きた。

- 最近の行事は、継続的な発展が必要であり産業会の全ての国と共同体を含めて緊急な行動を行っている。
- 前に進めるための必要な意見は何？

資料　B-2

Performance Related Tests　in Excipients

Kevin Moore
Scientist, United States Pharmacopeia

１．添加剤は不活発ではない！

添加剤は原薬や最終投与形態とはことなる物質である。安全性に対して適切に評価されて、DDS に含まれる。

① DDS の製造を通して処理の手助けとなる。
② 保護、支持、安定性の強化、バイオアベイラビリティ又は患者の同意
③ 製品の識別の援助や
④ 安全性　保存や使用を通して医薬品の全ての安全性、効果、投与の特性を優れたものにする。

２．添加剤

誰が気にかける？

・Formulators（処方を作る人）
・Analytical　（分析的）
・Quality Assurance/Control　（品質保証、品質管理）
・Regulatory Agencies　（規制当局）
・Pharmacopeias　（局方）

３．添加剤の基準における追加する試験を含めた適切な基準はおそらく添加剤のグレードを区別するための試験法の取り込み

◇ 粒径と分布
◇ 水分
◇ 表面積（活剤用）
◇ 密度（真密度、かさ密度、タップ密度）
◇ 置換度
◇ 粘度
◇ 分子量

この提案の長所は分析証明書にこれらの情報を報告されているおかげで、添加剤供給者は、実際には、これらを識別するために重要なことであり、恐らく重要な特性である。

4．局方に性能試験が導入されるスケジュール

2005		2006	2007	2008
EP は~100 の添加物のモノグラフに義務ではない FRC の項目を導入した。	USP において機能試験が必要であるかを添加剤製造メーカーとユーザーに調査を開始した。	USP と EP の調査結果の展望について共同討議がなされた。	一般情報 Chapter 1059> の刺激の項目 添加剤の機能は PF33（6）に公表されている。	USP, EM1, EM2, と EGC EC's メンバーによる合同会議において、第 2 章に発展させるための準備を申し入れた。

5．USP 30/NF 25 の機能別カテゴリー

錠剤／カプセル　希釈剤	錠剤／カプセル　結合剤	色
滑剤	コーテイング剤	ヌレ／可溶化剤
可塑剤	アンチケーキング剤／流動化剤	乾燥剤
防腐･保存剤	湿潤剤	凍結乾燥用増量剤
酸･アルカリ化剤	酸化防止剤	消泡剤
緩衝剤	キレート剤	甘味剤
アルコール変性剤	等張化剤	軟化剤
軟膏ベース	座剤基材	噴射剤
結合剤	金属イオン封鎖剤	溶剤
防湿剤	溶剤	賦形剤
ろ過助剤	増粘剤／分散剤	製薬用純水

＜1059＞に記載されている１４の優先度が高く代表的な機能別カテゴリー
開発に対して優先度が高い

6．添加剤の性能の概要表

Section	見出し	セクションの内容
1	解説	目的と用途の解説
2	機能作用	もしわかるのなら添加剤の機能の作用について解説
3	物理的な性質	関連性のある物理的な性質の解説
4	化学的な性質	一般的な化学の性質の解説
5	各章	添加剤の性能を評価するのに有用である一般試験法の章と概説の章の確認
6	その他の情報	その他の情報の規定

U.S. Pharmacopeia
The Standard of Quality℠

資料 C

JPEC-USP Meeting
Wednesday, September 17, 2008
2:00 p.m. – 5:00 p.m.
USP Headquarters, Rockville, Maryland
Bache Room, USP Meetings Center

Preliminary Agenda

Goals and Anticipated Outcomes

1. Overview and Introductions
2. Discuss general excipient topics
3. Discuss harmonization activities

Attendees

JPEC
Dr. K. Kijima, JPEC

USP
Roger L. Williams, M.D., Chair, Council of Experts
Darrell R. Abernethy, M.D., Ph.D., Chief Science Officer
Anthony J. DeStefano, Ph.D., Vice President, General Chapters
James C. Griffiths, Ph.D., Vice President, Food, Dietary Supplement and Excipient Standards.
Angela G. Long, Vice President, Volunteer and Organizational Affairs
Bei Ma, M.S., Compendial Project Manager
Kevin Moore, Ph.D., Scientist, Excipients and PDG Liaison
Catherine Sheehan, Director, Excipients
Mario A. Sindaco, MBA, Director, Compendial Project Management, VOA

2:00 p.m.	**Dr. Kijima Arrival and Informal Discussion** Meetings with Excipient Staff Members (James Griffiths, Catherine Sheehan and Kevin Moore, Mario Sindaco, Bei Ma)	
3:00 p.m.	**1. USP Welcome and Introductions**	Dr. Williams
3:15 p.m.	**2. JPEC Overview**	Dr. Kijima
3:30 p.m.	**3. General Excipient Discussion**	All
4:00 p.m.	**4. Applied Compendial Research Laboratory Tour**	Dr. Wahab
4:30 p.m.	**5. Museum Tour**	Ms. Tirumalai
5:00 p.m.	**6. Adjourn and Departures**	

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USP の会議資料

2008 年 9 月 17 日（水）に USP の Bache Room(USP meeting center)において R.L. Williams, M.D(Chair, Council of Experts)、Catherin Sheehan(Director, Excipients)らと医薬品添加剤の最近の情報について交換した。2008 年 6 月に行われた PDG meeting において話し合われた標準品、規格に関する議論の進捗状況および PDG/Tri PEC meeting についての話題が示された。USP が担当している各品目の進捗状況は次の通りである。

品目	Stage	対応
カルメロースナトリウム	4	改正 stage 4 案 2008.8 までに作成
ヒドロキシプロピルセルロース	4	TriPEC との合同会議
ヒドロキシプロピルセルロース、低置換		
マグネシウムステアレート	6	調和署名
ワセリン 白色ワセリン	4	改正 stage 4 案を 2008.7 までに作成
ポリエチレングリコール	4／3	EP は改正案を 6 月中に提案
デンプングリコール酸ナトリウム	Rev.2	
グリセリン	3	USP の改正案 TriPEC の意見を待つ
炭酸カルシウム	3－4	USP は次の案を作成
グリセリンモノステアレート	3	
ラウリル硫酸ナトリウム	3	USP は Stage 3 案を作成中

THE INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL
OF THE AMERICAS

IPEC-AMERICAS®
CERTIFICATE OF ANALYSIS GUIDE
FOR
BULK PHARMACEUTICAL EXCIPIENTS

The IPEC-Americas®
Certificate of Analysis Guide for Bulk Pharmaceutical Excipients

ACKNOWLEDGEMENTS

This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas), an industry association whose members consist of **excipient** manufacturers and pharmaceutical users. The company representatives who worked on this Guide are listed below.

David Schoneker, Colorcon - Chair
Katherine Blake, Merck and Company, Inc.
Christopher DeMerlis, Colorcon
Don Ewert, EM Industries
John Flanagan, Monsanto Pharmaceutical Ingredients
Sidney Goode, Pharm.D., The Dow Chemical Company
Scott Grare – National Starch and Chemical Company
Gary Gray, Rhodia, Inc.
Douglas Hecker, CyDex
Philip Merrell, Ph.D., Mallinckrodt Group, Inc.
Graham Moore, Ph.D., Hercules, Inc.
Christian Moreton, Ph.D., Penwest Pharmaceuticals Co.
Billy Pyle, BF Goodrich Performance Materials
Craig Scott, Penwest Pharmaceuticals Co.
Irwin Silverstein, Ph.D., ISP
Priscilla Stanley, Union Carbide Corporation
J. Mark Wiggins, Merck and Company, Inc.

TABLE OF CONTENTS

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 **Bulk Pharmaceutical Excipients (BPE).** The goal is to standardize the content and format of Certificates of Analysis for excipients, and to clearly define the roles and responsibilities for excipient **manufacturers, distributors,** and **users.** The detailed definitions and thorough discussions are intended to establish uniform considerations regarding Certificates of Analysis for excipient **suppliers** and users. By providing this foundation for mutual understanding, it is hoped that greater assurance of regulatory compliance will be achieved for excipients used in the manufacture of pharmaceutical products.

1.2 Scope

This guide is applicable to all excipients used in the manufacture of a pharmaceutical product.

1.3 Principles Adopted

This guide should be of international application, bearing in mind that pharmaceutical grade excipients are diverse and often have uses other than pharmaceutical applications. As an international guidance document, it cannot specify all national legal requirements nor cover in detail the particular characteristics of every excipient.

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

1.4 Layout

The guide is divided into several sections. The first part provides background discussion necessary for the design and required elements of a COA. A template is provided to show the format and placement of information in the COA. Detailed discussion is then provided to insure an understanding of the purpose and meaning of the specific information contained in the COA. This is followed by references and a glossary of terms used in this document. The first use of a term defined in the guide is noted by the use of bold type with no underline.

2. GENERAL GUIDANCE

2.1 Differentiation of Excipient Manufacture

An excipient is often used with a broad range of active pharmaceutical ingredients and in a diverse range of finished dosage forms. The excipient is often a natural substance, mixture, or polymer whose **chemical** and **physical properties** are more difficult to

quantify. For a thorough discussion of Good Manufacturing Practices (GMPs) that apply to excipient manufacture see the IPEC *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients.*

2. 2 Preparation and Appropriate Use of a Certificate of Analysis

The Certificate of Analysis for excipients should be prepared and issued by the supplier of the material, following the general guidelines discussed below. Primary responsibility for the preparation of the COA belongs to the excipient manufacturer. It is of the highest importance that a complete and accurate COA is provided to the excipient user for **specific lots** or **batches** intended for use in the pharmaceutical industry. Additional considerations must be made for the preparation and issuance of a COA by a distributor of excipients (see Section 9).

The user of a bulk pharmaceutical excipient should always receive a Certificate of Analysis for material to be used in the manufacture of a drug product. At a minimum, the user should perform adequate identification tests on each lot of excipient received, prior to release for use. Specific identity tests should be used whenever possible. It is a regulatory requirement that excipients be assessed for conformity with all appropriate **specifications**. However, testing of all specification parameters may not be required for lot release if adequate compliance assurances are provided on the supplier's Certificate of Analysis. Before utilizing an excipient in a pharmaceutical product based on COA data, the user also must have an understanding of the supplier's control systems and compliance to GMP, through appropriate auditing or qualification of the supplier.

To utilize test results from a COA, the user must also establish the reliability of the supplier's COA test results by periodically performing all required tests (where possible[1]) and comparing the results obtained to the supplier's test results. It is important to understand that these results may not always specifically correlate, especially when an excipient is produced as a continuous lot. However, the user's test results should demonstrate compliance to the specification requirement.

2.3 Use of Contract Facilities

Contract facilities are frequently used in the manufacture, testing and distribution of excipients. When such facilities are used, the supplier of the excipient has the obligation to ensure that the facilities operate under appropriate quality standards (i.e. cGMP, GLP, etc.).

3. DESIGN AND REQUIRED ELEMENTS OF A CERTIFICATE OF ANALYSIS

[1] *Occasionally, it may not be possible to perform all of the required tests due to special equipment requirements, etc. which may not be available to the user. This may be acceptable providing the reliability of the supplier has been adequately determined using other appropriate supplier qualification techniques*

Currently, there are few standardized requirements for the content or format of Certificates of Analysis for excipients. The requirements contained in other current guides on Certificates of Analysis, including the World Health Organization (WHO) GMP Guide 32nd Report, were considered when developing this guide.

The required elements of a COA listed below are included in the following "Certificate of Analysis Template" Section of the guide. The excipient supplier may organize the required elements on the COA at their discretion; however, the following "Template " sections were designed to present the required and optional information in a logical manner.

The origin and the identity of the excipient are typically established in a Header Section. The manufacturer and manufacturing **site** must be identified if different than supplier and supplier location, enabling the user to assure that the excipient is from a qualified source. Although the manufacturer must be made known to the user, the use of codes for manufacturers and manufacturing sites on the COA to protect confidentiality is acceptable. The identity of the excipient must be definitively established by stating compendial and trade name, the grade of the material, and applicable compendial designations.

A **lot/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. The lot number or other unique identification of the material, its **date of manufacture**, and product code or number must be stated and traceable to a specified lot. If applicable, the **expiration date, recommended re-evaluation 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). Any customer required information would also be included here.

The actual test results applicable to the material quantity covered by the COA are included in an Analysis Section. The test name, the result, the **acceptance criteria** or specifications, and a reference to the test method used must be included for each characteristic listed. Reporting of actual data and observations is recommended rather than non-specific "passes" or "conforms" statements. If the reported results are derived from a **Skip-Lot** or **Reduced Frequency Testing Program**, average or in-process test result, this must be noted on the COA (See Section 7 for a detailed discussion of considerations).

The Certification and Compliance Section is used to list various types of statements that may be required depending on the excipient and specific user needs. These statements are usually negotiated between supplier and user based on specific application requirements. (Examples of statements sometimes used are included in Section 4.) Any declaration of the supplier as to compliance to additional compendial and/or other regulatory requirements is typically included in this section.

Many excipients have applications other than pharmaceuticals, such as food, cosmetics, or industrial products. Any product listed as being in compliance with specific regulations must meet the specifications and requirements of that regulation and must be manufactured under appropriate good manufacturing practices.

The identity of the individual approving the content of the COA must appear on the COA (See Section 8 for a discussion of electronic signature considerations). The page number and total number of pages must also appear on the COA. This information is usually included in a Footer Section.

4. CERTIFICATE OF ANALYSIS TEMPLATE

Listed below is a template for the content and format of a COA.

4.1. Header

- Titled "Certificate of Analysis"
- Company Name, Address, Phone Number, and Identity of Manufacturer and Manufacturing site
- Name (compendial/trade) of Excipient
- Grade of Excipient
- Compendial Designation

4.2. Body

- Lot/Batch Number
- Date of Manufacture
- Product Code or Number
- Expiration Date (if required)
- Recommended Re-Evaluation Date (if required)
- Stability Statement (if required)
- Customer Required Information

4.3. Analysis

- Test Name
- Test Results
- Acceptance Criteria (i.e., Specifications)
- Reference to the Test Method
- Reference to Skip-lot Testing (if appropriate)
- Reference to Average or In-process Test Results (if appropriate)
- Date Retested (if appropriate)

4.4. Certification and Compliance Statements

- GMP compliance (IPEC Excipient GMPs)
- Additional Regulatory References
- Potential to meet additional Compendial Standards
- Content listing and grade of ingredients (if a mixture)
- Other specific compliance statements (e.g. Organic Volatile Impurities (OVI), Residual Solvents, Transmissible Spongiform Encephalopathy (TSE), etc.)

4.5. Footer

- Identity of authorized individual for approval
- Date of approval
- Page Number (i.e., 1 of __)

5. COMPENDIAL DESIGNATION

For a supplier to claim a compendial grade on the Certificate of Analysis for an excipient, there are two requirements that must be met. The first requirement is that the excipient must be manufactured according to recognized principles of good manufacturing practices. (See the General Notices in the USP and Ph.Eur., for example, and also IPEC's *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients*). Adequate conformance to GMPs must also be demonstrated for subsequent steps in the distribution of the excipient. The second requirement is that the excipient meets all of the specifications contained in the appropriate compendial monograph. When an excipient is listed as compendial grade, it is understood that the above requirements have been met for the material, and the user would be able to confirm this through an appropriate audit of the supplier.

Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The supplier's release specifications and compliance with good manufacturing practices are developed and followed to assure that the article will comply with compendial standards until its' expiration or recommended re-evaluation date when stored correctly.

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.

Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from examination of finished units drawn from the batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the supplier when judging compliance of the batch with the compendial standards. (See Section 7 for additional discussion.)

6. DATES ON A CERTIFICATE OF ANALYSIS

6.1 General Guidance

Part of the overall goal to standardize Certificates of Analysis for excipients includes a provision for the consistent reporting of appropriate, meaningful, and well-defined dates. The discussion below indicates specific dates that are expected on the Certificate of Analysis, along with definitions of the dates, in order to provide suppliers and users of excipients with a mutual understanding of their meaning. Use of the recommended terminology will be helpful in reducing questions regarding dating information reported for excipients. Use of terminology other than that discussed below is discouraged, as the terms may be ill defined and have different meanings for the excipient supplier and user. Examples of such terms that should not be used include Shelf Life, Use-By Date, Warranty Date, and Expiration Period.

In reporting dates on Certificates of Analysis 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 alpha designation be used for the month (may be abbreviated), rather than a numerical representation. It is also recommended that the year include all 4-digits (ie; Jan. 1, 2000 or 1 Jan., 2000, etc.).

6.2 Date of Manufacture

The Date of Manufacture must be included on the Certificate of Analysis for each excipient lot and should be assigned by the supplier based on their established policies and procedures. It is recognized that excipients may be manufactured using a variety of processes (e.g. continuous or batch) which may require a period of several days or more to complete. In addition, some excipients may be mixtures or blends of other excipients, and excipient production may include **reprocessing** steps. Because of this diversity, the Date of Manufacture should be clearly defined by the supplier and consistently applied for the particular excipient and process. In reporting the Date of Manufacture, the excipient supplier should indicate the date of completion of the final manufacturing process (as defined by the supplier).

It is important to note that **re-packaging** alone is not considered a **processing step** to be used in determining the Date of Manufacture. To provide traceability for a specific excipient lot, other dates may be required, in addition to the Date of Manufacture, to reflect additional steps, such as re-packaging.

6.3 Expiration Date and Recommended Re-Evaluation Date

The stability of excipients may be an important factor in the stability of the finished pharmaceutical dosage forms that contain them. Many excipients are very stable and may not require extensive testing to demonstrate continued conformance to appropriate specifications. Other excipients may undergo chemical, physical, and/or microbiological changes over time that cause the material to fall outside established specifications.

Appropriate Expiration and/or Recommended Re-Evaluation Dates for excipients should be established from the results of a documented stability-testing program, or from historical data. The testing program should include defined and controlled storage conditions (e.g. temperature and humidity), a consideration of different **packaging** types that may be used as market containers, and meaningful, specific test methods to adequately assess the stability characteristics of the excipient. Stability testing should determine whether possible degradation, moisture gain or loss, viscosity changes, or other possible changes occur to make the excipient unacceptable for use (e.g. unstable or hygroscopic materials). For additional information on excipient stability, see IPEC's *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients*, Section 4.9.

The Expiration Date for an excipient is defined as the date after which the supplier recommends that the material should not be used. Prior to the assigned Expiration Date, the excipient is expected to remain within established specifications, if stored according to the supplier's recommended conditions.

The Recommended Re-Evaluation Date for an excipient is the date suggested by the supplier when the material should be re-evaluated to insure continued compliance with specifications. Re-evaluation of the excipient may include physical inspection and/or appropriate chemical, physical, and microbiological testing. Prior to the Re-Evaluation Date, the excipient is expected to remain within established specifications, provided it has been stored according to the supplier's recommended conditions. But beyond the Recommended Re-Evaluation Date, the excipient should not be used without adequate evaluation, at appropriate intervals, to determine whether the material continues to be acceptable for use. The Recommended Re-Evaluation Date 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.

In reporting Expiration and Recommended Re-Evaluation Dates, the excipient supplier is providing important information to the user about the stability of the material. As discussed previously, the assignment of an Expiration Date and/or Recommended Re-Evaluation Date should be based on appropriate evaluation of potential changes that may occur in the material's properties. It is acceptable to report both an Expiration Date and a Recommended Re-Evaluation Date on the

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