The International Pharmaceutical Council

Co-processed Excipient Guide

For Pharmaceutical Excipients

First Version
2017

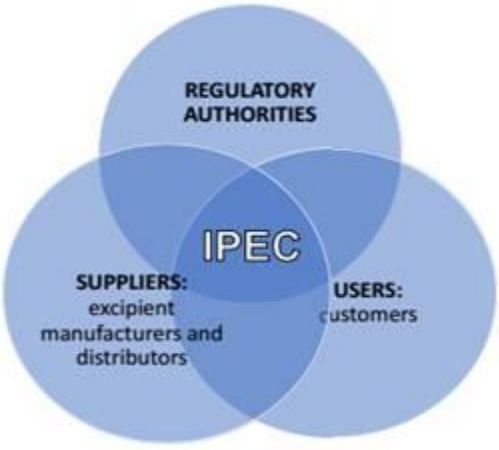
This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this Guide may be used to achieve an equivalent excipient quality assurance level.

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 document offers best practice and voluntary guidance on the development, manufacture and use of co-processed excipients. It is important that the reader confirm this is the latest version of the guide as found on (www.ipecamericas.org).

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

The ICH Common Technical Document refers to 'novel' excipients at 3.2.P.4.6. This terminology has been adopted, where appropriate, in this Guide (as opposed to the term 'new').[2]

[1] The International Pharmaceutical Excipient Council: General Glossary of Terms and Acronyms (www.ipecamericas.org)

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1); Quality Overall Summary Of Module 2 Module 3: Quality. Current *Step 4* Version Dated 12 September 2002. www.ich.org.

ACKNOWLEDGEMENTS

This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas®) and the International Pharmaceutical Excipients Council (IPEC) Europe, which are industry associations whose principal members consist of excipient manufacturers, distributors, and users. The company representatives who worked on this guide are listed below.

List of Contributors from IPEC-Americas

Professor Brian AC Carlin (Chair)
George Collins, Vanderbilt Chemicals LLC
David Klug, Sanofi US
Bretta Lichtenhan, MilliporeSigma
Brian McCarter, MilliporeSigma
Lisa Milano, Genentech
Christian Moreton, FinnBrit Consulting
Frank Murphy, ACEF Consulting
Carl Perini, Ashland, Inc
Dave Schoneker, Colorcon
Heather Sturtevant, J & J Consumer Healthcare
Katherine Ulman, KLU Consulting
Ann Van Meter, AVM Enterprises
Priscilla Zawislak, Dow Chemical Company
Joe Zeleznik, MEGGLE USA, Inc.

List of Contributors from IPEC Europe

Frank Milek, Aug. Hedinger GmbH & Co. KG
Frithof Holtz, Merck KGaA
Johanna Eisele, Evonik Nutrition & Care GmbH
Carl Mroz, Colorcon Ltd.

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1 INTRODUCTION

1.1 Purpose

This Guide is intended to provide support to both manufacturers and users of co-processed excipients. In addition, it is intended that this Guide should facilitate communication between excipient users and suppliers regarding the safety information required for regulatory filing for a product containing a novel co-processed excipient.

1.2 Scope

This Guide is applicable to co-processed excipients (not involving new covalent bonds as a result of co-processing) used in pharmaceutical formulations. However, not all options discussed in this Guide will be applicable to all co-processed excipients, and persons using this Guide should apply risk assessment and common sense to ascertain what options will apply in their particular circumstances.

1.3 Principles Adopted

This guide should have international application, bearing in mind that pharmaceutical excipients are diverse and often have uses other than pharmaceutical applications. As an international guidance document, it cannot specify all national legal requirements or cover in detail the particular characteristics of every co-processed excipient.

When considering how to use this guide, each excipient manufacturer should consider how it may apply to their product(s) and process(es). Each excipient user should consider how it might apply to their particular application(s) (formulation design and development project(s)).

The diversity of excipients means that some principles of the guide may not be applicable to certain co-processed excipients and applications. The terminology “should” and “it is recommended” does not mean “must” and common sense should be used in the application of this guide.

1.4 Layout

The advice given in this Guide is presented separately for excipient users and excipient manufacturers. This separation is to make it easier for both excipient users and manufacturers to obtain the requisite information.

1.5 General Considerations

Excipients are a chemically diverse group of materials, and including all states of matter (solid, liquid, gas and semi-solid). Some may be manufactured using **batch processing**, but many are manufactured using **continuous processing**. The scale of excipient manufacture is often much larger than for an API or finished product. In addition, very few excipients are manufactured exclusively for pharmaceutical use. Very often, the pharmaceutical usage of an excipient may represent a minor fraction of the other industrial uses.

Excipients are included in pharmaceutical finished products to overcome some of the limitations of the **active pharmaceutical ingredient**(s) (APIs) concerning the manufacture and stability of those products, and to facilitate their use and release and/or delivery of the drug after administration to the patient.

The number of nominally single ingredient pharmaceutical excipients is limited. There are gaps in the range of performance attributes (functionality) available from single ingredient excipients. The introduction of novel chemical excipients is both lengthy and economically risky.[3,4,5] Co-processed excipients provide a means whereby new excipient functionality can be introduced without the time and economic constraints relating to the introduction of novel chemical excipients.

As with other excipients, co-processed excipients may be manufactured using either batch or continuous processing. The requirements for safety and consistency of performance (variability) are the same for either type of processing.

2 CO-PROCESSED EXCIPIENTS

A co-processed excipient is not a simple blend. Co-processed excipients are defined as follows[1]:

> 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. However, in some instances, formation of necessary components may occur, such as *in-situ* salt formation.

From this definition, it can be seen that the key elements to be addressed by both the manufacturer and the excipient user are the composition of the co-processed excipient, and confirmation that the processing does indeed produce only a physical interaction, such as hydrogen bonding or ionic association, rather than a covalent chemical combination. In addition, as with any 'new' material there will need to be an assessment of the risk to patient safety when the excipient is intended for use in pharmaceutical products for human or veterinary use. Investigations to justify the ratio of ingredients, the necessary processing, and safety of the co-processed excipient, will need to be undertaken before the novel co-processed excipient is launched for commercial sale. The user of any co-processed excipient is responsible for assuring its fitness for purpose, and that the co-processed excipient and its components are manufactured to acceptable standards of **good manufacturing practice** (GMP). These elements will be discussed in more detail below.

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[3] Steinberg, M.; Borzelleca, J. F.; Enters, E. K.; Kinoshita, F. K.; Loper, A.; Mitchell, D. B.; Tamulinas, C. B.; Weiner, M. L., A new approach to the safety assessment of pharmaceutical excipients, Reg. Toxicol. Pharmacol (1996), 24(2, Pt. 1), 149-154.

[4] Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2005.

[5] Moreton, R.C., Tablet excipients to the year 2001: A look into the crystal ball, Drug Dev. Ind. Pharm., (1996), 22, (1), 11 - 23.

Communication between the co-processed excipient Manufacturer and user will be important for the success of any formulation project. It is strongly recommended that a confidential disclosure agreement (CDA) be implemented to allow for a more useful discussion.

3 CO-PROCESSED EXCIPIENT MANUFACTURERS

A manufacturer's co-processed excipient development program should anticipate likely questions from users, and provide the necessary information to show that the co-processed excipient is manufactured to a consistent specification.

3.1 Co-processed excipient development

A co-processed excipient usually offers a benefit beyond the simple mixture of the excipients. This benefit is likely to be in either manufacturing and/or drug delivery. The development program should be designed and executed to confirm the benefits and limits for acceptable performance (composition and processing).

3.2 Co-processed excipient composition and specification

A novel co-processed excipient will be launched for commercial sale with composition(s) that will provide the intended performance of the excipient. Limits for the composition may have been established based on achievement of the desired performance using model formulations.

The definition limits and other relevant tests should be incorporated into a general sales specification,[6] and eventually a compendial specification.

The format of the specification should include the tests that are likely to be included in an eventual compendial specification (see Section 3.11).

The precision of the ratio of the excipients being co-processed will be set by the capability of the process. If only the components are listed in the formula (instead of the co-processed entity) it may not be possible to declare compliance with the European GMP requirement for ±10% for the permitted variation in the content of each excipient, even if the co-processed excipient itself was added with a precision of ±10%.[7]

3.3 Analytical method development

Co-processed excipients are by definition more than simple mixtures of two or more components. It will be necessary to develop test methods that will allow the composition of the

[6] **Note:** there may also be other specifications such as the manufacturing specification and in-process specifications. It is common for the manufacturing and in-process specifications to be tighter than the general sales specification.

[7] In CPMP/QWP/486/95: Section 3 Manufacturing Formula it is required that excipients be 90-110% of the nominal quantity in the formulation. (As an example, the allowable ranges for each of the novel excipient's ingredients had been provided (e.g., 3.5 – 6.0% ingredient Y) in the CTD. The reviewer took these ranges and applied the limits of 90-110% to each ingredient as if each ingredient of the mixed excipient were a single excipient in the drug product formulation. In so doing, at the extremes of the ranges, the ingredients did not meet the 90-110% requirement.). See also Regulatory Rapporteur, Vol 11, No 7/8, July/August 2014, pp 14-15.

co-processed excipient to be determined on a routine basis, e.g. for quality control purposes, regardless of the control strategy used to release the excipient for sale (e.g. use of in-process test results). Where possible, quantification of the individual components used to prepare the co-processed excipient is preferred. However, this is not always possible, particularly for polymeric components. Nevertheless, quantification of sufficient components to define the composition of the co-processed excipient should be developed. In addition to the quantification of the components there are other tests which should also be considered (see also the IPEC Excipient Qualification Guide[8] and the USP Monograph Submission Guidelines for Excipients[9]). These additional tests may include, but are not limited to:

- Water content
- Residual solvents
- Elemental impurities
- Physical tests such as particle size and distribution, viscosity
- Degradation products
- Limit tests applicable to the individual excipient components

One further test that should be developed is an analytical test that can differentiate between the co-processed excipient and simple mixtures of the component excipients. Such a test will be necessary to eventually obtain a compendial monograph for the co-processed excipient (see Section 3.11 below). This test should not rely on in-use performance, but should use appropriate analytical methods that are routinely performed in an analytical laboratory.

The required packaging should also be confirmed with the appropriate storage instructions.

3.4 Co-processed excipient composition profile

The composition profile for the co-processed excipient will comprise the composition profiles for the individual component excipients, together with any other minor concomitant components.

While the full composition may not be tested on every batch, the excipient developer/manufacturer should be aware of as much of the composition profile as is possible, and what, if anything, changes with time.

The excipient manufacturer should justify the specified variance in the ratio of the individual excipients making up the co-processed excipient. The variance may depend on the process capability but should not impact the intended performance of the co-processed excipient. The user should be aware that in some cases such variance may be greater than the typical GMP precision of ±10% component addition.

[8] IPEC Qualification of Excipients for use in Pharmaceuticals 2008 - www.ipecamericas.org

[9] USP Guideline for Submitting Requests for Revision to USP–NF: Submission Guideline for Chemical Medicines (http://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/chemical_medicines_rfr_guideline_-28apr16.pdf)

3.5 Co-processed excipient stability

As with any excipient, the stability of the co-processed excipient should be established. The stability studies should address both the chemical stability and the physical stability of the co-processed excipient, including the 'stability' of the improved performance. The stability studies should be carried out under storage conditions that properly simulate the commercial packaging alternatives.[10]

3.6 Novel co-processed excipients and patient safety

Co-processing of excipients creates a novel regulatory entity but not a novel chemical entity. As with any novel excipient, there is a requirement to assess the potential risk to the patient from the novel co-processed excipient. The potential risk to the patient and safety data depends upon the type of 'newness'. For a novel co-processed excipient, the risk to the patient may still be minimal; however, this should be justified (see Figure 1 below).

Since the objective with a co-processed excipient is to avoid new covalently bonded material, it follows that it would be logical to link (bridge) the safety of the co-processed excipient to the safety of its component excipients. In order to be able to do this, it is necessary to demonstrate that such bridging is valid.

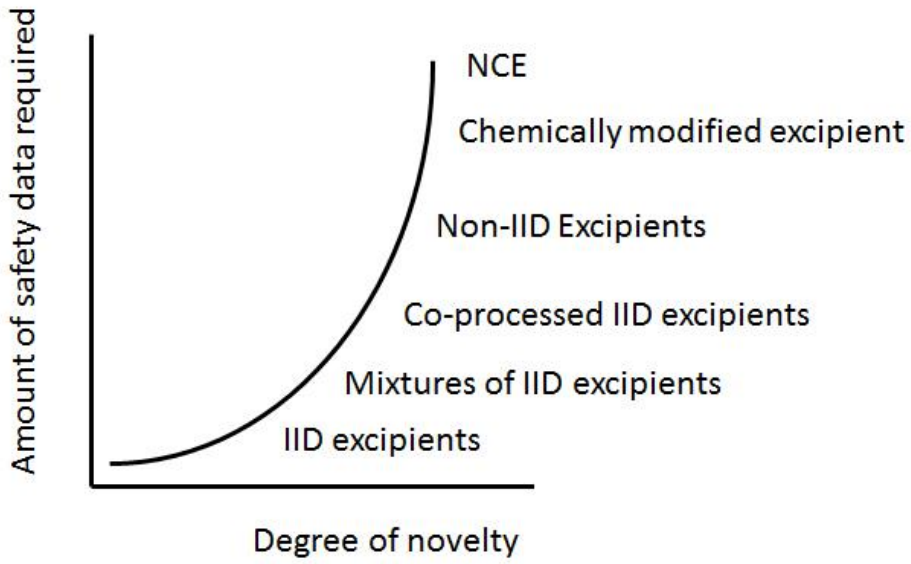

Figure 1 Safety data requirements for novel excipients (NCE=New Chemical Entity)

3.6.1 Safety Bridging

The safety of a novel co-processed excipient may be based on the safety and toxicology of the individual components. It should be demonstrated that the components have only been physically combined, and not covalently altered in comparison to the corresponding physical

[10] The IPEC Excipient Stability Program Guide, 2010 (www.ipecamericas.org)

blend. The safety of the co-processed excipient can then be bridged to the safety of the individual components, by analytical rather than toxicological means.

3.6.1.1 Co-Processed Excipient Risk Analysis

The initial evaluation of the novel co-processed excipient begins with a risk assessment of potential reactions from the co-processing of the individual components. Analytical methods should be developed to confirm the components remain chemically separate after co-processing. The exact nature of such studies will depend on the nature of the individual components, and the form of the co-processed excipient. The composition profile should be compared, qualitatively and quantitatively, with and without the co-processing. A scientific rationale should be provided to justify that the analytical techniques used are sufficient to demonstrate absence of significant chemical change.

Caution should be exercised since some techniques are capable of picking up physical interactions including changes in hydrogen bonding. Such effects should not be confused with covalent bonding. Changes in hydrogen bonding, or the detection of other physical interactions (e.g. hydrophobic interactions) should be anticipated for co-processed excipients. It is recommended that the co-processed excipient be subjected to a battery of different tests, since a single test will probably not exclude the formation of covalent bonding.

If the results of such bridging studies do not clearly exclude new chemistry, further assessment will be necessary, and an in vivo safety evaluation may be required (see below).

If no new covalent chemistry is observed during the investigations, then a scientific justification for bridging the safety assessment of the co-processed excipient to the safety of the individual components can be documented.

It is further recommended that the scientific justification, experimental methods and results be peer reviewed to provide added assurance that nothing was overlooked in the investigation, report or justification to support the safety assessment.

This review can be performed by a third party independent consultant (see section 3.6.2 below). The results could then be submitted for publication in a peer-reviewed scientific journal, or simply included in the Type IV excipient DMF and referenced in the excipient user's marketing application; **New Drug Application** (NDA) or **Abbreviated New Drug Application** (ANDA).

3.6.2 IPEC New Excipient Safety Evaluation Scheme[11]

Safety assessment can be complemented by an independent review service whereby the excipient manufacturer's proposed co-processed excipient safety and analytical data package, along with their bridging argument, can be reviewed by toxicology experts to assess the likelihood of acceptance by regulatory authorities in support of a drug filing.

[11] For further information please see the IPEC-Americas website; (www.ipecamericas.org).

3.7 Manufacture of co-processed excipients

As with any excipient, it is possible to manufacture co-processed excipients using either batch processing, continuous processing, or a hybrid of both.

Co-processed excipients (and their components) used in the manufacture of pharmaceutical products for human or veterinary use should be manufactured to an acceptable standard of GMP.[12] There are generally accepted standards that can be implemented.[13,14,15,16]

3.7.1 Co-processed excipient and process robustness

It is necessary to establish the robustness of the manufacturing process and its ability to produce a co-processed excipient that meets the requirements of both composition and performance on a routine basis.

In pharmaceutical product manufacturing, this would be referred to as validation. In the chemical industry, and particularly with continuous processing, it is more usual to consider process capability, and the use of process capability indices is common.

However, for co-processed excipients there is a further consideration; that the performance enhancement (meeting the unmet need) also be robust because the use of the co-processed excipient is predicated on the performance enhancement.

3.8 Regulatory affairs

For a novel co-processed excipient to be accepted, it must be included in approved products regulated by the national regulatory agency (national competent authority in the European Union). There are differences in how co-processed excipients are handled in the major regions (Europe, Japan and the United States).

In Europe, since there is no Excipient Master File system, the full details relating to any excipient are included in the Marketing Application. The application, either for an Investigational Medicinal Product (IMP) or Marketing Authorization should be referenced in Section 3.2.P.4 Control of Excipients in the Common Technical Document (ICH M4Q(R1)[17]), specifically

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[12] See for example, USP 37-NF32, General Notices 3.10 Applicability of Standards. Although these General Notices strictly apply to official substances, the FDA has stated that the same requirements apply to non-compendial excipients. Similar requirement are found in Europe, Japan, and other countries.

[13] The International Pharmaceutical Excipient Council & The Pharmaceutical Quality Group The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients 2017 – (www.ipecamericas.org)

[14] EXCiPACT™ Certification Standards for Pharmaceutical Excipient Suppliers, Issue 1, January 2012, EXCiPACT™, Brussels, Belgium, (www.excipact.org/).

[15] NSF/IPEC/ANSI 363-2016 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients.

[16] USP 37-NF32, General Chapter <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients, USP Convention, Inc., Rockville MD, 2014.

[17] International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1). Quality Overall

3.2.P.4.6 Novel Excipients, and the detailed information provided in Appendix 3, Novel Excipients. All the necessary information is required to be filed by the applicant.

In Japan, co-processed excipients are referred to as premixed excipients. Japan has an Excipient Master File system, and their DMF system can be used for premixed excipients.[18]

The US FDA has a well-established Drug Master File (DMF) system for excipients. The chemistry, manufacturing and controls information for excipients can be submitted as a Type IV DMF. The format for such a submission should follow the guidelines from the ICH M4Q(R1)[7] document. If safety data beyond the analytical bridging argument is required, the FDA should be consulted as to the appropriate DMF format.

[**Note:** There is no formal independent review of the data and approval of an excipient by the FDA. The FDA will accept the filing of the DMF(s); however, they will not be reviewed until they are included in a NDA or ANDA application.]

3.9 Quality-by-Design

It is likely that potential users and existing users will be undertaking formulation development projects according to the principles of Quality-by-Design (QbD). The excipient Manufacturer should thus anticipate questions relating to the performance and composition of the co-processed excipient. In order to facilitate prompt responses to such questions, it is recommended that the excipient development follow QbD principles or equivalent in developing the co-processed excipient.

[Note: It is not suggested that all such information be shared with potential customers or customers routinely. Some of this information may be regarded as proprietary, and may need to be disclosed under confidential disclosure agreement (CDA).]

3.10 Provision of samples of co-processed excipients

In order for any novel excipient, once launched, to be accepted in the market place, it will be necessary for samples to be provided to potential customers. Even after market acceptance, it will still be necessary to provide samples for potential new customers.

With the increasing adoption of QbD by the pharmaceutical industry, the provision of samples has assumed a greater importance. In the event that the co-processed excipient is selected for a particular application (formulation development project), the excipient user will likely want to obtain experimental samples that represent the limit of composition and/or acceptable performance for their use. The provision of such samples may not be straightforward. The reader is referred to the IPEC-Americas Quality by Design (QbD) Sampling Guide, 2016.[19]

Summary of Module 2. Module 3: Quality. Current Step 4 version dated 12 September 2002. (http://www.ich.org/products/ctd.html)

[18] Drug Approval and Licensing Procedures in Japan, Chapter 2: Handling of Pharmaceutical Excipients, Jiho, Inc, Tokyo, Japan, pages 463 - 468

[19] The IPEC-Americas Quality by Design (QbD) Sampling Guide, 2016- (www.ipecamericas.org)

In the event that experimental QbD samples are made available to the user, the terms under which they are supplied should be clearly defined (e.g. for non-GMP use only, not commercially available, etc.). See IPEC-Americas QbD Sampling Guide 2016.

3.11 Pharmacopeia monograph

Once the co-processed excipient is known to be included in an approved commercial pharmaceutical finished product, it becomes eligible to be considered for a monograph in the relevant pharmacopeia. Each of the three major pharmacopeias has different rules and procedures for submission of a monograph proposal, and the acceptability of monograph proposals for co-processed materials. See links below:

- European Pharmacopoeia[20]
- Japanese Pharmacopoeia and Japanese Pharmaceutical Excipients[21]
- United States Pharmacopeia – National Formulary[9]

4 CO-PROCESSED EXCIPIENT USERS

Before using the co-processed excipient, the user should undertake appropriate due diligence. The excipient manufacturer will likely provide information on the performance of the co-processed excipient during development and testing. The user should:

- Determine if the co-processed excipient meets their needs, including fitness for intended purpose
- Consider the potential regulatory (and safety) hurdles associated with the use of the co-processed excipient, if any
- Assure that the co-processed excipient and its components are manufactured to an acceptable standard of GMP
- Determine that there are no potential supply issues with the co-processed excipient

4.1 Co-processed excipient technical data package

The technical data package for the co-processed excipient may include some or all of, but is not limited to, the following:

- Description of the co-processed excipient
- Composition, including statement of no new covalent bonds
- The benefits or addressed unmet technical need(s)

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[20] EDQM Submitting drafts and requests for monograph revision: (http://www.edqm.eu/en/European-Pharmacopoeia-participate-54.html)

[21] There is no precedence to indicate that the Japanese Pharmacopoeia (JP) will accept a monograph proposal for a co-processed excipient. However, there is an alternative publication Japanese Pharmaceutical Excipients (JPE) that does accept monographs for co-processed excipients. JPE is edited by the Japanese Pharmaceutical Excipients Council (JPEC) and published by Yakuji Nippo Ltd. For further information, please contact JPEC (office@jpec.gr.jp)

- Intellectual property statement
- General manufacturing process
- Performance evaluations
- Sales specification
- Analytical methods
- Batch analytical data
- Stability data
- Handling and storage
- Other standard statements (e.g. safety, environmental, Genetically Modified Organism (GMO), residual solvent, elemental impurities, standard of GMP)

It is the user's responsibility to determine whether or not the information in the co-processed excipient technical data package meets their requirements, with respect to their technical need(s), long term project objectives, and anticipated supply requirements.

During development, the excipient manufacturer may have tested the performance of the excipient using model formulations. Again, it is the user's responsibility to evaluate the data from such examples and assess the relevance to their particular needs.

4.2 Regulatory and safety

Co-processed excipients, when they are first introduced into the market place are considered to be 'novel' excipients for regulatory purposes. As with any 'novel' excipient, it will be necessary for the users to assure themselves that the co-processed excipient is safe for its intended use in human or veterinary medicines.

Since co-processed excipients, by definition, are not intended to introduce new covalently bonded molecules, it should be possible to bridge the safety of a novel co-processed excipient to the safety of the individual components.

The excipient manufacturer should have safety data and/or a statement concerning the safety and lack of formation of new covalent bonds between the component excipients. The user has ultimate responsibility to assure that the co-processed excipient is safe for their intended application. For a co-processed excipient, the safety assessment may only involve analytical studies to demonstrate that no new covalently bonded material was formed during co-processing. The types of analytical studies that may be relevant to the co-processed excipient are listed in Section 3.3., and they will not be discussed in detail here. The user should satisfy themselves as to the tests and methods used, the organization carrying out the tests, the results obtained, and that the tests adequately demonstrate the absence of new covalent bonds between the component excipients.

The need for additional animal tests for a co-processed excipient may be based in part on the results from the analytical investigations. In addition, if a particular excipient component of the co-processed excipient exceeds the recorded use level for the particular route of administration a further safety argument may be required. In the US, the FDA's Inactive Ingredient Database

(IID) provides useful information as to the acceptable use levels of the individual component excipients.[22]

4.3 Co-processed excipient manufacture

Co-processed excipients (and their components) used in the manufacture of pharmaceutical products for human or veterinary use should be manufactured to an acceptable standard of GMP.14 The user should confirm this through on-site audit, and verify how the manufacturer has determined the appropriate standard of GMP. The user is strongly advised to exercise technical due diligence on the excipient manufacture to understand the manufacturing process and the limitations of the co-processed excipient.

4.4 Fitness for purpose

As with all excipients, it is the user's responsibility to determine that the co-processed excipient fulfills their needs for the application. A representative number of co-processed excipient batches should be assessed.

The regulatory authorities require justification of the choice of excipients, including the rationale for use of the co-processed excipient. The user should scientifically justify the selection of the excipient and assess the robustness of the finished product and manufacturing process, and establish the Control Strategy.

4.5 Supply

The user should discuss with the excipient manufacturer among other things, the quantities required, the timing of the first commercial quantities, and the projected re-supply timings and quantities. It is strongly recommended that the user enter into a supply agreement with the excipient manufacturer to ensure supply.

5 SUMMARY

Co-processed excipients, as defined in this guide, support QbD by offering novel attribute combinations without novel chemistries. By restricting the definition to physical combinations, the inherent safety of the co-processed excipient can be demonstrated by analytical bridging methods without the need for the extensive safety testing required for new chemical entities. This guide helps to clarify what is necessary to fully define co-processed excipient safety and quality, and the points in this guide should be considered during development of co-processed excipients. Better understanding of the concepts in this guide should facilitate the development and adoption of new co-processed excipients.

[22] Inactive Ingredient Database, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm)

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