The IPEC Excipient Composition Guide

2009

IPEC COMPOSITION GUIDE

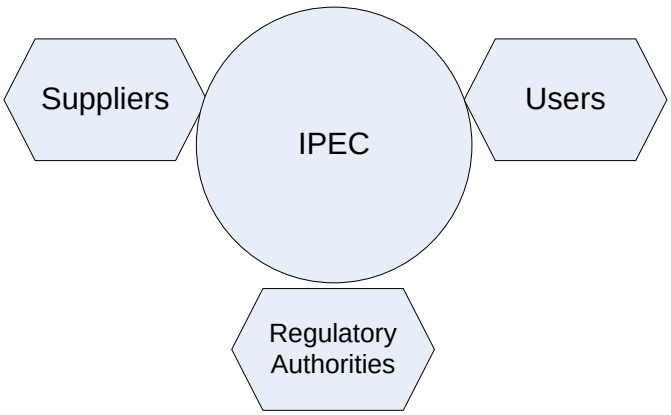
This document represents voluntary guidance for the pharmaceutical excipient industry and the contents should not be interpreted as regulatory requirements. Alternative approaches to those described in this guide may be implemented.

FOREWORD

The IPEC Federation is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association currently comprising four regional and country pharmaceutical excipient industry associations covering the United States, Europe, Japan and China (which are known respectively as IPEC-Americas, IPEC Europe, Japan PEC and IPEC China). The IPEC Federation's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of best practice and guidance concerning excipients.

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, who are considered suppliers in this document,
2. Pharmaceutical manufacturers, who are called users, and
3. Regulatory authorities who regulate medicines.



This document offers best practice and guidance in the consideration of an excipient composition profile. The excipient supplier may be a manufacturer or a distributor (or both). The Guide highlights the factors to consider when assessing an excipient composition profile, particularly in the context of Design Space and Quality by Design.

IPEC COMPOSITION GUIDE

ACKNOWLEDGEMENTS

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

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Some information discussed in this Guide may be considered proprietary or trade secret by the owner. Such information may not be available to the other party, even under Confidential Disclosure Agreement.

1 Introduction

1.1 Purpose

This guide provides an approach for an excipient manufacturer to establish a composition profile for a pharmaceutical excipient. A composition profile may be used for regulatory purposes, quality consistency, manufacturing process monitoring and change control, product specification setting or for safety evaluation by the excipient supplier and/or user.

1.2 Scope

This Guideline is intended to cover all excipients, including both existing and new chemical entities. The guide is intended to provide excipient manufacturers with strategies for assessment of the overall composition of their excipients, and how this information may be disclosed to users and regulators. It may also provide excipient users with a means of understanding what affects the composition of an excipient and how this could impact their medicinal products. However the guide does not consider functionality or route of administration of excipients which must be evaluated on a case-by-case basis for each application. In addition this guide only applies to substances used as excipients, even if they can also function as **active pharmaceutical ingredients** (APIs) (see Section 2.1).

When implementing this guide, each manufacturer must consider how it may apply to his specific products and processes. Furthermore, it is recognized that the development of a composition profile may not be technically feasible for certain excipients. The terminology “should” and “it is recommended” does not mean “must” and common sense must be used in the application of this guide.

It is not the intention of this guide to make public excipient manufacturers’ proprietary information. For recommendations on how to supply relevant information to excipient users, see Sections 7 and 8.The confidentiality of some excipient composition information must be recognized by users and handled appropriately under confidentiality agreements, etc. to meet regulatory needs and to protect the manufacturer’s intellectual property. This may result in some excipient composition information being supplied directly to regulators by the excipient manufacturer through mechanisms such as **drug master files**, etc.

1.3 Principles Adopted

This guide should be of international application, bearing in mind that excipients often have uses other than pharmaceutical applications. In addition, a pharmaceutical excipient is often used with a broad range of APIs and in a diverse range of finished **dosage forms**. As an international guidance, this document does not specify legal requirements nor cover particular characteristics of every excipient. Current guidelines like ICH[1] Q3A (R2)[2] *Impurities for New*

[1] ICH: *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*: http://www.ich.org

[2] ICH Q3A (R2): *Impurities in New Drug Substances*, Step 4, 25 October 2006, http://www.ich.org/LOB/media/MEDIA422.pdf

Drug Substances do not apply to either existing or new excipients which are by nature and definition inactive ingredients and should not be subjected to those standards.

1.4 Layout

This guide is divided into several sections. Firstly the General Guidance section provides background discussion necessary for considering the nature and origin of components found in pharmaceutical excipients. The subsequent sections contain guidance on the type and source of components, establishing a composition profile and communication of such information to excipient users and/or regulators. The final part contains definitions and references to other documents and websites useful in developing a composition profile.

2 General Guidance

2.1 Differentiation of Excipients and APIs

In the context of API and medicinal products, impurities have been defined as follows:

- *Impurity*: Any component of the new drug substance that is not the chemical entity defined as the new drug substance (ICH Q3A (R2))

- *Impurity*: Any component of the new drug product that is not the drug substance or an excipient in the drug product (ICH Q3B[3])

- *Impurity*: Any component of the intermediate or API that is not the desired entity (ICH Q7[4])

For excipients the situation is more complex as they are frequently multicomponent, and may be less well defined. Their functionality may be dependent on the presence of components other than the labeled entity. The definition of the term 'impurity' as used above is thus misleading when applied to excipients. In order to distinguish these components from true impurities the appropriate term when discussing excipients is 'minor component' or 'concomitant component', e.g. the water of crystallization in magnesium stearate required for optimum lubricant efficacy.

Some excipients can also be used as APIs. However, the approach adopted in this guide is specific for excipients, and may not satisfy the requirements if used as an API.

2.2 Definition of Excipients

Pharmaceutical excipients are substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can:

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

[3] ICH Q3B (R2): *Impurities in New Drug Products*, Step 4, 2 June 2006, http://www.ich.org/LOB/media/MEDIA421.pdf

[4] ICH Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, Step 4, 10 November, 2000, http://www.ich.org/LOB/media/MEDIA433.pdf

Due to the diversity of pharmaceutical excipients, including highly complex mixtures from animal, botanical, mineral and/or synthetic sources, differing approaches to characterizing their properties may be required. More complex excipients including excipients produced by biotechnological methods will require extensive physico-chemical characterization to fully understand their composition.

2.3 Intended Uses of Excipients

As described above, pharmaceutical excipients are a diverse group of materials which are used for the vast range of available drug products. Excipients intended for use by different routes of administration may require different understanding of the composition profile. The manufacturer of an excipient should seek to establish how it will be used. However, in commerce, this information is not always available from the user.

3 Types of Excipients

3.1 Standard Excipients

Standard excipients are defined as compendial or non-compendial substances that are neither mixed excipients (see 3.2) nor co-processed excipients (see 3.3). They may contain other components including concomitant components, residual processing aids and/or additives (see Appendix 1).

3.2 Mixed Excipients

A mixed excipient is defined as a **simple physical mixture** of two or more compendial or non-compendial excipients produced by means of a **low- to medium-shear process** where the individual components are mixed but remain as discrete chemical entities, i.e. the nature of the components is not chemically changed,. Mixed excipients may be either solid or liquid. Simple physical mixing is typically of **short duration**. It will be appreciated that for extended duration of mixing, or high energy inputs, this type of combination may have to be regarded as co-processing.

3.3 Co-processed Excipients

A co-processed excipient is a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing**,** and without significant chemical change.[5,6] However in some instances, formation of necessary components may occur, such as *in-situ* salt formation. Many different co-processing methods may be used, including standard unit operations such as granulation, spray drying, melt extrusion, milling etc. The choice for a specific application will depend on the materials used, their form (e.g. whether dry powders or liquid) and the specific physical properties desired. Likewise the ratios of the components may vary depending on the desired performance.

4 Assessment of Composition Profile

Some information discussed in this section of the Guide may be considered proprietary or trade secret by the owner. Such proprietary information may be made available to the user under a Confidential Disclosure Agreement (see section 8), or provided directly to the

[5] It is the responsibility of the excipient developer/manufacturer to justify their definition of significant chemical change according to the principles of good science.

[6] Further guidance on how to handle significant change is under development and will be included in a later version of this guideline.

regulatory authorities via inclusion in an excipient drug master file (DMF) in countries such as the US and Japan. No comparable excipient DMF system is available in Europe, but the voluntary Certificate of Suitability scheme may cover some of the confidentiality issues for those excipients having a Ph.Eur. monograph.

4.1 Types of Components and Physico-Chemical Characterization of Excipients

The composition profile of a pharmaceutical excipient may be defined as a description of the components present in a typical lot of excipient produced by a given manufacturing process. The main components of an excipient are those which in most cases contribute to the excipient being able to perform its function in the drug product(s) in which it is used (also known as '**nomina**l' components; see Appendix 1). Other necessary components may also be present, i.e. concomitant components, additives, and processing aids. Unreacted starting materials, by-products, degradants and residual solvents may also be present as a direct result of the excipient's manufacturing process. These components may arise at different stages in the excipient processing (see Appendix 1), and are considered part of the excipient composition profile, and discussed in more detail in the rest of Section 4.3 below.

Finally contaminants may be present, i.e. substances resulting not directly from the excipient's manufacturing process (synthesis and/or purification), but as a consequence of extraneous factors such as the environment (e.g. personnel, equipment, packaging, other products). Contaminants would not be regarded as part of the composition profile; however, they should be controlled through **Good Manufacturing Practices**[7] (GMP).

As excipients are typically used without further purification excipient manufacturers should identify and set appropriate limits for components as necessary. These limits should be based on appropriate safety data, limits described in official compendia or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled so that any undesirable components do not exceed such established limits.

For many excipients it may not be possible to classify and quantify all components. The composition related methods and specifications should be justified. There are many traditional, 'qualified by use', well-established excipients for which it is neither feasible, nor necessary for safety purposes to identify all components and to (re-)evaluate their safety, unless scientific evidence becomes available that suggests otherwise. Where feasible the generation of a composition profile should involve the identification, classification and quantification (expressed as a range) of each component or, if unidentified, an appropriate qualitative description such as peak retention time. A reasonable reporting threshold is available from the ICH Q3A (R2) guideline.

4.2 Concomitant Components

There is often a balance between excipient composition and functionality. Excipients frequently function because they contain concomitant components (substances in addition to the main components). These components should be considered as part of the composition profile, and thus not be construed as being undesirable, nor confused with the presence of added substances (additives, processing aids or other components). Note: Water can be classified as either a concomitant component or an undesirable inorganic component depending on its role in the pharmaceutical excipient.

[7] The Joint IPEC – PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006.*

4.3 Additives

Additives are chemical substances which are intentionally added to excipients to improve their physico-chemical properties, e.g. antioxidants, stabilizers, pH modifiers or flow aids. Typically additives are incorporated by simple mixing procedures during manufacture of the excipient and are present only in the amounts required to provide their intended effect. While an additive need not be of compendial grade, it should be of an appropriate quality for the intended application and its safety must have been evaluated as suitable for its proposed use. Therefore, the additive must have no detrimental impact on either the excipient function or the final drug product efficacy/safety.

4.4 Processing Aids

Processing aids are chemical substances which are used for a specific processing need or benefit in an excipient's manufacturing process, e.g. to provide stabilization during the manufacturing process, to enhance a chemical synthesis reaction, to improve chemical or physical processability (e.g. filter aids) or to increase excipient yield. As for additives, the safety of processing aids must have been evaluated and shown to be suitable for the intended application. Processing aids may be removed during the excipient manufacturing process or, depending on the process clearance capability, may remain as low level residuals in the final excipient, in which case they should not impair the safety or efficacy of the finished drug products in which the excipient is used.

4.5 Degradants

Some excipients may degrade with time due to a variety of factors, e.g. thermal instability, absorption and reaction with airborne moisture in humid environments and reaction with oxygen, residual catalysts, raw/packaging materials or additives and APIs or other excipients in the formulation. The products of such reactions are collectively known as degradants. For new chemical excipients, where practicable, degradants should be identified using for example **forced degradation**/**stress testing** studies. If the degradants have any toxic potential, they should also be quantified.

4.6 Residual Solvents

Residual solvents are either organic or inorganic liquids (regardless of the source) that remain in the excipient due to incomplete removal via the manufacturing process. Note: a residual solvent can also be classified as a concomitant component. No specific guideline exists for directly addressing residual solvents in excipients. Residual solvents in medicinal products are described in ICH Q3C (R3)**.**[8] Since excipients are part of the medicinal product, their contribution to the overall content of residual solvents in the medicinal product must be assessed. Some excipients will have residual solvent levels that exceed the limits given in ICH Q3C (R3). This is acceptable; however, ICH Q3C (R3) Option 2 must be used in such cases. It is important that excipient manufacturers and users communicate clearly on this issue.

4.7 Other Components

In addition to the components listed above, other components that may be present are either organic or inorganic substances that are not the defined entity (main/concomitant components) of the excipient, but are present as a direct result of variables in the excipient's manufacturing process, e.g.:

[8] ICH Q3C (R3): *Impurities, Guideline for Residual Solvents*, Step 4, 17 July 1887 plus revisions incorporated November 2005, http://www.ich.org/LOB/media/MEDIA423.pdf

- unreacted starting materials such as monomers used in a polymerization;
- residual catalysts or metal reagents;
- reaction by-products (e.g. isomers & side reactions);
- **raw material** components (especially for naturally sourced materials).

4.7.1 Unreacted Starting Materials

Unreacted starting materials may be present in the final product if there is excess of one reactant over the stoichiometry required for the production of the product, and the reactant is not removed fully by subsequent processing steps. They can also result from a reaction that has not progressed to completion in which case all starting materials may be present at some level. For example, in many synthetic polymers unreacted monomers are common and therefore should be adequately controlled within acceptable limits.

4.7.2 Residual catalysts or metal reagents

A catalyst may be used in the production processes of both excipients leading to the possibility of some residual catalyst being present in the final excipient which may need to be quantified. Recently, the EMEA has published a guideline for residual metal catalysts and metal reagents in drug products.[9] If any of these materials are present in the excipient they should be controlled in a suitable manner (e.g. through supplier qualification and/or appropriate controls), and included in the excipient specification.

4.7.3 Reaction By-products

A component may originate from a side reaction of the process chemistry. Indeed, many reactions may have several side reactions. These side reactions may include the formation of isomers of the desired product. If there is any potential for toxicity of the by-product, the by-products should be identified, quantified and a limit set.

4.7.4 Raw Material Components

Many raw materials used in the manufacture of excipients, especially those of natural origin, will exhibit variable composition. This is inherent in the origin of these materials as a result of geographical, seasonal and/or species variations. In addition, raw material impurities may be carried through the process and may be present in the final excipient. It is important to identify, quantify and control these impurities if there is any potential for toxicity.

4.8 Components having Exposure Concerns

Where possible, excipient manufacturers should identify and set appropriate limits for any components having exposure concerns, e.g. endocrine disrupters, allergens, genotoxins, endotoxins in excipients for parenteral use, etc.

For example, components with a genotoxic potential (**genotoxic impurities**) may be present in pharmaceutical excipients. If genotoxic impurities are detected in an excipient, their toxicological potential should be assessed and acceptable limits determined for their levels as above. While no specific guideline exists for addressing components having exposure concerns in excipients, the EMEA's genotoxic impurities guidance[10] may be of assistance in setting limits for new excipients. (For existing excipients with an established history of safe

[9] Committee for Human Medicinal Products (CHMP): CPMP/SWP/QWP/4446/2000 *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents*, 21 February, 2008

[10] Committee for Human Medicinal Products (CHMP): CPMP/SWP/5199/02 *Guideline on the Limits for Genotoxic Impurities*, 28 June, 2006

use, it is not necessary for further control beyond the accepted levels, unless new information becomes available.)

5 Establishing an Excipient Composition Profile

Where possible, the excipient manufacturer should establish a composition profile in which the main components of the excipient are identified and their normal range of concentration determined. Acceptable limits, where required, should be based on a risk assessment using sound science.

The evaluation of the excipient composition profile should be performed by the manufacturer using their knowledge and understanding of the manufacturing process and associated potential undesirable components. Excipient components (i.e. main/concomitant components, additives, processing aids and undesirable components) should be identified and quantified using suitable analytical techniques wherever possible. Appropriate analytical methods may be either compendial or suitably qualified manufacturer-specific methods. The material used for composition profile development should be representative and sampled in the same way as that used for Quality Control lot release (i.e. same sampling technique and sampling point in the manufacturing process).

For the purpose of developing a composition profile, excipients may be classified as either those for which purity can be measured directly (e.g. an excipient where its specification or monograph includes a requirement for purity), or those where purity cannot be measured directly (e.g. polymers or derivatives of natural occurring products).

For excipients for which purity can be measured directly, any undesirable organic and inorganic components present at or above 0.1% should be identified and assessed to determine the need (if any) for quantitative limits. If quantitative limits are needed, appropriate analytical techniques as outlined above should be used. If identification/quantification is not possible, a qualitative description, such as chromatographic retention time, should be assigned.

For excipients for which direct measurement of purity is not feasible, indirect techniques (such as assay minima, extractables maxima, LOD or ROI) should be used to provide an estimate of overall excipient purity. Levels of residual solvents, potentially toxic components and genotoxic components should be assessed and reported in line with the guidelines described in sections 3.6, 3.7 and 3.8 of this guide.

6 Process Change

If the excipient manufacturer decides to modify the process, they should use the IPEC Significant Change Guide to determine if the process changes will require customer notification.[11] The composition profile may not be fully disclosed to the customer. However, it will be an important consideration in evaluating the effects of a change.

7 Communication of Excipient Composition

Excipient composition information is needed by users and regulators to assess the performance and safety of excipients used in drug applications. Therefore it is necessary to

[11] See IPEC-Americas *Significant Change Guide, 2005* together with FDA comments on the USP proposed General Information Chapter <1195> (as published with the amendments in *Pharmacopeial Forum* Vol. 33(6) [Nov.–Dec. 2007]).

assess what level of excipient composition information will be required, and how it should be communicated. Appropriate measures need to be taken to protect the confidential intellectual property of the excipient manufacturer while allowing the transfer of key excipient composition information to both the excipient users for their product formulations and the regulators responsible for product registration (see section 8).

7.1 Regulatory Requirements

For excipients that have pharmacopeial monographs, requirements related to excipient composition are found in the General Notices, monographs and General Chapters of the appropriate compendium. Compliance with the monograph alone is not sufficient to claim compliance with the pharmacopeia. General Chapters that are referenced in the monograph are mandatory for that monograph.

Not all excipients are the subject of a pharmacopeial monograph. This will vary for different countries or global regions. In addition, for some materials used as pharmaceutical excipients, other legal requirements related to composition may also apply.

For all excipients the following points should be assessed:

- Pharmacopeial requirements
- Country/regional requirements
- Manufacturer requirements (grade differentiation, GMP, etc)
- User requirements (included in regulatory filings)

7.2 Information Disclosure

The IPEC Excipient Information Package[12] should contain the standard information to be disclosed to the excipient user, including non-confidential composition profile information. Additional information relating to the composition profile may be available upon request, subject to a Confidential Disclosure Agreement if necessary (see section 8).

8 Confidentiality Agreements

During discussion of excipient composition between the excipient supplier and excipient user, there will be a need to exchange information, some of which may be considered proprietary by either the supplier or the user. A confidential disclosure agreement (CDA) is a legal agreement that allows parties to exchange such information whilst emphasizing its proprietary/confidential nature. Since a CDA is a legal contract, it is recommended that the review and negotiation of terms be conducted by the Legal Representatives of the organizations.

With respect to confidential composition information, a CDA is essential if the excipient manufacturer is required to set limits for a particular user's application. However, the existence of a CDA does not ensure that all information will be supplied. There may be instances where a party considers the information too sensitive to be made available to the other party regardless of the existence of a CDA. In this case the information can be provided to regulatory authorities via a Drug Master File, Certificate of Suitability of the European Pharmacopoeia (CEP), or analogous application.

[12] IPEC *Excipient Information Package and Template User Guide*, 2009

9 Glossary

Active Pharmaceutical Ingredient (API): Any substance or mixture of substances used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure of any function of the body of humans or animals.

Dosage Form: The physical state of the drug product. This can include solid oral dosage forms such as tablets or beads, liquid forms for oral ingestion, liquid forms for parenteral injections, etc.

Drug Master File (DMF): Detailed information about the manufacture of an excipient that can be submitted to some regulatory authorities including the United States Food and Drug Administration, Health Canada and the Japanese Pharmaceutical and Medical Devices Agency.

Feedstock: is an alternative name for a raw material used in certain sectors of the chemical industry.

Forced degradation/Stress testing:[13] Forced degradation studies are used to determine the intrinsic chemical stability of the excipient by investigating and confirming chemical degradation pathways, and to confirm the stability-indicating potential of analytical procedures.

Genotoxic Impurities: Impurities present in the finished dosage form that may cause changes to the genome.

Good Manufacturing Practices: Requirements for the overall quality system under which the drug products and their ingredients are manufactured, tested, and released. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For the purposes of this guide the terms GMP and cGMP are equivalent.

Low- to medium-shear Process: in the context of mixed excipients refers to processing that does not alter the physical or chemical characteristics of the components being mixed.

Nominal Component: refers to the component by which a particular excipient is named.

Raw Material: refers to a component from which the pharmaceutical excipient is made.

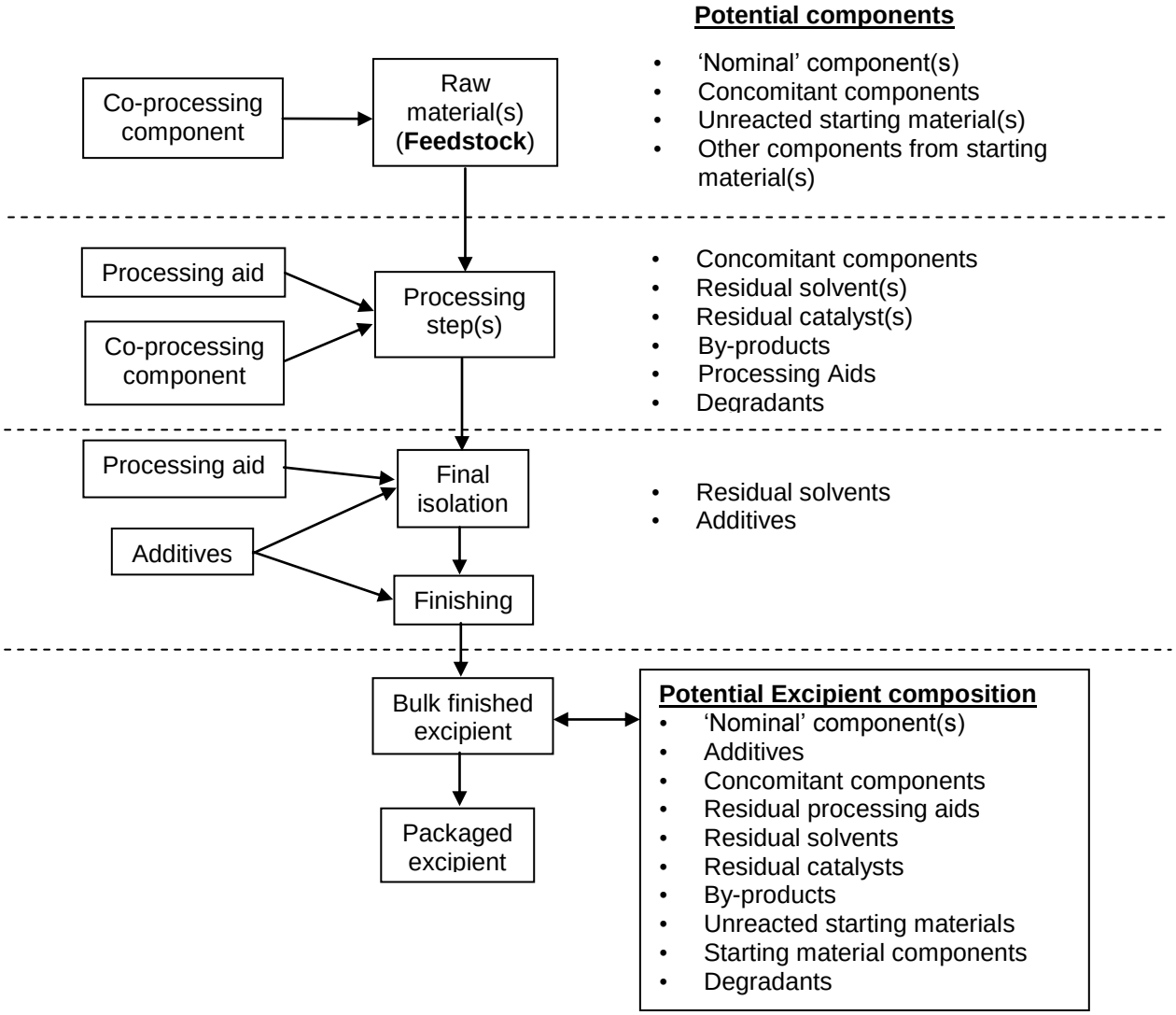
Short Duration: in the context of mixed excipients refers to a process that is typically timed in minutes and does not alter the physical or chemical characteristics of the components being processed.

[13] ICH Q1A(R2); *Stability Testing of New Drug Substances and Products* uses the term ‘stress testing’. Such studies are also known as ‘forced degradation’ studies.

Simple Physical Mixture: refers to the blending of two, or more, different materials in a way that is not intended to change the physical or chemical characteristics of the components. The blending process is generally low shear and of short duration, with limits dependent on the nature of the components being mixed. The process usually involves the use of mechanical agitation which can include paddles within a vessel, or the tumbling of the vessel that contains the different materials.

APPENDIX 1:

Potential Components of an Excipient and their Origins



[NOTE: this diagram is intended to show how excipient components might arise and is not intended to be definitive. Not every type of component will be present in all excipients.]