Design and Required Elements

- Body of the CoA
  - A batch number
    - Or other means of uniquely identifying the material
    - Unique identification of the excipient links the CoA to the relevant specification
  - The date of manufacture
  - The expiration date if applicable
  - Recommended retest date
  - Other relevant statement regarding the stability of the excipient is typically included in this section
  - User required information could also be included

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Design and Required Elements Continued

- Analysis section contains actual test results
- Acceptance criteria and test results 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
- Actual data and observations are recommended
  - "passes" or "conforms" statements should only be used when test is qualitative or as listed in compendium or other specification

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Design and Required Elements Continued

- If the reported results are not derived from sampling the finished excipient batch, it should be noted on the analysis section of the CoA
- In such cases alternative options for the origin of test results other than Quality Control laboratory testing include for example:
  - In-process testing, or
  - Continuous monitoring of an attribute or variable and application of appropriate
- Statistical Process Control (SPC) methods

DEFINING QUALITY

Design and Required Elements Continued

- 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 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

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CoA Content

- The following information should appear on the COA or by reference:
  - Numbered pages, including total number
- **Identifying Information**
  - Title "Certificate of Analysis"
  - Identity and address of original manufacturing site: name or other identifier
  - Trade Name
  - Grade
  - Batch Number
  - Name (compendial or chemical) and Compendial Designation

Example:

Certificate of Analysis

[sample tests, limits and estimates 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 manufacture 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 (1% solution)	USP	3.0 – 7.0	6.0
Residue on Ignition	JPE	NMT 1.0% (850 –550C)	0.0 %
Viscosity (1% solution)	Ph.Eur.	0.0 – 7.0 mPa·s (@25c)	0.0 mPa·s
Water Insoluble Sub	USP	NMT 0.1%	0.0 %
Loss on Drying (105C)	USP	NMT 5.0%	0.0 %
Loss on Drying (105C)	JPE	NMT 6.0%	0.0 %
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 as 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.

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CoA Content

- **Body**
  - Date of Manufacture
  - Expiration or Retest Date (as applicable) or Stability Statement
  - Unique identifier to the excipient specification
  - Specification
    - Test Name
    - Reference to the Test Method
    - Acceptance Criteria
  - Analysis
    - Test Results based on finished excipient sample
    - Alternative test results, as appropriate
    - Date Retested (if appropriate)

Example:

Certificate of Analysis

[sample tests, limits and estimates 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
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Water Insoluble Sub	USP	NMT 0.1%	0.0 %
Loss on Drying (105C)	USP	NMT 5.0%	0.0 %
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\# This test is performed quarterly based on process validation.

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CoA Content

- **Certification and Compliance Statements**
  - May be provided in other documents
  - Standard of GMP applied (e.g., IPEC-PQG Excipient, EXCIPACT)
  - Potential to meet additional Compendial Standards
  - Additional compliance statements and applicable references to standards
  - Content listing and grade of ingredients (if a mixture)
  - Customer specified information
- **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)

Example:

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 Practices.

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 Pharmacopeia of 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.

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Further Details on Requirements

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Requirements for Compendial Designation

Two requirements to claim compendial grade[‡]

1. Excipient is manufactured according to recognized principles of GMP
2. 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 Chapters <1225>, <1226>

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Establishing Dates on a CoA

Date of Manufacture

- The Date of Manufacture should be clearly defined by the original manufacturer
  - Consistently applied for the particular excipient and process
  - Based on established policies and procedures
- 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

Expiration Date and Recommended Retest Date

- It is important that the CoA indicates stability of the excipient either by reporting the Expiration Date and/or the recommended Retest Date
- When excipient is re-packed
  - Effect of operation and new packaging materials on the expiry or retest date should be evaluated
  - Determine if 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

Expiration Date and Recommended Retest Date - Continued

- Re-evaluation of the excipient may include physical inspection and/or appropriate chemical, physical, or microbiological testing
- 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 Excipient Stability Program 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

Date Retested

- If retesting is performed by an excipient supplier 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

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Establishing Dates on a CoA

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

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Reporting of Data

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 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
- Periodic testing of all parameters should be performed to confirm continuing compliance

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Reporting of Data

General Guidance part II

- 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
- For excipients that are not included in any pharmacopeia specifications should be set by the supplier
  - 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

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Reporting of Data

Data versus Conformance – Part I

- 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
- 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

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Reporting of Data

Data versus Conformance - Part II

- 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

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Reporting of Data

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

Reporting of Data

Alternatives to Excipient Testing – Part I

- 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
- 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
  - Note that ICH Q6A allows for periodic/skip lot testing of the drug product and drug substance
  - See PharmTech article from 2007 - Joint Position Paper on Pharmaceutical Excipient Testing and Control Strategies

Reporting of Data

Alternatives to Excipient Testing – Part II

- 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
  - Acceptable to rely on tests or measurements conducted on samples of material taken at an in-process stage of production
    - Provided that 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

Use of Electronically Generated Certificates of Analysis

- Certificates of Analysis issued from computer systems without a handwritten signature
  - Common place
  - 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
    - Change of individual password at an appropriate frequency
  - Confirmation of the integrity and accuracy of the information stored in the system
    - Transferred to printed record should be completed during implementation and then periodically checked thereafter
  - CoA information and changes should be accompanied by time- and date-stamped audit trails

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

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THANK YOU!

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Discussion

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