Certificate of Analysis for excipients if applicable, but both dates may not always be required. Expiration and Recommended Re-Evaluation Dates should not be reported by a supplier without sufficient stability data or product history to support the assigned dates.

For excipients determined to be very stable (greater than two years), either the specific Expiration and/or Recommended Re-Evaluation Dates should be reported on the Certificate of Analysis for the material, or a general stability statement may be included (e.g. stability greater than two years). If available data indicates that an excipient has limited stability (two years or less) under anticipated storage conditions, then specific Expiration and/or Recommended Re-Evaluation Dates must be reported on the Certificate of Analysis for the material.

If long-term stability data is not available for an excipient, then an appropriate statement should be included on the Certificate of Analysis 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 and the results are used to extend the length of time that the material may be used, then the **Date Retested** should also be reported on the Certificate of Analysis. 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 Re-Evaluation Date should be reported on the Certificate of Analysis.

6.5 Additional Dates

Other dates may appear on a Certificate of Analysis, 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 Certificate of Analysis for excipients must include a clear indication of what the date represents or means.

7. TESTING FREQUENCY

7.1 General Guidance

Many excipients are listed in the United States Pharmacopeia/National Formulary, European Pharmacopoeia, Japanese Pharmacopoeia/Japanese Pharmaceutical Excipients or other standard reference and the product specifications are set by the supplier to include all parameters listed in the monograph. The Pharmacopeias do not require that analysis of all specification parameters be made on each lot[2]. However, sufficient analysis and process validation data must exist to assure that the lot meets all specifications before it is released. This is an established practice that

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

has been successfully used in industry for many years. Periodic testing of all parameters should be performed to re-validate the control system. The frequency of these periodic tests should be determined by the supplier based on their understanding of the manufacturing control system. At a minimum, the parameters should be checked once a year.

For excipients that are not included in any standard Pharmacopeia, specifications should be set by the supplier to insure that the quality of the material is maintained on a continuing basis, and reflects both the excipient manufacturing process and inherent properties. The analytical methods used to evaluate the characteristics of non-compendial excipients may be the same as those contained in the compendia, or may be unique to the supplier and/or the material. The methods should be demonstrated to provide accurate, reproducible, and consistent results for the characteristic being tested. It may be appropriate for non-compendial excipients to have some tests performed at reduced frequency, as discussed in Section 7.2.

The excipient user should evaluate the supplier's specifications and methods to insure that they are appropriate and acceptable for the quality control needed for the manufacturing process of their drug product. The user must determine which of the supplier's specifications and methods are required for release of the excipient for use in their process. If additional tests or alternate methods are required by the user, appropriate specifications and methods, along with responsibility for performing the testing, must be agreed upon by the excipient supplier and user.

7.2 Reduced Frequency Testing

When analysis of some parameters are carried out at a reduced frequency (for example every tenth lot), this must be clearly stated on the Certificate of Analysis. Each specific test subject to reduced frequency testing must be indicated. Reduced frequency testing should only be used for excipients made using a **stable process**. There must be a sound technical basis and sufficient documentation to support testing any parameter at a reduced frequency. This would normally include the following points:

- Appropriate Validation of the Manufacturing Process
- Process Control – Attribute Charting (when appropriate)
- GMP Controls

As part of the justification for reduced testing, it is important that there be assurances in place showing that the manufacturer's process complies with appropriate excipient GMP requirements (as defined by IPEC's *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients*).

Some tests, due to their significance should always be tested on each lot, whereas others may be candidates for reduced frequency testing. Attribute testing results in qualitative data. Such data is exemplified by pass/fail results or less than or greater

than a specified value. The result merely establishes compliance with a specification parameter. There is no data to indicate how well the material complies, as would be obtained from variable or quantitative test results.

Reduced frequency testing of an attribute requires that the manufacturer show the qualitative parameter is in a state of statistical control. This necessitates tabulating the test results for consecutive lots produced.

Skip-Lot testing may be applied to an excipient that is made by either a **batch** or **continuous process**. Various commonly accepted statistical sampling plans may be used to demonstrate appropriate process control. Examples of each are listed below:

Example 1: For an Average Outgoing Quality Level (AOQL) of 1% and a test frequency of 1 in 10, the supplier must find 100 consecutive lots in conformance. At a 2% AOQL and a test frequency of 1 in 10, the supplier would test 50 consecutive lots. For a 1% AOQL and a 1 in 5 test frequency, the supplier must test 70 consecutive lots. Nomographs are available to determine the test requirements.

Example 2: When the excipient is manufactured by a continuous process, no discrete lot is produced. The sampling plan again is based upon the risk of approving a lot that was nonconforming. By testing 140 consecutive lots before going to a test frequency of 1 in 10, the plan establishes a low risk of approving a lot that is non-compliant.

Once the requirement is met, the supplier can monitor conformance to the specification parameter by testing 1 in 10 lots. Should any lot fail the analysis, the supplier must return to 100% testing until the results once again meet the specification as above.

Since excipients vary greatly in chemical and physical properties, the supplier of the excipient should determine which tests should be routinely performed and which tests may be appropriate for reduced testing. This determination must be justified and documented based on the adequacy of the supplier's control system. Documentation must be kept detailing the assumptions and the data supporting the Skip-Lot testing plan.

Only certain types of tests are appropriate for reduced frequency testing. Type A are defined as those tests that may not be easily controlled through standard process control techniques or may change with time. These tests should normally be performed on each lot. Type B are defined as those tests that normally can be controlled utilizing standard process control techniques and are not expected to change with time. These tests are candidates for reduced frequency testing. Examples of both types of tests are listed below:

Type A - Examples of tests that typically need to be performed on every lot:

Identification - required by GMPs for users (candidate for reduced frequency testing by suppliers)
Assay – critical quality parameter (if specified)
Viscosity – usually indicates grade
Loss on drying (or moisture determination) – indication of stability and appropriate process controls
Color - indication of stability and appropriate process controls
pH - indication of stability and appropriate process controls

Type B - Examples of tests that may be candidates for reduced frequency testing:

Manufacturing **impurities** based on starting materials and process. (Examples: Chloride, Sulfate, Nitrate, Glyoxal, etc.)
Heavy Metals
Lead
Arsenic
Residue on Ignition
Residual Solvents

This is not meant to be an exhaustive list of tests. It simply provides some direction on how a supplier can assess the importance of each test to the overall control of the process. Tests listed as possible candidates for reduced frequency testing (Type B) may need to be routinely tested (Type A), depending on the raw materials and process. Determinations can also be made for some Type A tests to become Type B tests. In a dedicated facility, identification testing by the supplier may not be necessary.

7.3 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 reduced frequency testing. This documentation should also include procedures for handling the impact of **significant changes** on the reduced frequency testing program. For further information regarding excipient changes, see the IPEC Americas Significant Change Guide for Bulk Pharmaceutical Excipients.

The minimum number of lots to be fully tested for all specification parameters after a change has been made depends on the process and the significance of the change and should be based on sound statistical considerations.

Additionally, the documentation should contain procedures for re-evaluating the reduced frequency testing program when a testing failure occurs. Decisions regarding the continuance of reduced frequency testing must be justified based on the reasons for the failure and the supplier's ability to provide assurances that the

reduced frequency testing program or other in-process parameters would identify these types of failures in the future.

7.4 Examples

The following are examples of situations where reduced frequency testing might be justified. These are not the only situations where a sound technical basis can be demonstrated.

- 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 customer 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 (see Appendix 1 for further definition of this concept and for determining levels of control).

- 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 lot would be redundant

- An analysis that is determined on every lot has been shown to strongly correlate with an analysis that is run at a reduced frequency. The correlation shows that if a lot is within specification on the first analysis, it will be within specification on the second analysis.

8. USE OF ELECTRONIC SIGNATURES

With the growing dependence on computers and the need to accommodate paperless record systems, an electronic alternative to handwritten records and signatures is required. Excipient suppliers have added computer information systems to enhance productivity.

The primary issue with transfer of Certificates of Analysis without a handwritten signature is the validation of data. There are several considerations that must be met before an electronic signature or name attachment to a COA is considered acceptable.

- Computer systems access must be limited to authorized individuals. Access is gained only after inputting a user name and a password. The system should require frequent changes of each individual password.

- A confirmation of the integrity and accuracy of the information stored in the system must be completed.

- The operation of the system must be checked routinely to insure the correct information is transferred from the database to the printed record.

- Data entered into a database from which information is extracted for a Certificate of Analysis must be accompanied by time- and date-stamped audit trails.

With these criteria met, the issuance of COAs with electronic signatures or the responsible person's name attached to the document, in lieu of a handwritten signature, is acceptable.

Note: Computer systems are currently regulated by 21 CFR 11. Users should monitor the FDA's approach to compliance in this area.

9. DISTRIBUTOR INFORMATION

9.1 General Guidance

The presentation of a COA issued by a distributor presents some challenges. Since COAs are important documents characterizing the excipients and the state of the quality, the source of that information becomes very important to the end user(s). Because distributors take on different roles in fulfilling the services for which they are contracted, it is necessary to assure that procedures and methods are appropriate for the functions performed.

Distributors function in a number of capacities for the movement of excipients and services. Some are simply pass through locations in which nothing is done to the excipient with the exception of storage and handling. Others serve as extensions of the manufacturer's process taking bulk quantities and re-packaging for the manufacturer. Still others purchase excipients and re-package it under a different label for sale and distribution. These scenarios need to be understood and properly documented with programs that will protect the integrity and safety of the excipients while moving through the distribution process.

9.2 Original Manufacturer and Manufacturing Site

The identity of the original manufacturer and the manufacturing site must be included on the Certificate of Analysis for excipients. This information is important for providing traceability for specific excipient lots, and in assuring the excipient users that they are consistently obtaining material from the same manufacturer and site.

Reporting the identity and location of the manufacturer does not represent an issue when the original manufacturer is also the direct supplier of the excipient to the pharmaceutical customers. However, it is recognized that this information may be considered proprietary by an excipient distributor. To adequately address this issue, excipient distributors must either list the specific information identifying the original manufacturer and location, or provide the information by reporting an appropriate code, which is assigned to unambiguously identify the original manufacturer and manufacturing site. To protect the secrecy of this information, the meaning of the code does not have to be revealed to intermediary distributors.

9.3 Certificate of Analysis Data

When a distributor is primarily used as a "pass through" of the excipient without any changes to the excipient and packaging, the COA that accompanies the excipient from the manufacturer can be passed on in the original form. If the data is extracted, translated or rewritten on other letterhead, a system must be in place to check the rewritten information, and justification should be demonstrated upon request. Alternatively, the source of the data should be indicated on the document.

For a distributor that takes bulk quantities of excipient from a manufacturer, introduces it into a process (e.g. conveyance and storage system), analysis of the packaged excipient should be performed to demonstrate the same quality as the lot (batch) introduced. Appropriate analytical data should be included on the COA to verify the quality. The distributor must use equivalent methodology and equipment for the analytical evaluation. Some data may be used from the original manufacturers' Certificate of Analysis with appropriate justification.

In all scenarios, it is expected that the distributor will have the appropriate level of good manufacturing practice in place.

10. REFERENCES

International Pharmaceutical Excipients Council *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients*

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

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Glossary and Tables for Statistical Quality Control, 3rd Edition, ASQC Statistics Division, ASQC Quality Press, Milwaukee, WI

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

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

11. GLOSSARY

Acceptance Criteria: The specifications and acceptance/rejection limits, such as acceptable quality level and unacceptable quality level, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or excipient.

Batch: A defined quantity of excipient processed so that it could be expected to be homogeneous. In a continuous process, a batch corresponds to a defined portion of the production, based on time or quantity (e.g. vessel's volume, one day's production, etc.).

Batch Number: A unique and distinctive combination of numbers and/or letters from which the complete history of the manufacture, processing, packaging, coding and distribution of a batch can be determined.

Batch Process: A manufacturing process that produces the excipient from a discrete supply of the raw materials that are present before the completion of the reaction.

Bulk Pharmaceutical Excipient (BPE): See "Excipient".

Certificate of Analysis (COA): A document relating specifically to the results of testing a representative sample drawn from the batch of material to be delivered.

Chemical Property: A quality parameter that is measured by chemical or physiochemical test methods.

Continuous Process: A manufacturing process that continually produces the excipient from a continuous supply of raw material.

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

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

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

Distributor: A party other than the manufacturer who sells the excipient.

Excipient: Any substance other than the active pharmaceutical ingredient or drug product which has been appropriately evaluated for safety and is included in a drug delivery system to either aid the processing of the drug delivery system during manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Expiration Date: The date after which the supplier recommends that the material should not be used.

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

Lot: See "Batch".

Lot Number: See "Batch Number".

Manufacturer: A party who performs the final processing step.

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

Periodic Testing Program: See "Skip-Lot Testing".

Physical Property: A quality parameter that can be measured solely with mechanical equipment.

Process: The set of operating instructions describing how the excipient is to be synthesized, isolated, purified, etc.

Process Capability Index (Cp): A statistical measurement that can be used to assess whether or not the process is adequate to meet specifications. A "State of Statistical Control" can be said to exist if the random variation in test results for a process parameter is such that the calculated process capability is greater than 1.33 (see Appendix 1 for further definition).

Process Step: An instruction to the excipient manufacturing personnel directing that an operation be done.

Recommended Re-Evaluation Date: Date suggested by the supplier when the material should be re-evaluated to insure continued compliance with specifications. Differs from the Expiration Date in that the excipient may be re-evaluated to extend the length of time the material may be used, if supported by the results of the evaluation and appropriate stability data.

Reduced Frequency Testing Program: See "Skip-Lot Testing".

Re-packaging: Transfer of an excipient from one container to another.

Reprocessing: Introducing previously processed material that did not conform to standards or specifications, back into the process and repeating steps that are already part of the normal manufacturing process.

Significant Change: Any change that alters an excipient physical or chemical property from the norm or that is likely to alter the excipient performance in the dosage form.

Site: A location where the excipient is manufactured. This may be within the facility but in a different operational area or at a remote facility including a contract manufacturer.

Skip-Lot Testing Program: Periodic or intermittent testing performed for a particular test parameter, which is justified by historical data demonstrating a state of statistical process control.

Specification: The quality parameters to which the excipient, component or intermediate must conform and that serve as a basis for quality evaluation.

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

Supplier: A manufacturer or distributor who directly provides the excipient to the user.

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

APPENDIX 1

State of Statistical Control

Process Capability Parameters for Determining Levels of Control

A process is considered to be in a 'state of statistical control' if variations among the observed sampling results from the process can be attributed to a constant system of chance causes.

Process Capability Index (Cp) or Capability Index Adjusted for the Process Average (Cpk) or Performance Index (Pp) or Performance Index Adjusted for the Process Average (Ppk) can be used to assess whether or not the process is adequate to meet specifications. Values of these parameters exceeding 1.33 show the process is adequate to meet specifications. Values between 1.00 and 1.33 indicate the process, while adequate to meet specifications, will require close control. Values below 1.00 indicate the process is not adequate to meet specifications and that the process and/or specifications must be changed. Pp/Ppk will always be less than or equal to Cp/Cpk respectively. The essential difference between the Capability and Performance Indices is the data used. Capability indices require the calculation of σ, the population standard deviation, whereas the Performance indices require the calculation of s, the sample standard deviation. Thus for pharmaceutical excipients a "State of Statistical Control" can be said to exist if the random variation in test results for a process parameter is such that the calculated process capability or performance index is greater than 1.33.

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1655 North Fort Myer Drive, Suite 700
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Tel: (703) 875-2127
Fax: (703) 525-5157
Email: ipecamer@aol.com

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調査したガイドラインの概要

調査したガイドライの概要を以下の表にまとめた。上段には各ガイドラインの［目的］又は［制定の背景］を下段にはそれによる影響や実施の事象をまとめた。

Significant Change Guide for Bulk Pharmaceutical Excipients	本ガイドは、医薬品添加剤の製造に関わる変更の重要度を評価するための統一的な条件の確立を意図している。ここでの評価とは、変更事項の内容について添加剤の使用者と規制当局への報告が必要かどうかを決定することを目的としている。
	適用範囲 本ガイドは医薬品製品の製造に用いられる全ての添加剤に適用される。GMP の適用される製造工程より適用されねばならない。
Excipient Qualification Guide	本ガイドは、添加剤製造業者及び医薬品企業添加剤ユーザーによる、添加剤成分の適格性を判定するものである。医薬品に添加剤を配合するために支援する情報確立また医薬品企業が使用に向けての要望を確立するための段階を示すことである。
	1．　医薬品に用いられる全ての添加剤に適用。 2．各添加剤製造業者は、製品及び製造工程にどのように適用されるかを考える必要がある。 3．本ガイドにおける「すべき」「勧告する」は「ｍｕｓｔ」を意味するものではない。
Certificate of　Analysis (COA) Guide	本ガイドはバルク医薬品添加剤の分析証明書の準備と適切な使用に対するガイドを提供することである。添加剤の COA の構成とフォーマットの標準化及び添加剤製造者、販売業者、ユーザーのための規則と責任を明らかにすることを目標はとする。共通の理解のための基礎を準備することは、医薬品の製造に使用される添加剤に関して規程された承諾事項の保証となる。
	1．　医薬品に用いられる全ての添加剤に適用。 2．　各添加剤製造業者は、製品及び製造工程にどのように適用されるかを考える必要がある。 3．　本ガイドにおける「すべき」「勧告する」は［ｍｕｓｔ」を意味するものではない。
Stadardized Excipient Information Protocol User Guide　(EIP)	医薬品添加剤に関する、添加剤メーカ側とユーザー側における、情報の標準化のためのプロトコールのガイド。多くの必要な情報が双方に有意義に交換できるような標準書を制定する。
	添加剤供給者と添加剤ユーザーとの間でもっと意味のある課題を解決することが出来る。
The IPEC Good Distribution Practices Audit Guideline 2008	医薬品添加物を販売、貯蔵、もしくは小分け（いずれの組合せを含む）を行う流通業者の基準並びに品質システムを評価する為の手段とされている。この査察ガイドは IPEC Good Distribution Practice Guide (WHO Good Trade and Distribution Practice for Pharmaceutical Starting Materials をベースとしている）とリンクしており、それ故に同じ構成となっている。

	この査察ガイドは、医薬品添加物が製造元の製品管理システムの管理下より出荷された時点を初めとして全ての流通・サプライチェーンのステップに適用される。この文書は査察に於ける調査内容並びに査察目的の基準を決定する査察者へのフレームワークを与える事を目的とする。
IPEC Good Distribution Practices Guide For Pharmaceutical Excipients 2006	医薬品添加物のサプライチェインに関わる会社への助言を提供する為に書かれている。 この査察ガイドラインは IPEC Good Distribution Practices Guide と共に使用する。本ガイドライン中の注記は査察官が最も効果的な査察が行えるように実際の経験に基づく実施例が GDP の活用を促進する為に提供されている。しかしながら、補助的な活用も可能である。 このガイドが目的とする流通業者とは、輸入・販売業者、再加工業者、小分け業者、運輸・倉庫業者、搬送業者、ブローカー、貿易業者並びに製造者以外の供給者を含む。この査察ガイドは IPEC Good Distribution Practice Guide (WHO Good Trade and Distribution Practice for Pharmaceutical Starting Materials をベースとしている)とリンクしており、それ故に同じ構成となっている。
	この査察ガイドは、医薬品添加物が製造元の製品管理システムのコントロール下より出荷された時点を初めとして全ての流通・サプライチェーン ステップに適用される。 このサプライチェーンに関与する業者は、医薬品グレードとはその添加物が局方規格、 該当する法規制（もし関連する添加物があれば）を遵守して製造、小分けされ、添加物 GMP (例えば IPEC PQG GMP [2], WHO Excipient GMP [6] 等)に基づいて取り扱われる製品をさす事を認識しなければならない。 テクニカルグレードもしくは工業グレード品の、局方モノグラフの要求規格に基づく 分析値のみの適合性による医薬品グレードへのアップグレードは受け入れられない基準で ある。
The Joint IPEC-PQG Good Manufacturing Practices Audit Guideline 2008	製薬工業において、医薬品製造者は 全ての出発原料と投与形態での最終製品の製造に使用、配合する他の組成物の品質を保証する責務がある。監査を通して医薬品添加剤の生産者、ユーザーは適切な保障に替えることを可能にする。生産者が適切な品質の製品を製造することを目的とした、GMP監査に関するガイドライン
	添加剤製造業者や下請け業者にいつでも適用される監査である。
Qualification of Excipients for use in Pharmaceuticals Phase1	添加剤供給業者及び医薬品企業ユーザーのために添加剤の必要要件を提示するものである。必要用件として

	考えられる事項は1．添加剤のマーケティングの決定、2．安全性と毒性の問題、3．添加剤ドラッグマスターファイル、4．使用用途のための望ましい性質、5．公定書の要求事項.
	最終目標は、添加剤として販売される物質の医薬品業界への導入を支援するための情報を確立すること及び医薬品企業が添加剤として使用する際の要望事項を確立するための手順を示すことにある。 o 本ガイドを使うにあたっては、各添加剤製造業者自身がこれをどのように製品やプロセスに適用できるかを考えなければならない。 o これに加え製薬企業は彼らの処方の中で添加剤を適正に使う方法を考えねばならない。本ガイドでは、ステップを一連の流れとして提示している
Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients	医薬品または生物製品の構成成分としての新添加剤の使用する時の、安全性プロファイルの作成に関するガイダンスを提供する。医薬品評価研究センター（Center for Drug Evaluation and Research, CDER）及び生物製品評価研究センター（Center for Biologics Evaluation and Research, CBER）の審査担当者，並びに業界関係者の使用を目的としている。添加剤開発のために実施しなければならない非臨床安全性試験に対するCDER 及び CBER の現時点の考え方を製薬企業及び添加剤企業に伝えること，並びに添加剤の非臨床安全性評価に対する期待を CDER 及び CBER 内で統一することにより新添加剤の開発を促進し効率良く行うことも目的としている。
	本ガイダンスでは，規制当局がヒト医薬品に使用する新添加剤の安全性を評価するために必要とする毒性データの種類を記載した。
Excipient Master file guide	米国のドラッグマスターファイル（DMF）制度は、連邦規則§314.420（21 CFR §314.420）により規定されている。その制度利用に関するガイドラインは1989年 9 月にドラッグマスターファイルガイドライン（Guideline for Drug Master Files） としてＦＤＡより通知された。 本制度では、ＤＭＦに登録できるタイプを以下の４種類に規定している。 Type Ⅱ ： 原薬、原薬中間体、及びそれらの原料、または医薬品（製剤）に関する情報 Type Ⅲ： 包装資材に関する情報 Type Ⅳ： 添加剤、着色剤、香料、エッセンス及びこれらに使用される物質に関する情報 Type Ⅴ ： ＦＤＡの承認した参考情報 医薬品添加物は Type Ⅳ に登録することができる。 タイプⅣ添加剤マスターファイル（Type Ⅳ DMF）は FDA への提出書類であり、臨床試験承認申請(Investigational New Drug Application、IND)、新薬承認申請(New Drug Application、NDA)、簡略承認申請(Abbreviated New Drug Application, ANDA)、生物学的ライセンス承認申請（Biological License Application, BLA)、動物薬承認申請（Veterinary Drug Application、他の DMF 或いは輸出承認申請をサポートするために

	使用される情報を含んでいる。
	添加剤 DMF は法律や FDA 規制を必要とされない。それは保有者の自由裁量だけで提出される。それは許可或いは拒絶されるものでもない。DMF は添加剤製造業者の文書による同意なくして第三者に提出できない秘密文書として維持される。DMF は製造と管理に関する情報及び添加剤の安全性と品質を裏付けるける技術データを含む。
Exicipient biological SafetyEvaluation Guideline	医薬品として種々の投与経路で用いられる新添加物の安全性を確保するために、適切なデータベースを作るプロトコールをしめした。
	プロトコールの内容は 1．安全性評価ガイドライン 2．必須データ 3．基礎的な毒性試験 4．特定の投与経路における追加試験
The_safety_of_pharmaceutical_excipients	添加物の主要分類とその副作用について検討を行う。 毒性学的評価は、 (a)固有の毒性、又は対象者全体から求めた有害事象、 (b)遺伝性疾患を持つ保因者で認められる、又 はアレルギー、過敏症の方に一般的にかかり やすい特有の毒性に分けて行った。 報告書の項目は 1. 添加物の定義 2. 添加物の由来及び供給元 3. 添加物に求められる主なもの 4. 添加物の製造、販売及び使用 5. 医薬品-添加物の相互作用 6. 添加物の毒性 について報告されている。
	添加物の安全性についての全般的な評価、考え方のレビュー。

(1078)医薬品添加物バルクの医薬品適正製造規準(GMP)

背景

本章における一般的な原則の多くは、適切な医薬品適正製造規準（GMP）の実施並びに適用範囲について国際ガイドラインに由来するものである。 添加物が有する品質、純度、安全性、適正使用を製品として適切に推進するために、その使用方法、施設及び製造管理方法について添加物製造者を支援することにある。

本章における原則、情報はヒト用医薬品、動物用医薬品、生物製剤での使用を念頭に全ての医薬品添加物（以下添加物）製造業者に適用することができる。 顧客への配送まで一連の製品を通して必要な品質管理システム、医薬品適正製造規準(GMP)の及ぶ限りの範囲となる。 国際的なガイドライン書として、全ての国々の法的要件に対応するものではなく、全ての添加物の詳細な特定の特性を補うこともない。 本章の構成である品質管理システム基準は、製造のために適切なISO9002としている。 添加物に特定な情報も加えている。 添加物は多様であることから本章の情報の原則では、一部の製品や処理工程には適用できない可能性もある。

この章では、現在の行政機関の規制である医薬品適正製造規準(GMP)の原則と国際標準化機構(ISO)によって展開された国際品質管理システム要件を合わせたものである。 医薬品産業のグローバル化の拡大及び医薬品登録要件の調和を考慮して、両者の考えに従うことが必要となる。 従って、この章を通じて両者の製造に対する考え方における関連部分を用いた。

一般的なガイドライン部分は添加物製造業者に適用できる適切な製造基準の概要、添加物適正製造規準(GMP)及び品質管理システムの適用する場合のポイントを提供するものである。 また、この項では、別紙1に本章で用いた用語一覧と定義、添加物の限界汚染についての対策を提言している。 添加物品質管理システムの項では、添加物品質システムの実施と該当するGMPに遵守するために必要な要件の情報を提供している。 製造施設の要件に関する情報は工程管理の項に記載している。 特定の添加物に特有な事項を記載することはない。 別紙2では、一般的な監査(Audit)の考慮すべき点を添加物製造施設の監査における重要な基準を用いて説明する。

一般的なガイドライン

医薬品規制についての国際規約では、医薬品の成分はGMP基準に従って製造、加工、包装することを求めている。 その他の医薬品製品及び成分とは異なり、医薬品添加物バルクの製造に対するガイドラインは特にない。

添加物は最終製剤の薬理活性成分以外の物質で、ドラッグ・デリバリー・システムを含めて安全性が適切と評価され、 1) 製造中のドラッグ・デリバリー・システムの処理、2) 安定性・バイオアベイラビリティ・特許受諾の確保、支援、向上、3) 製剤の識別、4) その他