



The International Pharmaceutical Excipients Council

Qualification of Excipients for Use in Pharmaceuticals Guide & Checklist

Second Version
2020

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

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

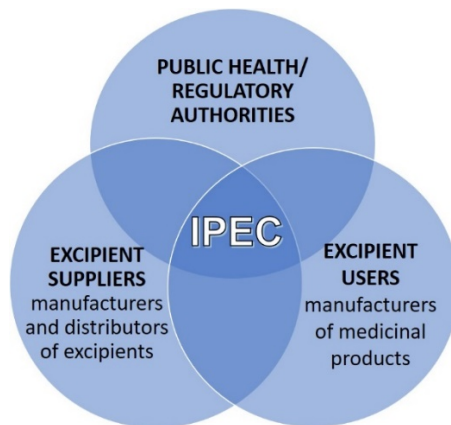
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FOREWORD

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

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, defined as *excipient suppliers* in this document
2. Pharmaceutical manufacturers, defined as *excipient users* in this document
3. Public health and regulatory authorities



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of users of the guide to determine whether there are any additional legal or regulatory requirements, in addition to the recommendation given in this guide, applicable to a particular region or country in which they are doing business.

This guide offers best practice and guidance in the establishment of an effective relationship between an excipient supplier and excipient users. The excipient supplier may be an excipient manufacturer or a distributor (or both). This guide concentrates on the issues that the two parties are likely to encounter and offers advice as to how to address them, thereby ensuring a smoother relationship and easier use of the excipient by the excipient user and in their dealings with the regulatory authorities.

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

ACKNOWLEDGEMENTS

This guide was developed by representatives of many International Pharmaceutical Excipients Council members. IPEC is a global industry association whose members consist of excipient manufacturers, distributors, and users, as well as experts from academia. The association representatives who worked on this guide are listed below:

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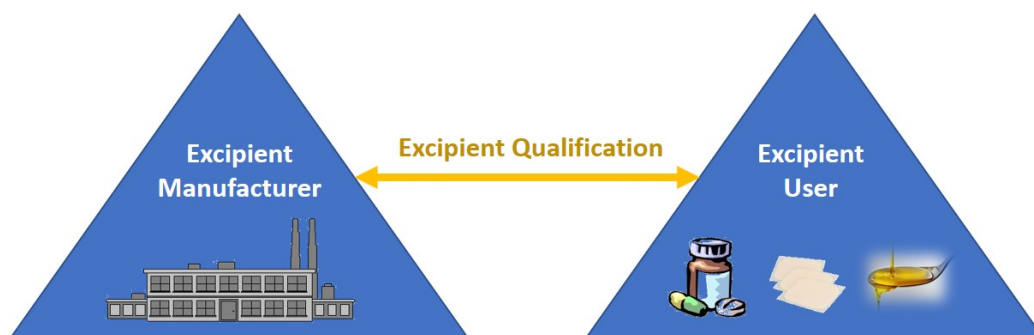
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1 INTRODUCTION

1.1 Purpose and Scope

This document is meant as a guide for excipient qualification (i.e. to establish the information needed to support the development of products and marketing materials used as excipients, as well as to describe the necessary information for excipient use by pharmaceutical companies). For manufacturers who have not previously made products for the pharmaceutical industry, additional details are provided to explain the requirements and expectations of this industry.

Materials used as excipients are diverse and often have uses other than in pharmaceutical applications (e.g., industrial use, food additive, or cosmetic ingredient). A material manufacturer may discover that their products are being used by the pharmaceutical industry as excipients. If the material manufacturer wants to market their product as an excipient, additional quality and regulatory requirements may be applicable. This guide will be especially valuable in such situations because many of the issues described could be new or otherwise unknown to the material manufacturer.



Components of medicinal products are required to be manufactured under applicable **good manufacturing practices (GMP)** and supplied using applicable **good distribution practices (GDP)**. The level of GMP or GDP will depend on the materials in question (e.g., excipient, drug substance, packaging materials, etc.) and regulations where the materials will be used. Within this guide, the terms GMP and GDP are relative to excipients.

NOTE: Some excipients may be used as “atypical actives” (i.e. substances which have been registered as an active ingredient in a medicinal product but whose primary use is not ordinarily as a drug substance [2, 3]). Atypical actives are not in the scope of this guide.

1.2 Principles Adopted

When considering how to use this guide, the reader should consider if and how each step applies to their materials and processes. The use of some excipients may require more stringent requirements than those found in this guide. Although the steps in this guide are organized in a

specific sequence, excipient suppliers and excipient users are not required to follow that sequence through their own excipient qualification process. The terminology “should” and “it is recommended” do not necessarily mean “must” unless referencing regulatory requirements.

While this guide primarily highlights issues specific to the European Union and the United States, the principles in this guide can be applied worldwide to any excipient supplier-user relationship. However, as an international guide, this document does not address the specific legal or excipient qualification requirements of every nation or locality.

Like all IPEC guides, this guide is not meant to be proscriptive. Excipient suppliers and excipient users may follow the guideline as written or find their own manner to address the subjects highlighted. This guide is intended cover essential aspects of the excipient supplier-user relationship. In this regard, not every topic may be appropriate for all relationships.

NOTE: Throughout this guide, the term “batch” will be used to represent either lot or batch of an excipient.

1.3 Layout, Annex and Reference Numbers

This guide describes the excipient qualification process.

Table 1 Guide Layout and Contents

Section 1	Introduction: describes the scope, purpose, and layout of this guide.
The Excipient Suppliers’ Process	
Section 2	General Guidance: provides background concerning excipient manufacture, regulation, and controls.
Section 3	Excipient Development and Specification Process: provides guidance to excipient suppliers on the development of an excipient and its specifications.
The Excipient Users’ Process	
Section 4	Excipient Selection Criteria: provides guidance on how excipient users should assess excipients for inclusion in their formulations.
Annex A	Checklist that provides: <ul style="list-style-type: none"> A. actions that a material manufacturer may take to evaluate the market and regulatory requirements for a potential excipient as well as the minimum quality-relevant actions needed prior to market launch, and B. considerations generally made by an excipient user during medicinal product formulation with respect to excipient and excipient supplier evaluation”

The checklists found in [Annex A](#) summarize responsibilities of the excipient supplier and user.

2 GENERAL GUIDANCE

2.1 Differentiation of Excipient Manufacture

Many materials used as excipients are marketed for use in non-pharmaceutical applications, such as food additives, cosmetic ingredients, or industrial products. Thus, environmental conditions, equipment, and operational techniques employed in excipient manufacture more often resemble those of the chemical industry than the pharmaceutical industry. Additionally, the raw materials used to manufacture excipients are often not manufactured in accordance with GMP requirements (for example as found in the IPEC-PQG GMP Guide [4]) because they are technical grade materials. The excipient manufacturer should conduct a risk assessment of these materials to ensure their suitability for the use in the manufacture of an excipient.

The same GMP principles apply to materials sold as excipients by distributors. In these cases, the IPEC Good Distribution Practice (GDP) Guide [5] is an appropriate reference for defining the quality assurance standards and systems required of the distributor.

Many excipients have pharmacopeial monographs that define specifications that address key quality attributes. Excipients are typically not single components or “pure” materials like APIs. As described in the IPEC Excipient Composition Guide [6], excipients have an excipient composition profile that includes **concomitant components**. However, these concomitant components should not be confused with **impurities** [6]. The presence of concomitant components may have beneficial effects on excipient performance, but controls are sometimes needed to assure that the presence of concomitant components is at a consistent level and that undesirable deleterious components are kept to a minimum. Specifications should be considered for concomitant components where control is deemed necessary.

Excipient users are highly dependent on excipient suppliers to provide materials that are uniform and reproducible in chemical, physical, microbiological, and performance characteristics. This is particularly important in the context of the pharmaceutical product approval process, where bioequivalence comparisons are made between pivotal, clinical trial batch (also known as “biobatch”¹) production and commercial scale-up batches. To provide adequate assurance of consistent finished product performance, excipients used to manufacture commercial batches should not differ significantly in composition from those used in biobatches. Therefore, it is important to minimize variation between different excipient batches, as well as within the excipient batch itself. If significant differences do occur between excipient batches used in clinical and commercial medicinal product batches, additional testing by excipient users may be required to establish medicinal product bioequivalence.

¹ biobatch is a development batch intended for patient use and requires the same excipient GMP as for a commercial product.

2.2 Excipient Functionality

Excipients will be expected to provide various functions in dosage forms or their processing, including but not limited to:

- Binder
- Compression Aid
- Disintegrant
- Color/Pigment
- Flavor (taste masker)
- Filler
- Sweetener
- Lubricant
- Glidant/Flow Aid
- Humectant
- Buffer
- pH Adjuster
- Release Modifier
- Adhesive
- Penetrant
- Preservative
- Suspending/Dispersing Agent
- Identity (through printing with ink)
- Surface Active Agent
- Coating/Film Former
- Vehicle
- Thickener
- Solubilization
- Wetting

Excipient combinations are commonly used in medicinal product formulations since, typically, no single excipient can provide the complete range of functions necessary to produce the desired drug delivery system in the dosage. Such combinations may be obtained by different physical processes, such as mixing or co-processing.

Excipients*:

- aid in the processing of drug delivery systems during manufacture,
- protect, support or enhance stability, bioavailability or patient acceptability,
- assist in product identification,
- enhance any other attribute of the overall safety, effectiveness or delivery of the medicinal product during storage or use [4].

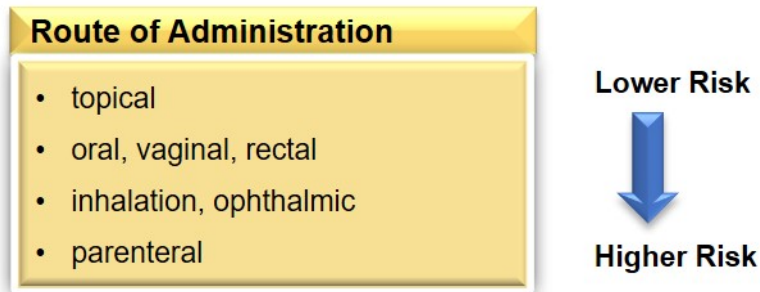
* refer to bulleted list above for additional functions

2.3 Preliminary Excipient Marketing Decision

It is not appropriate for a supplier to offer a non-pharmaceutical grade material as an excipient. The **original manufacturer** begins the process of offering an excipient to the pharmaceutical market, using regulatory and GMP principles outlined in this and other IPEC guides.

2.3.1 Determination of the Intended Target Market and Route of Administration

Excipient users should identify appropriate regulatory and GMP requirements based on the medicinal product's intended route of administration. The route of administration is critical to defining requirements for excipients because the key principle throughout the pharmaceutical supply chain is protecting patients. Risks to patients are directly proportional to the route of administration:



Parenteral dosage forms normally require excipients to have a low bioburden or be produced as **pyrogen-free**. Excipients used in **sterile** medicinal products may be required either to be sterile or capable of remaining unchanged by the excipient users' sterilization process. The excipient manufacturer is responsible for ensuring that excipients meet the claims they are making, including claims for the presence of bacterial **endotoxin** and/or pyrogen.

2.4 Regulatory Assessment

Although excipient qualification does not directly involve regulatory authorities, regulators set many of the conditions that must be satisfied for users to incorporate excipients into medicinal products.

2.4.1 Safety, Toxicological, and Precedence of Use Issues

There are several safety related issues that should be assessed by the excipient manufacturer as part of their decision to market excipients to the pharmaceutical industry. Excipient manufacturers should first assess whether the excipient has a precedence of use in countries where it is intended to be marketed.

In the United States, precedence of use is demonstrated by excipients being listed in the FDA Inactive Ingredient Database (IID) [7]. In the IID, excipients are listed by name, route of administration, dosage form, and the maximum amount of excipient contained in approved medicinal product of that listed route of administration and dosage form. Care must be exercised in searching the database because excipients can be listed by various names, including trade name, compendial name, chemical name, or generic description (for dyes and flavors).

In Japan, an assessment for precedence of use can be made by referring to the Japanese Pharmaceutical Excipients Dictionary (JPED), which is edited by the Japan Pharmaceutical Excipients Council in conjunction with the Ministry of Health, Labor, and Welfare (MHLW). The JPED is a compilation of all excipients for which there is a precedence of use in medicinal products in Japan. It includes monographs from the Japanese Pharmacopoeia (JP) or Japanese Pharmaceutical Excipients (JPE) as well as all non-monograph excipients that have been previously used. Each monograph lists the nonproprietary name and synonyms along with the

application and maximum dosages for the various routes of administration in approved medicinal products².

Europe does not have a multinational list of excipients used in approved medicinal products. Therefore, in order to establish precedence of use, it is necessary to review national medicinal product catalogues such as the “Vidal” (France), “Die Rote Liste” (Germany), or “The Electronic Medicines Compendium” (UK) [8].

As of March 21, 2016, excipient users/medicinal product manufacturers in the EU were legally mandated to implement GMP requirements, including completed risk assessments, for each excipient used [9]. In support of Directive 2011/62/EC, the European Commission (EC) issued guidelines in March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use [10]. Section 2.2 of that guideline states “quality risk management principles should be used to assess the risks presented to the quality, safety and function of each excipient and to classify the excipient in question, e.g., as low risk, medium risk or high risk.”

Areas for risk consideration include, but are not limited to:

- prepared from materials derived from a TSE-relevant animal species (excluding lactose)
- derived from human/animal material with potential viral contamination risk
- used in sterile application
- controlled for endotoxin/pyrogen controlled, or
- deemed high risk (e.g., glycerin).

If there is no precedence of use in a medicinal product, then the material is to be considered a **novel excipient** (see 2.4.2 and 2.4.5).

Additional considerations may be applicable when the excipient is used for a medicinal product applied to a more sensitive patient population such as children. Higher safety concerns are of relevance here because of a different and less developed metabolism in this patient group. Therefore, evaluation for precedence of use in pediatrics may be appropriate.

2.4.2 Novel Excipients

Excipients used for the first time in medicinal products or by new routes of administration are classified as novel according to the ICH Guideline M4 [11] and US FDA [12]. A novel excipient is referred to as a new excipient throughout the EU [13].

When excipients have not previously been used in a pharmaceutical dosage form, there are a number of conditions established by the US and European regulatory authorities to allow for their use.

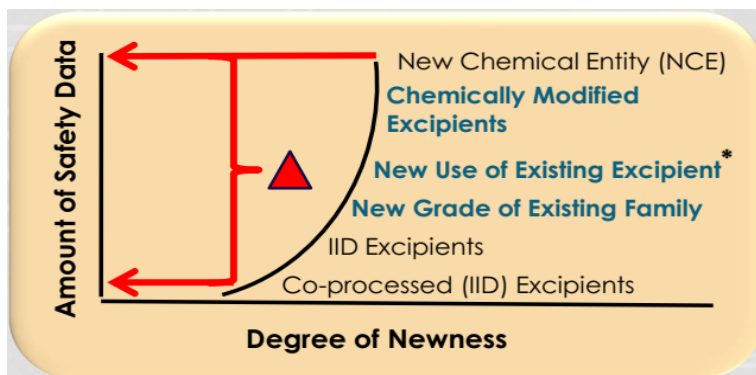
² Maximum dosage information is only contained in the Japanese language version of the JPED.

The US FDA has guidance concerning the safety testing required for novel excipients [14]. IPEC-Americas published “*A New Approach to the Safety Assessment of Pharmaceutical Excipients*” [15], which is the basis for USP General Chapter <1074>, Excipient Biological Safety Evaluation Guidelines [16]. Similarly, IPEC Europe’s Safety Committee published “*The Proposed Guidelines for the Safety Evaluation of New Excipients*” [17]. A new IPEC guide [18] is currently under development to combine and update topics covered in these two articles. The information in these documents is useful for assessing the safety of chemical entities for use as excipients. The manufacturers of novel excipients should develop the safety information recommended in these guides, appropriate to their intended marketed use. This information provides the basis for excipient users to establish the suitability for materials used as excipients in their medicinal products.

The degree of novelty can impact the amount of safety data needed by regulators to authorize an excipient for use in a medicinal application.

As shown below, nonclinical safety assessment data requirements for novel excipients are proportional to their “degree of newness”:

- New chemical entities (NCEs)
- Chemically modified excipients
- New use of an existing excipient
- New grade within an existing family of excipients
- Different level of use, grade, or route of administration than previously reviewed in an approved medicinal product (listed in the US FDA Inactive Ingredient Database, IID)
- Co-processed excipient where individual excipients were previously used in an approved medicinal product



The initial step in bringing novel excipients to market is to determine **functionality** based on intended use (i.e. route of administration).

Novel excipients will not have compendial monographs until a medicinal product containing the excipients has been approved by a regulatory authority. Therefore, excipient users need to

establish that there is sufficient characterization, safety and toxicological information available to support the intended use and to reference this information in their medicinal product application. Excipient manufacturers can provide this information directly to the excipient user or confidentially through a DMF or any appropriate dossier submitted directly to a regulatory authority. Other sources of characterization, safety and toxicological data (e.g., peer-reviewed articles) may also be relevant.

2.4.3 Compendial Requirements

General Comments

Where included in a pharmacopeia, the excipient must comply with the monograph requirements and the General Notices. It is the excipient user's responsibility to confirm that excipients meet compendial requirements in the region where the final medicinal product will be marketed.

There are multiple compendia used around the world. Most referenced are the United States Pharmacopeia–National Formulary (USP-NF), the European Pharmacopoeia (Ph. Eur.), Chinese Pharmacopeia (ChP), the Japanese Pharmacopoeia (JP), and the Japanese Pharmaceutical Excipients (JPE). Compendia establish analytical specifications, test methods, and other attributes to demonstrate the quality of the articles used in pharmaceutical products [19, 20].

When a compendial monograph does not exist, excipient users should determine if other regulations, compendia, or guidelines (e.g., Food Chemical Codex [21], Codex Alimentarius [22], JFECA [23], or the European Food Safety Authorities [24] (e.g., E numbers, Flavis numbers)) can be used to characterize suitable quality.

In some instances, specific requirements may be included in a monograph when an excipient is used for specific routes of administration (e.g., inhalation or parenteral applications) as discussed above (see 2.3.1).

Additives and **processing aids** are commonly found in excipients. The issue of including these materials in compendial monographs or General Chapters is still under active consideration by the compendia. Therefore, it is suggested that excipient manufacturers compile information related to the identity and quantity of additives and processing aids that are or may be present in excipients[6]. This is because their presence may affect patient safety, finished medicinal product testing, and/or stability.

For excipients that may be marketed for global use (i.e., listed in multiple compendia), excipient manufacturers are advised to ascertain excipient conformance to the monograph requirements found in each applicable compendia. While considerable efforts are underway to harmonize excipient monograph requirements in the major compendia, currently there are often different monograph requirements found among these compendia.

In order for excipients to be included in the USP-NF, Ph. Eur., JP or JPE they must have been used in an approved medicinal product in the respective country or region.

Additionally, excipients must be manufactured according to appropriate GMP to comply with compendial monographs. These expectations are described in the various compendia, e.g., USP General Notices 3.10 [19] and Ph. Eur. 1.1 [20].

2.4.4 *Desired Properties for Marketed Use*

Excipient suppliers may have a range of data available describing material functionality if the material has been used in other applications, e.g., food, cosmetics. This information can be valuable to excipient users when defining excipient functionality and the safety profile. However, some of this data and knowledge can be considered proprietary. If it is to be shared with excipient users, suitable confidentiality agreements may be needed.

For new chemical entities intended for use as excipients, data are needed demonstrating functionality and safety by the intended route(s) of administration.

2.4.5 *Excipient Master Files and Other Filings*

Excipient Drug Master Files (DMFs) are a compilation of proprietary technical details related to excipient manufacture. The document's format is aligned with the ICH Common Technical Document (CTD) format [11]. Depending on whether the DMF covers compendial or non-compendial excipient(s), it can include:

- proprietary information related to raw material specifications and test methods,
- a description of the manufacturing process,
- in-process and finished excipient controls,
- packaging and labeling details,
- stability information, and
- safety data.

2.4.5.1 *Excipient DMF*

Excipient manufacturers will often submit DMFs to provide confidential information to the relative health authority regarding excipients, their safety, and conformance with appropriate GMP requirements. Regulators in the US, Canada, and Japan have an excipient DMF system. In the EU, although a DMF (**Active Substance Master File, ASMF**) system exists for drug substances, a Master File system is not available for excipients. See IPEC-Americas DMF Guide [25].

2.4.5.2 *Certificate of Suitability (CEP)*

Certificates of Suitability are voluntary documents issued by the European Directorate for the Quality of Medicines (EDQM). There are two types of CEPs. One type demonstrates compliance to a Ph. Eur. monograph.

The other type of CEP demonstrates that the risk of transmitting Transmissible Spongiform Encephalopathies (TSE, including bovine spongiform encephalopathy, BSE) has been minimized to an acceptable level as laid down in EMA410/01 [26]. These CEPs are applicable to drug

substances and excipients, including those without a Ph. Eur. monograph. They certify that the article meets the requirements of Ph. Eur Chapter 1483, hence the risk of TSE transmission to humans through the medicinal product is suitably controlled.

In the EU, regulators use a CEP to provide confidential information in support of the following three types of drug marketing authorization procedures:

- centralized procedure (submission to the European Medicines Agency (EMA)),
- mutual recognition procedure (MRP - submission to and approval by one EU member state, which then becomes the reference country for extension within the EU), and
- decentralized procedure (submission to all EU countries desired, one of them identified as the reference country).

Independent of the drug marketing authorization procedure used, relevant data should be provided by excipient manufacturers directly to excipient users, marketing authorization holders (MAH) or the relevant regulatory agency for inclusion in the medicinal product application. Proprietary information is often provided to excipient users and/or MAHs under confidentiality agreement.

If no CEP is available, the excipient manufacturer should be willing to provide excipient information directly to the MAH for inclusion in the drug application. A confidentiality agreement can be used to facilitate disclosure of confidential information.

2.4.5.3 Chinese Excipients Dossier

The Chinese Joint Bundling Review Excipient Dossier documents relevant details of the excipient and its manufacture. This information is submitted to the regulatory authorities, and in some cases can be provided to the MAH. The dossier is used during the review and approval of medicinal products. Separate dossiers are required for each excipient or excipient family, manufacturing location, and route of administration of the excipient. The dossier has to be submitted even if the excipient is listed in the Chinese Pharmacopoeia. A list of excipients has been identified by the Chinese National Medical Products Administration (NMPA) for exclusion from these registration requirements; a list of excipients which have dossiers and their status is available on the web.

2.4.6 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

ICH guidelines apply to drug substances and medicinal products but these guidelines are not directly applicable to excipients. However, elements of the guidelines may provide direction for topics relevant to excipients, such as GMP manufacturing. As such, ICH guidelines have been referenced in the development of IPEC guides.

2.4.6.1 *Stability*

IPEC-Americas and IPEC Europe developed the IPEC Excipient Stability Program Guide [27], because ICH Q1A(R2) [28] is not applicable to excipients. Some reasons that ICH Q1A(R2) are not applicable to excipients include:

- medicinal products are packaged in small containers relative to excipients (e.g., pill bottles and blister packs) and often stored under controlled conditions,
- excipients are usually stored in large containers in uncontrolled warehouses, and
- stability chambers are often too small for excipient packages.

2.4.6.2 *Impurities*

The ICH Q3A Guideline [29] for drug substances is not directly applicable to excipients; however, it may be useful to address components that are potentially harmful. IPEC recommends that a **composition profile** [6] be developed to define all components of the excipient.

2.4.6.3 *Residual Solvents*

The excipient manufacturer is expected to communicate to excipient users the presence and concentration of residual solvents in the excipient as identified in ICH Q3C [30]. This information allows excipient users to calculate the quantity of residual solvents found in their medicinal products and demonstrate that their medicinal product meets the required limits specified in ICH Q3C.

This ICH guideline for residual solvents has been adopted by the Ph. Eur. as Chapter 5.4, and the USP as General Chapter, Residual Solvents <467>. These chapters are applicable to all compendial articles.

2.4.6.4 *Elemental Impurities*

Unless otherwise described in monograph requirements, there is no regulatory requirement for excipient manufacturers to test for or to communicate elemental impurity data according to ICH Q3D Guideline for elemental impurities [31]. Nevertheless, it is useful for excipient users to have this information for use in calculating the quantity of elemental impurities found in their finished dosage forms. To help facilitate exchange of information between excipient manufacturers and excipient users, IPEC developed and published an IPEC Elemental Impurities Template [32] and cover letter [33] for capturing and reporting available excipient elemental impurity information.

2.4.7 *Specific Safety Issues*

Excipient quality and origin may have implications for patient safety and/or religious purity (e.g., Kosher, Halal) certifications. Therefore, excipient suppliers should have knowledge of, and control over, the following aspects of their processes:

- Origin of Raw Materials

- Animal derived materials may lead to concerns related to BSE (or other TSE), Halal and/or Kosher certification.
- Excipients produced from raw materials having human or animal origin may require viral safety information demonstrating that materials used in excipient production are safe, and the methods used to test, evaluate, and eliminate potential risks during manufacturing are suitable.
- Substances derived from certain other natural sources (e.g., wheat protein, peanuts, eggs) may be of concern since some materials can lead to negative and/or allergic reactions in patients.
- Excipients produced from genetically modified organisms (GMOs) such as corn (maize) or soy products may be subject to restrictions or labeling requirements in certain regions [e.g., Regulations (EC) 1829/2003 and (EC) 1830/2003].
- Degradation Products of the Excipient
 - Excipient manufacturers generally know if and how excipients degrade with time, with atypical processing conditions, or with thermal and/or mechanical stress (e.g., particle size degradation during transportation). Such knowledge should be made available to excipient users. Results from formal stability and/or transportation studies can provide similar information (see 2.5.1).
- Elemental Impurities [31, 32, 33].
- Residual Solvents
- Additives and Processing Aids
 - Certain additives or process aids such as biocides, anti-oxidants, or stabilizers, may be present, although they are not always declared.
 - A composition profile should be developed to determine the presence of process-related components and their concentrations.
 - Excipient suppliers should ensure consistent concentration of these components in excipients.

Excipient suppliers should understand, document, and communicate to excipient users the safety aspects (e.g., toxicity) of the excipient.

2.4.8 Concluding Comments on the Regulatory Assessment

Upon the completion of the regulatory assessment, minimum requirements for the intended market(s) will have been established along with any regulatory constraints. Excipient manufacturers should demonstrate that materials can be suitably produced for intended marketed use.

Since regulations change rapidly, excipient manufacturers (as well as excipient users) should monitor and understand changes in regulatory requirements for their intended market, and determine the impact on the excipient for any emerging regulatory topics.

2.5 Manufacturing and Packaging

From the point where GMP starts [4], all operations including packaging and distribution should be conducted in conformance with appropriate excipient GMP requirements. It is important that excipients are produced using a manufacturing process that is in a state of control, often referred to as a capable process. Whether the process is continuous or by batch, there should be written manufacturing instructions listing raw materials, operating equipment, operating conditions, in-process controls, sampling plan, packaging operations, packaging components, and labeling materials, including labeling content. As described in the IPEC Excipient GMP Guide [4], while dedicated manufacturing equipment is preferred, multi-use equipment is acceptable provided there is a verified, documented process to avoid incidental carryover of **contaminants** from the manufacture of other materials.

Packaging operations often have the potential to expose the excipient to environmental contamination; therefore, suitable controls are needed to ensure excipient quality. A risk assessment should be conducted and documented to determine necessary controls.

Packaging materials should suitably protect excipients from degradation and potential environmental contamination while minimizing the potential for contamination from the packaging components, including labels, themselves.

Excipients should be supplied in tamper-evident packaging [4, 34, 35]; for example: security tape, embossed metal seals (for bulk shipments), and excipient supplier-branded bung seals.

Container labels should be applied at the manufacturing site and meet local transportation regulations, but at a minimum include [4, 5]:

- the name of the excipient and grade, if applicable,
- the excipient manufacturer's and/or distributor's name and address,
- the batch number from which the complete batch history can be determined, and
- special storage conditions, if applicable, required to assure excipient quality.

For bulk shipments (e.g., tank trucks, rail cars, ships, etc.), the above information can be provided on a bill-of-lading (BoL) and/or container placard. This information can be applied either at the manufacture site or prior to shipment to the excipient user.

2.5.1 Process Validation³

Excipient manufacturers should be able to demonstrate that manufacturing processes are capable of consistently producing excipients meeting their specifications (i.e. process validation). Process capability may be demonstrated by manufacturing work processes, including process capability studies, continuous process verification, design of experiments, statistical techniques,

³ The full validation program that is typically performed in the pharmaceutical industry may not always be carried out by the excipient manufacturer. Refer to IPEC GMP Guide section 7.5.2

classic pharmaceutical validation, etc. The method(s) used should provide a high degree of assurance that a specific process or system will consistently produce the desired results. The excipient manufacturer should be able to justify methods used for validation activities [36, 37, 38].

2.5.2 Test Methods and Method Validation

Excipients labeled as meeting compendial requirements must conform to that compendium and its acceptance criteria. Excipient manufacturers must follow compendial monograph test methods or develop appropriate internal quality control test methods. Internal test methods can be developed for various reasons; however, in-house test methods used to replace compendial methods must be validated against the compendial method and provide equivalent or better results. Method verification (for compendial methods) or validation (for non-compendial methods) must be documented.

2.5.3 Excipient Specifications

A material specification is a list of tests to be performed together with their acceptance criteria. If an excipient has a compendial monograph and is labeled as meeting the monograph, the excipient must meet all the criteria specified in the compendia. For excipients that do not have a compendial monograph, specifications need to be established taking into consideration **critical quality and material attributes** as well as the manufacturer's marketed use [39].

Where differences exist between the excipient user's purchase specifications and the excipient manufacturer's standard product specifications, the excipient manufacturer should review their process capabilities to determine the feasibility of meeting the excipient user's purchase specification. Caution should be exercised before agreeing to meet the purchase specification through batch selection when process capabilities are insufficient to reliably supply the excipient.

2.5.4 Excipient Stability

Excipient suppliers should have data demonstrating material stability under established storage conditions in the commercial packaging. It is up to the excipient manufacturer to define and communicate an expiration period or retest interval for the excipient. Packaging should protect the excipient from degradation through the supply chain. Excipients must remain in conformance with specifications until the end of their **expiration period** (or the start of their first **re-evaluation** or **retest interval**), when stored in the original, unopened packaging and maintained under the established storage conditions.

New stability data may have to be developed after significant changes are made. See the IPEC Significant Change Guide [40]. If stability data are not available, excipient users may need to generate them independently. See IPEC Excipient Stability Program Guide [27].

3 EXCIPIENT DEVELOPMENT AND SPECIFICATION PROCESS

3.1 Excipient Consistency and Control

The manufacturing process should be controlled to ensure that the excipient consistently meets required specifications. As described above in Section 2.5.1, excipients are normally subject to various in-process tests to demonstrate that a manufacturing process is in a state of control (continuous process verification). Based upon the operating parameters, a process control plan should be developed. In-process controls (i.e. inspection and/or testing) should be performed by analyzing actual samples or by monitoring process parameters against established acceptance criteria.

Excipient manufacturers should establish composition profiles [6]. Components in an excipient composition profile arise from their presence in raw materials or their development during the manufacturing process. The later can occur either as reaction by-products or as residues from catalysts, solvents, process aids, polymerization initiators, etc. Specifications for these components, where applicable, should be based on appropriate toxicological data (or as described in compendia) as well as manufacturing processes and reaction chemistries.

3.2 Performance Indicators

Conformance to compendial General Notices as well as monograph requirements or product specifications is sufficient to establish consistent excipient quality. Since excipients perform functional roles, the manufacturer should also develop appropriate performance indicators for the intended marketed use. These indicators should be evaluated after significant changes have been made to the manufacturing process.

As an example, if the intended target use is solid dosage forms, several tests are available to establish performance characteristics in the dosage form, such as dissolution testing and tablet friability. In this example, the excipient manufacturer might determine baseline performance characteristics for the excipient in the target dosage form, e.g., using a model formulation. Excipient performance characteristics might then be correlated with physical properties, such as particle shape, size and size distribution, specific gravity, viscosity, hygroscopicity of the excipient, etc. It is also possible that these baseline performance characteristics can be correlated to the excipient's chemical composition, such as the level of concomitant and other components. Excipient manufacturers can only evaluate the impact of process changes on performance characteristics by comparing these functional properties before and after any changes were made.

Collaboration between excipient manufacturers and excipient users is always recommended, but this is especially important for critical applications to minimize potential impact to the patient.

3.3 In-Process Limits, Product Specification, and Batch Record

Separate specifications may be developed for excipient production (internal) and release (sales). The **product specification** includes those requirements that assure conformance with both the release specification and any regulatory requirements. Typically, production specifications are narrower than release specifications.

Refer to IPEC-PQG GMP Guide [4] for excipient batch record guidance.

3.4 Product Information

The following information should be made available by excipient manufacturers to excipient users:

- sales specification, including in-house test methods,
- safety data sheet (SDS),
- excipient information package (EIP) [41], and
- technical literature including, as available, storage and stability information.

When available, technical literature may describe excipient performance in intended applications. Product literature should clearly identify the material as an excipient [4], be version controlled, and be periodically reviewed to ensure alignment with the intended use and regulatory requirements.

Customers requiring additional information should contact their supplier.

3.5 Post Product Launch

New excipients are often launched with only a small number of batches having been produced. As excipient manufacturers gain production experience, the ability to produce a more consistent product increases. Thus, excipient manufacturers should, throughout the product's lifecycle, periodically reevaluate process capability.

3.6 Confidential Information

Excipient users may require detailed manufacturing and quality information from excipient manufacturers for inclusion in their drug registration documentation. Excipient manufacturers may consider some information confidential. Excipient manufacturers should decide how confidential information could be made available for regulatory review. Two potential options are:

- providing detailed data directly to excipient users (after both parties have signed a mutual confidential disclosure agreement, CDA) and
- where such systems exist, making an excipient regulatory submission (see 2.3.5, e.g., DMFs in the US, Japan and Canada, CEPs in Europe, and excipient dossiers in China).

It should be noted that for some countries (e.g., Canada and several European countries) having mutual recognition agreements (MRAs) with the European Union, reference to the CEP may be made in regulatory filings.

The subject of confidentiality agreements is normally addressed by the legal departments of both parties and will not be further addressed in this guide.

3.7 Additional Considerations for Custom Made Products

Most excipients are made-to-stock; however, excipient manufacturers may agree to supply excipient users with excipients that meet special requirements (e.g., specifications, packaging, shipping, labeling) that would not necessarily render the excipient as custom. In the case where an excipient is custom made, additional agreements between excipient manufacturer and excipient user may be developed to establish specific requirements.

4 EXCIPIENT SELECTION CRITERIA

Excipient users identify many criteria when evaluating and specifying excipients. These criteria include excipient specifications (quality, chemical, biological and physical), performance characteristics, and potential supply sources based on specific dosage form and route of administration. These are often decided based on risk. Tools found in ICH Q9, Quality Risk Management [42], may facilitate their evaluation.

4.1 Specifications

Specifications for compendial excipients are often sufficient; however, excipient users should determine if additional specifications or requirements (i.e. purchase specifications) are needed.

These would require communications and documented agreement between both parties. Agreements should involve technical reviews conducted by relevant functions within each organization, including quality, regulatory, manufacturing and technical services.

When compendial grade materials are not available, the excipient user prepares a documented risk assessment to justify use of the non-compendial material as an excipient or considers in-house processing (see 4.6).

4.2 Additional Compositional Considerations

Compositional information may be provided as part of an excipient information package [41]; however, this information may be considered proprietary. Confidential composition information may be available in a Drug Master File (if one exists) or provided to the user via a confidentiality agreement with the excipient manufacturer.

The degree of excipient GMP implementation needed should be defined by a risk assessment that considers the intended use [10].

4.3 Performance Characteristics

Excipient users must demonstrate that excipients are compatible with:

- the drug substance [43],
- other excipients in the formulation, and
- packaging materials.

Excipient users must also demonstrate that excipients provide the desired functionality (see 2.2) and stability in the medicinal product at the proposed concentration. Therefore, excipients should interact predictably and reproducibly during medicinal product analytical testing. Quality by Design (QbD) principles can be used for this purpose and should be applied as early as possible in the development process [39].

4.4 Supply Considerations

Beyond the considerations identified above, excipient users should:

- Evaluate the need to qualify multiple sources for each excipient used in a medicinal product formulation.
- Consult any internal list of currently approved excipients and suppliers.
- Identify original manufacturers and manufacturing sites/locations.
- Consider the supply chain complexity and security, including whether excipients are being purchased directly from original manufacturers or through distribution channels (e.g., distributor, trader, broker).
- Determine the commercial availability of the materials to ensure supply continuity, including a business continuity plan.
- Evaluate a distributor's conformance to good distribution practices [5].
- Establish quality agreements in alignment with the IPEC QA Guide [44].
- Establish supply agreements to address supply-related topics, for example:
 - special shipping requirements, including the need for pre or co-shipment samples,
 - specified manufacturing facility,
 - maximum number of batches per receipt,
 - remaining shelf life or reevaluation interval upon receipt, and
 - custom packaging.

4.5 Excipient Manufacturer Qualification

The following should be considered during excipient manufacturer qualification and, as applicable, during ongoing performance review:

- audit findings and/or audit history,
- production experience and capability for the excipient under consideration,
- reliable sourcing (e.g., performance history for quality, availability and delivery),
- verification of excipient supplier's COA (i.e., reliability of the excipient manufacturer's measurements reported on the COA) [45],
- excipient information package (EIP) [41],
- complaint history, if applicable,
- confirmation that samples received (for evaluation) are representative of commercial production by the excipient manufacturer, and
- technical competence and support available from the excipient manufacturer.

For all excipients and their distribution, excipient users should generate audit information through site visits, using either internal audit resources or qualified third-party audit providers.

Questionnaires and remote audits should not be used as a substitute for an initial onsite assessment. Questionnaires and remote audits should only be considered for a surveillance assessment under exceptional circumstances and with a documented risk assessment. Excipient users should refer to additional regional regulatory requirements that may exist. The excipient user should evaluate audit information (i.e., audit report and supplier response) to confirm suitability of the excipient supplier's quality system for the intended purpose.

4.6 In-House Processing

When available, compendial grade excipients must be used. It is not acceptable to purchase a "technical" or "industrial" or "food" grade material and simply test it using compendial monographs to confirm that it conforms to compendial specification limits. Without production in conformance to appropriate GMP requirements, the material remains unsuitable for use as an excipient [4, 5, 46].

When compendial grade excipients are not available, excipient users can purchase a non-pharmaceutical grade of material. In this scenario, an excipient user would apply appropriate GMPs to adjust the quality and improve the composition profile in order to meet the expected quality (e.g., GMPs and specifications), regulatory requirements, and user specifications for their intended use. Such activities should be justified in the regulatory submission.

In-house processing by the excipient user is also practical in circumstances where certain physical excipient properties are desired, such as finer or more uniform particle size. Further processing of an excipient produced under GMP might include modifications to chemical properties such as purification, removal of a specified impurity or concomitant component, or pH adjustment.

4.7 Regulatory Considerations

Excipient users should identify excipient regulatory requirements (e.g., US FDA SUPAC [47], EU variation regulation [48] and other regional regulatory requirements). For example:

- assessment of the excipient regulatory status in the intended market(s)
- ensure sufficient "novel excipient" information is available to support filing(s) [11, 25]
- evaluate safety aspects as part of their own regulatory assessment (refer to Section 2.4.7).

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ANNEX A - Qualification Check List

Section	Action for excipient manufacturers
2.1	Consider developing specifications for concomitant components where their control is deemed necessary
2.3.1	Identify the appropriate regulatory and GMP requirements.
2.4.1	Assess safety related issues as part of decision to market an excipient to the pharmaceutical industry.
2.41	Assess whether the excipient has a precedent of use in countries where it is intended to be marketed.
2.4.1	Assess the risks presented and classify the quality, safety and function of each excipient to classify the overall risk of the excipient in question, e.g., as low risk, medium risk or high risk.
2.4.2	For novel excipients, develop the safety information appropriate to their marketed use.
2.4.3	For non-compendial excipients determine if other regulations, compendia, or guidelines can be used to define a suitable quality
2.4.6.2	Establish specification limits, where appropriate.
2.4.6.2	Identify and list components in a composition profile.
2.4.6.3	Identify and communicate the presence and concentration of residual solvents.
2.4.7	Understand and control origin of raw materials, degradation products, elemental impurities and process related components, as additives and processing aids.
2.4.7	Understand, document, and communicate safety aspects of excipient quality.
2.4.8	Demonstrate that the material can be suitably produced for the intended marketed use.
2.4.8	Monitor and understand changes in regulatory requirements.
2.5	Conduct all operations (from the point where GMP starts) in conformance with appropriate excipient GMP or GDP requirements.
2.5	Produce excipients in a state of control using a written set of manufacturing instructions.
2.5	Conduct and document a risk assessment to determine necessary controls.
2.5	Consider packaging and labeling materials that suitably protect the excipient from degradation and potential environmental contamination, minimizing contamination from packaging components, including labels.
2.5	Supply excipients in tamper-evident packaging.
2.5	Apply container label at the manufacturing site, meeting local transportation regulations.
2.5.1	Produce excipients consistently meeting established specifications.
2.5.2	Use methods that provide a high degree of assurance that a specific process or system will consistently produce the desired results.
2.5.2	Justify methods used for verification activities.

Section	Actions for excipient manufacturers continued
2.5.3	Develop draft specifications in accordance with: <ul style="list-style-type: none"> • accepted standards, • manufacturing process, • process capability, • marketed use, • user requirements.
2.5.3	When non-standard user requirements exist, review process capabilities to determine the feasibility of meeting these requirements.
2.5.3 2.5.6	Exercise caution when agreeing to batch selection in order meet an excipient user's purchase specification.
2.5.4	Generate data demonstrating stability in the commercial packaging at defined storage conditions.
3.1	Control each step of the excipient manufacturing process to ensure that the excipient consistently meets required specifications.
3.1	Develop a plan for process control based on operating parameters.
3.1	Perform in-process inspection and testing.
3.1	Establish composition profiles, identifying components and normal concentration ranges.
3.1	Establish specifications for excipient components.
3.1	Establish limits based on toxicological data, manufacturing processes and reaction chemistries.
3.1	Establish and document process parameters.
3.2	Establish performance indicators for the intended target use.
3.2	Ensure collaboration between the excipient manufacturer and the excipient user to minimize potential impact to the patient.
3.3	Develop separate internal and external specifications.
3.4	Make excipient labeling information available to the excipient user.
3.4	Clearly identify the material as an excipient in product literature.
3.4	Version control and periodically review product literature.
3.4	Describe routine sampling practices and make available to the excipient user.
3.5	Periodically reevaluate process capability.
3.6	Decide how confidential information will be made available for regulatory review.

Section	Actions for excipient users
4.1	Determine if additional specifications or requirements are needed.
4.1	Secure agreement regarding technical reviews.
4.2	Obtain excipient composition profile.
4.2	Define level of excipient GMP required based on risk assessment.
4.3	Ensure excipient interacts predictably and reproducibly during analytical testing.
4.3	Use QbD principles as early as possible in the development process.
4.4	Consider supply chain variables.
4.5	Consider the following during excipient supplier qualification: <ul style="list-style-type: none"> • audit findings and/or audit history, • production experience and capability for the excipient under consideration, • reliable sourcing (e.g., performance history for quality, availability and delivery), • verification of excipient supplier's COA (i.e., reliability of the excipient manufacturer's measurements reported on the COA) [45], • Excipient Information Package (EIP) [41], • complaint history, if applicable, • confirmation that samples received (for evaluation) are representative of commercial production by the excipient manufacturer, and • technical competence and support available from the excipient manufacturer.
4.5	Generate and evaluate audit information as part of the on-going excipient supplier performance review.
4.6	Document justification for use of a non-pharmaceutical grade material.
4.7	Identify regulatory requirements.
4.7	Evaluate safety aspects as part of regulatory assessment.