IPEC FEDERATION

The International Pharmaceutical Excipients Council

# Composition Guide

## For Pharmaceutical Excipients

Version 2
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 excipient quality assurance level.**

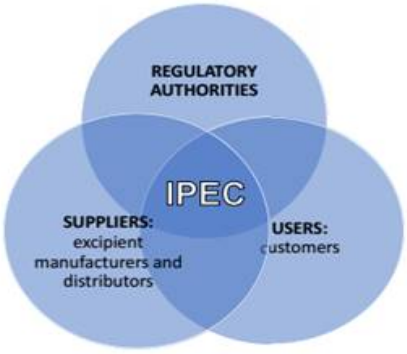
**This guide was created to help companies understand current expectation on this topic and is not intended for use by third parties to conduct audits. The content of this guide cannot be reproduced without the written authorization of the IPEC Federation Management Body.**

## FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors, and end-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, useful new excipient development and introduction, and the best practice and guidance development concerning excipients.

IPEC has three major stakeholder groups;

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




This guide offers current best practices and voluntary guidance in the consideration of excipient composition. Excipient suppliers may be manufacturers or distributors (or both). This Guide highlights factors to consider when assessing excipient composition profiles, particularly as related to **design space** and **quality by design** (QbD) [1] Reference to various ICH or other API related guidelines are for informational purposes only and are not fully applicable to excipients. **NOTE:** Refer to the "International Pharmaceutical Excipient Council General Glossary of Terms and Acronyms" for definitions [2].

The first use of a term found in the glossary will be **BOLD**.





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## ACKNOWLEDGEMENTS

This guide was developed by representatives from many International Pharmaceutical Excipients Council member companies. IPEC is an industry association whose members consist of excipient manufacturers, distributors, and 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 excipient manufacturers to establish excipient composition profiles. Composition profiles may be used for regulatory purposes, assessing quality consistency, manufacturing process monitoring and change control, establishing product specifications, or evaluating excipient safety by excipient suppliers and/or users.

## 1.2 Scope

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

When employing this guide, manufacturers must consider how the guide may apply to specific products and processes. Furthermore, it is recognized that composition profile development may not be feasible for all 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 guide’s intention to make public excipient manufacturers ‘proprietary information. For recommendations regarding how to provide relevant information to excipient users or regulators, see Sections 7 and 8. Excipient composition information confidentiality must be recognized by users and managed appropriately under Confidential Disclosure Agreements (section 8), or other suitable means, to address regulatory needs and protect manufacturers’ intellectual property. This may result in some excipient composition information being supplied directly to regulators by excipient manufacturers through mechanisms such as a **Drug Master File** (DMF), **Certificate of Suitability to the European Pharmacopeia** (CEP), etc.

## 1.3 Principles Adopted

This guide should be applied internationally, acknowledging that chemicals used as excipients in pharmaceutical drug products often have uses other than pharmaceutical ingredients. In




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addition, excipients are often used within broad and diverse finished **dosage form** ranges. As an international guide, this document does not specify legal requirements or apply to particular characteristics of all excipients. Current guidelines like International Conference on Harmonisation (ICH [3]) Q3A (R2) [4] *Impurities for New 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. First, the General Guidance section provides background necessary for considering the nature and origin of components found in excipients. The subsequent sections contain information related to excipient component types and sources, establishing composition profiles, and communicating such information to excipient users and/or regulators. The final part contains definitions and references to other documents and websites useful in developing excipient composition profiles.

## 2 GENERAL GUIDANCE

### 2.1 Differentiation of Excipients and APIs

Regarding 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) [4]).
- *Impurity*: Any component of the new drug product that is not the drug substance or an excipient in the drug product (ICH Q3B (R2) [5]).
- *Impurity*: Any component of the intermediate or API that is not the desired entity (ICH Q7 [6]).

Excipients are typically more complex since they are frequently multicomponent and may be less well-defined. Excipient functionality may be dependent on the components present other than the labeled entity. The definition “impurity” as used above is misleading due to the multicomponent nature of many excipients.

Excipients used as atypical actives are outside the scope of the guide. The approach adopted in this guide is specific for excipients and may not satisfy the requirements for excipients used as APIs.

### 2.2 Definition of Excipients

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

- aid in drug delivery system processing during manufacture,




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- protect, support, or enhance stability, bioavailability, or patient acceptability,
- assist in product identification, or
- enhance other attributes that promote overall drug safety, effectiveness, or delivery during storage or use.

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

### 2.3 Intended Uses of Excipients

As described above, excipients are a diverse group of materials used for the vast range of drug products. Excipients intended for use by different routes of administration may require different understanding of the composition profile. Excipient manufacturers should seek to establish how an excipient will be used in a drug product and for a specific route of administration. Excipient application information is not always available from users; however, users should be encouraged to share intended use to address any information gaps.

## 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). Standard excipients may contain other components including **concomitant components**, residual **processing aids**, and/or **additives** (see Annex 1).

### 3.2 Mixed Excipients

Mixed excipients are defined as *simple physical mixtures* of two or more compendial or non-compendial excipients produced by means of *low- to medium-energy processes* where individual components are mixed but remain as discrete chemical entities, i.e. components maintain individual chemical identities. Mixed excipients may be solid, liquid, or semi-solid. Simple physical mixing is typically *short duration*. For extended mixing times, or high energy processes, individually or in combination, excipients produced may have to be regarded as co-processed.

### 3.3 Co-processed Excipients

Co-processed excipients comprise two or more compendial or non-compendial excipients designed to physically modify physical and/or functional properties in a manner not achievable by




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simple physical mixing**,** and without significant chemical change [7,8].[1] 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. Specific applications will depend on ingredients used, their form (e.g. whether dry powders or liquid), and desired physical and/or functional properties. Likewise, excipient ratios may vary depending on the desired physical and/or functional characteristics.

## 4 COMPOSITION PROFILE ASSESSMENT

Some excipient composition details may be considered proprietary by the excipient owner. Such proprietary information may be made available to the user under a Confidential Disclosure Agreement (see section 8) or other suitable mechanism, or provided directly to the regulatory authorities via inclusion in an excipient DMF in countries such as the US, Canada, and Japan. Since no comparable excipient DMF system is available in Europe, the voluntary CEP scheme may provide the confidentiality needed for those excipients having a Ph. Eur. monograph.

### 4.1 Types of Components and Physico-Chemical Characterization of Excipients

An excipient composition profile may be defined as a description of the components present in typical excipient lots produced by a defined manufacturing process. The primary excipient components are those which, in most cases, contribute to excipient performance in drug products where used (also known as "**nominal**" components; see Annex 1). Other necessary components may also be present, i.e. concomitant components, additives, and processing aids, which contribute to excipient performance. Unreacted starting materials, reaction by-products, **degradants**, elemental impurities, and **residual solvents** also may be present as a result of the excipient manufacturing process. These components may arise at different stages during excipient manufacture (see Annex 1) and are considered part of the excipient composition profile, and discussed in more detail in Section 4.3 below.

**Contaminants** may be present, i.e. unintended substances resulting from the excipient manufacturing process (synthesis and/or purification), and 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** [9] (GMPs).

As excipients are typically used without further purification, excipient manufacturers should identify and establish appropriate limits for components, as necessary and where possible. Limits should be based on appropriate safety data, limits described in official compendia, or other

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




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requirements and sound GMP considerations. Manufacturing processes should be adequately controlled so that undesirable components do not exceed established limits.

Safety of any Potential Components (Annex 1) must be evaluated with respect to the impact to overall excipient and/or the final drug product function, safety, and efficacy.

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 well-established excipients for which it is neither feasible nor necessary for safety purposes to identify all components and to (re-)evaluate safety unless scientific evidence becomes available that suggests otherwise. Where feasible, composition profile generation should involve 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 should be no more prescriptive than for APIs as found in ICH Q3A (R2) [4] guideline.

## 4.2 Concomitant Components

There is often a balance between excipient composition and functionality. Excipients frequently function because they contain concomitant components (substances present in addition to the nominal components).

Concomitant components should be considered part of the composition profile, and thus, not be regarded as 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 excipient.

## 4.3 Additives

Additives are chemical substances 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 excipient manufacture 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 appropriate quality for the intended application (i.e. suitable for use in the manufacture of pharmaceutical products).

## 4.4 Processing Aids

Processing aids are chemical substances used for specific processing needs or benefits in excipient manufacturing processes, e.g. to provide stabilization during manufacture, to enhance chemical synthesis reactions, improve chemical or physical processability (e.g. filter aids), or to increase excipient yield. Processing aids are not intended to contribute to the overall excipient function. Processing aids may be removed during the excipient manufacturing process, or,




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depending on the process clearance capability, may remain as low-level residuals in the final excipient.

## 4.5 Degradants

Some excipients may degrade with time due to various factors. Examples include, but are not limited to 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. Degradants should be identified for new chemical excipients, where practicable (e.g. **forced degradation/stress testing** studies). If degradants have any toxic potential, they should also be quantified.

## 4.6 Residual Solvents

Residual solvents are either organic or inorganic liquids (regardless of source) that remain in the excipient due to incomplete removal via manufacturing processes. Note: residual solvents can also be classified as concomitant components. No specific guideline exists for directly addressing residual solvents in excipients. Residual solvents in medicinal products are described in ICH Q3C (R6) [10]**.** 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 limits given in ICH Q3C (R6). This is acceptable; however, ICH Q3C (R6) 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 excipient manufacturing processes, e.g.:

- unreacted starting materials such as monomers used in a polymerization;
- residual elemental impurities;
- 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 excipient product if excess of one reactant over the stoichiometry required for excipient production, and the reactant is not removed fully by subsequent processing steps. Unreacted starting materials can also result from reactions that have not progressed to completion, in which case, all starting materials may be present at some




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level. For example, in many synthetic polymers unreacted monomers are common and therefore should be adequately controlled within acceptable limits.

### *4.7.2 Residual elemental impurities*

Metal catalysts, reagents, or equipment may impart elemental impurities during excipient manufacture [11]. If any of these materials are likely to be present in the excipient, they should be reasonably understood and communicated.

### *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 limits set.

### *4.7.4 Raw Material Components*

Many raw materials used in excipient manufacture, 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. Monomers used in the manufacture of synthetic polymers may contain trace amounts of substances inhibiting uncontrolled polymerization. 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 components having exposure concerns, e.g. endocrine disrupters, allergens, genotoxins, and endotoxins in excipients for parenteral use, etc. Exposure risks should be evaluated as appropriate and limits established if necessary. For example, components with genotoxic potential (**genotoxic impurities**) may be present in excipients. Refer to ICH M7 (R1) for additional information [12].

# 5 ESTABLISHING AN EXCIPIENT COMPOSITION PROFILE

Where possible, excipient manufacturers should establish composition profiles where the nominal excipient components are identified and normal concentration range determined. Acceptable limits, where required, should be based on a risk assessment using sound science.

Excipient composition profile evaluation should be performed by excipient manufacturers using manufacturing process and associated potential undesirable component knowledge and understandings. Excipient components (i.e. primary/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 materials used for composition profile development should be representative and sampled in the same way as used




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for Quality Control lot release (i.e. same sampling technique and sampling point in the manufacturing process).

For the purpose of developing composition profiles, 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 where 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 measurement, such as chromatographic retention time, should be assigned.

It is not always possible to make specific, direct assay measurements for some excipients (e.g. MCC, starch, synthetic polymers without functional groups). 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 and genotoxic components should be assessed and reported in line with the guidelines described in sections 4.6, 4.7 and 4.8 of this guide.

## 6 PROCESS CHANGE

If excipient manufacturers decide to modify processes, the IPEC Significant Change Guide should be used to determine if the process changes require customer notification [7]. Composition profiles may not be fully disclosed to the customer; however, it will be an important consideration in evaluating the effects of change.

## 7 COMMUNICATION OF EXCIPIENT COMPOSITION

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

Where a monograph exists, the excipient is expected to comply with the monograph as well as other requirements in the pharmacopeia General Notices and applicable mandatory General Chapters. In many regions, including the US, EU, UK and Japan, pharmacopeia compliance also




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includes manufacture to appropriate GMP standards, which is noted in either the General Notices or other regulations.

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

For all excipients the following points should be assessed:

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

### 7.2 Information Disclosure

The IPEC Excipient Information Package User Guide [13] contains standard information for disclosure to excipient users, including non-confidential composition profile information. Additional information relating to the composition profile may be available upon request, subject to Confidential Disclosure Agreement, if necessary (see section 8).

## 8 CONFIDENTIAL DISCLOSURE AGREEMENT (CDA)

During excipient composition discussion between excipient suppliers and users, there will be a need to exchange information, some of which, may be considered proprietary by supplier and/or user. In the case where confidential is shared, a CDA is advised. Since CDAs are legal contracts, it is recommended that review and negotiation of terms be conducted by the legal representatives of the organizations.

There may be instances where a party considers the information too sensitive to be made available to the other party regardless of CDA existence, for example, trade secrets. In this case, information can be provided directly to regulatory authorities via a DMF, CEP, or equivalent mechanism.




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## 9 REFERENCES


1. The International Pharmaceutical Excipients Council *Incorporation of Pharmaceutical Excipients into a Quality-by-Design (QbD) Development Project Guide for Pharmaceutical Excipients*, 2018 (www.ipecamericas.org).
2. The International Pharmaceutical Excipient Council: *General Glossary of Terms and Acronyms*. (ipec-federation.org)
3. ICH: *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*: http://www.ich.org.
4. ICH Q3A (R2): *Impurities in New Drug Substances*, Step 4, October 2006, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf
5. ICH Q3B (R2): *Impurities in New Drug Products*, Step 4, June 2006, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf
6. ICH Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Excipients*, Step 4 November 2004, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf
7. The IPEC *Significant Change Guide for Pharmaceutical Excipients*, 3rd Revision 2014
8. The IPEC *Co-processed Excipient Guide for Pharmaceutical Excipients*, First Version 2017.
9. The Joint IPEC – PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2017.*
10. ICH Q3C (R6): *Impurities, Guideline for Residual Solvents*, Step 4, October 2016, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C__R6__Step_4.pdf
11. ICH Q3D (R1): *Impurities, Guideline For Elemental Impurities*, Step 4, March 2019, https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf
12. ICH M7 (R1): *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_31Mar2017.pdf
13. The International Pharmaceutical Excipient Council *Excipient Information Package User Guide*, Version 4, 2020.






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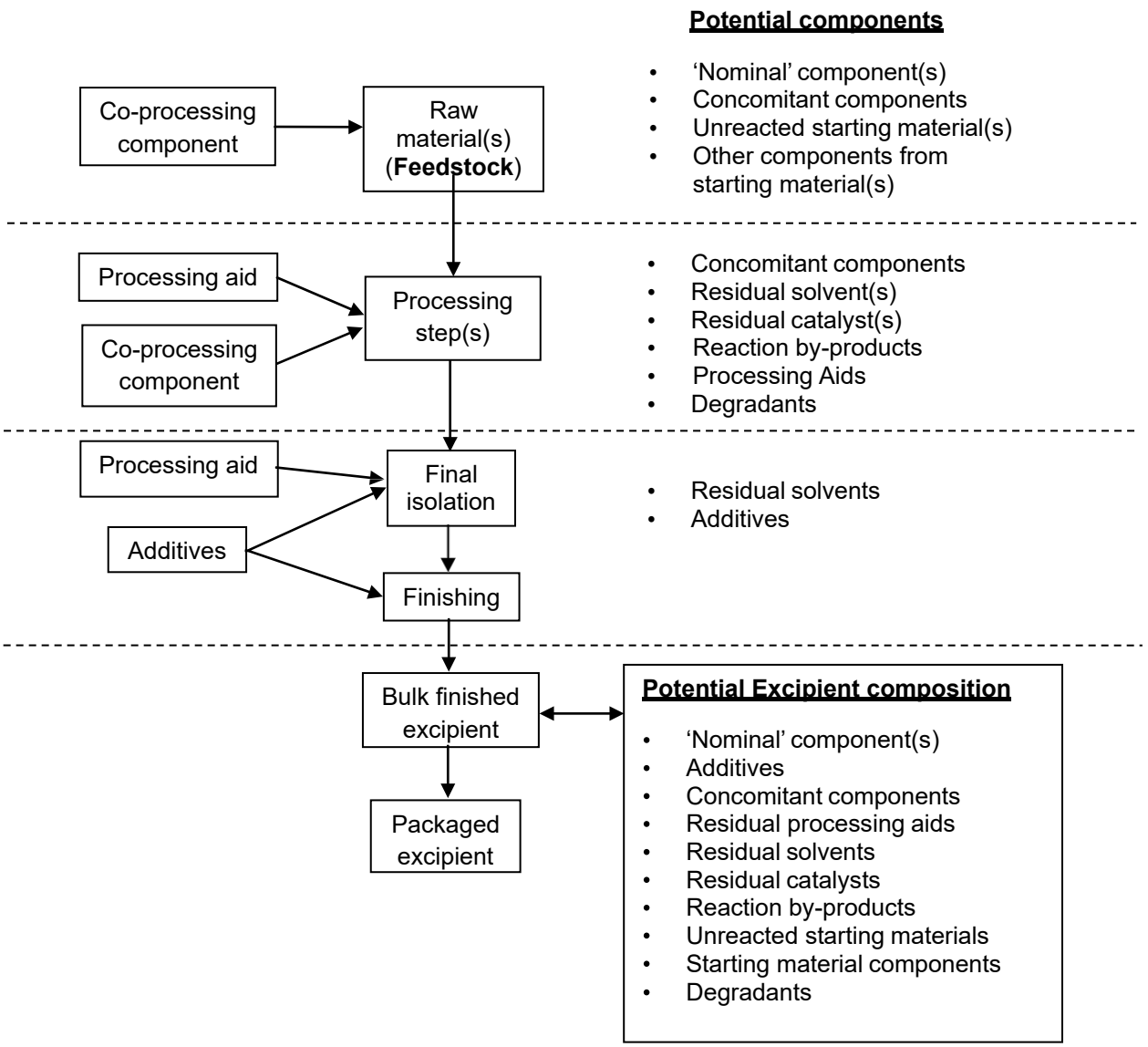
## ANNEX 1 - Potential Components of an Excipient and their Origins




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.]





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