資料 B-1

Globalization of Pharmacuetical Manufacturing：Impact on Exipients
医薬品製造のグローバル化　：添加剤に与える影響

1．　ヘパリンは緊急の注意が必要

- ✧ 最終製品の 30%以上が汚染
- ✧ 多くの原薬が世界中に存在する：多くの国に影響を与える。
- ✧ 受け入れ試験と出荷試験で検出されていない。
- ✧ 調査の誘因となる重篤有害事象となっても薬の供給に固守
- ✧ サプライチエーンとグローバル設定の完全な警戒において回復する。

2．海外で製造された医薬品の数は 2001 年から倍になっている。

- ✧ グラフ

3．ＦＤＡに規制された海外の医薬品は 2001 年から 2 倍以上になっている。
　査察の数は査察回数の率が４１%減少しているにもかかわらず増加している。

- ✧　グラフ

4．ＡＮＤＡ（FDA 医薬品簡略承認申請）といわれる遠方の海外施設が増加。
　2/3 の処方箋薬はジェネリック医薬品である。

- ✧ グラフ

5．医薬品輸入に対して多くの可能な拠点

- ✧ 地図

6．アメリカのグーロバリゼーションの課題への展望

- ✧ 製造された医薬品の数　　アメリカは 2001 年から 2 倍以上
- ✧ 査察対象が 37%に減少しているにもかかわらず、査察の数は増加している。
- ✧ 実地調査では減少しているが、輸入経路は 2001 年来 2 倍になっている。
  通関手続きが出来る港は３１２
- ✧ アメリカ市民はジェネリック医薬品（６５%）の増加を期待している。原薬のほとんどはアメリカ郊外で作られている。
- ✧ FDA[において 2003 年来、医薬品に投入された人的資源は段階的に減少している。

7．重要な課題

- 世界的に拡大する生産の急増
- サプライチエーンの煩雑さの増加
- 開発のためのより大きな可能性（模造品、テロリズム）
- 世界的な規制システムはまだ統一されていない
- (アメリカ)数十年間にわたって検査の対象は減退
- （アメリカ）近代ITの不足（登録とリスト化、査察の追跡、輸入）

8．グローバリゼーションの処理の実態

- FDAは世界から供給される医薬品の査察は出来ない。査察は一つの重要な成分に対してのみである。
- 製造業者、輸入業者、仲介業者、販売業者はサプライチエーンを通して医薬品の品質に重要な責任をはたさなければならない。
- 立法者と一般市民は全ての関係者の責任に注意を払っている。

9．アメリカがいま進めることは何か？

- 国際規制の調和に焦点を当てる。
- 国際的な活動
- FDAは国境のかなた
- ITの改善；在庫の記録をつける
- 21世紀の戦略に対する継続的な医薬品の品質
- 会議への関心

１０．国際調和

われわれが行くべきところ。

- 途切れのない効果的なグローバル規制への協調
  - ○　世界的なセーフティーネット
  - ○　発展途上国における査察の有効性の増大
- 品質規格の完全な調和（ＩＣＨと非ＩＣＨの領域　：　ＩＣＨ　Ｑ１０　供給者の資格認定）

  ○添加剤にＧＭＰは必要？
- 製造の近代化
- 調和された局方の標準（例えば　ＵＳＰの残留溶媒）
- 同意　：　サプライチェーンの方法における安全性／完全性
- ＩＴ：自動化と世界的な在庫管理の標準化

１１．任務と責任

- 製造業者は医薬品の品質とサプライチェーン完全性に最終的な責任がある。
- 規制当局の仕事
  - ○ 公表／品質標準の承認
  - ○ 保証する標準はそろっている
  - ○ 悪い品質に対しては行動する
  - ○ 継続的な改良を可能にする
- 標準と技術組織

  技術基準の合意を展開する
- 専門家と技術協会と標準開発機関
  - ○ 開発に参画する／最新の国際的な技術標準（例えば IPEC の自主基準）
  - ○ 標準の普及と世界的な教育機会の均等の準備

１２．国際的な支援活動

- 地域の調和の主導権
  - ○ APEC： アジア太平洋経済協力
  - ○ ASEAN ： 東南アジア諸国連合
  - ○ GCC ：湾岸協力会議
  - ○ PANDRH ：全米医薬品規制調和ネッワーク
  - ○ SADC ： 南部アフリカ開発共同体
- ICH（日米欧医薬品規制ハーモナイゼーション国際会議）国際協力 ：

  2008 年 6 月に参加が拡大された
- FDA の太平洋諸島センターへの参加
- ICH における規制当局者の公開討論

１３．FDA はわれわれの国外に

- さまざまな地域に FDA 事務所の設立
- 中国とアメリカ間の覚書
- 中国における FDA 事務所の設立 ： 2008 年 3 月
- 世界中の多数の地域に FDA 事務所の設立の計画
- 海外査察を実行するためにさらなる人材の雇用

１４． 在庫の足跡を残す／医薬品の動向

- 新たな登録と電子的医薬品登録システム（ e-DRLS：Electronic Drug Registration and Listing Systems）
  - ○ 電子登録とリスト化は現在進行している。

○ ストラクチャードプロダクト表示を使用
○ 企業識別コードの利用
- 国境におけるより良い調査 —— リスト管理の電子認証に近づく
- 無線 IC タグのような発達した技術を促進するよう継続する

１５． ２１世紀の医薬品の品質 ： 次のステップ

- 最終規制 ：GMP
- 品質設計 ：規制協約指針

○ 品質設計は添加剤の重要な規則であることを強調している。
- 各種の製造補足書に対するファイリング管理のガイダンス
- 薬事監視制度を活性化する
- 継続的な開発リスク 再調査と実況見分の見直し

１６．議会の興味

- ヘパリン事件を通して三つ議会聴聞（会）
- 輸入後に関する問題 ：
  - ○ ペットフード中のメラミン
  - ○ ヘパリンの汚染（コンタミネーション）
  - ○ 食物による複合的な突発的な病気
- いくつかの法案の議論が始まった
- 全ての FDA に登録された製品と色々な方法で FDA の前例の増加への大部分を含む措置
- 継続的な開発の期待

１７．グローバリゼーションがもたらす問題に取り組むには他になにかやるべきことは？

- 沢山ある
- 最新の調和の標準の実施に継続的に向かう
- 完全に調和された再調査と実況見分の両方に対する国際的な基本骨格を策定する
- 継続的な発達プランの行動を策定する。

１８．まとめ

- 製造の国際化は産業と規制に対する挑戦に類似する。
- 多くの発展は提案と GMP の期待に対する調和の標準化の中で過去 20 年間になされて

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

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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**	

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