



The International Pharmaceutical Excipients Council

# Significant Change Guide

For Pharmaceutical Excipients

Version 5  
2023

Copyright © 2023 The International Pharmaceutical Excipients Council

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

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

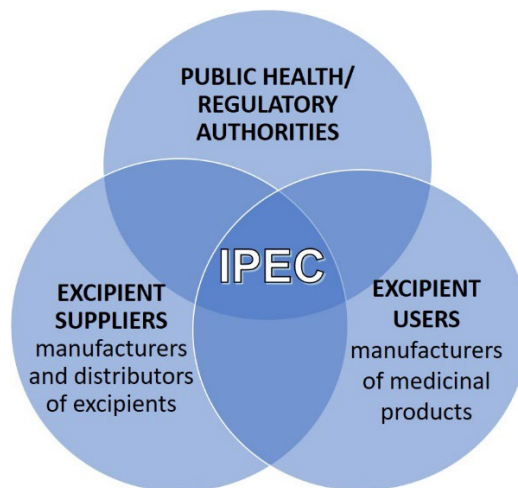
**The content of this guide cannot be reproduced without the written authorisation of the IPEC Federation Management Body.**

## 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, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient development.

IPEC has three major stakeholder groups:

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



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the laws and regulations applying to excipients will vary from region-to-region and country-to-country. In addition, rules and regulations are continually

evolving. It is the responsibility of the reader to review the most current version of any applicable regulatory requirement. Versions referenced in the guide were based on versions available at the time the guide was published.

In this guide, pharmaceutical excipient(s) will be referred as excipient(s). This guide may be applied to veterinary medicines, as appropriate and include reference to specific veterinary guidances and regulations.

Throughout the guide, “justification” means that a decision is made based on a scientific, quality and/or regulatory considerations.

This document offers best practice and guidance on the content of an excipient **Significant Change Guide**. It is important that the reader confirm this is the latest version of the guide as found at <https://ipecamericas.org/> or <https://www.ipec-europe.org/> or <https://ipec-federation.org/>

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

## ACKNOWLEDGEMENTS

This Guide was developed by representatives of the associations which constitute the IPEC Federation (IPEC). The IPEC Federation greatly appreciates the many hours devoted by the core team of individuals and other contributors listed below, to make this guide available to IPEC members and the broader excipient community. Equally, IPEC extends its thanks to the employers of those same contributors who provided the necessary time and resources, without which, this guide would not be possible.

### *List of Contributors from IPEC-Americas*

Courtney Arumugam, GADA

Ann Gulau, IFF

Jennifer Putnam, Perrigo

Katherine Ulman, KLU Consulting, LLC

Priscilla Zawislak, IFF

### *List of Contributors from IPEC Europe*

Jeffrey Brambora, BlackTower Quality Group

Anne Reiff, Hedinger

Rebecca Teversham, Colorcon

## Table of Contents

<b>ACKNOWLEDGEMENTS</b> .....	<b>4</b>
<b>1 INTRODUCTION</b> .....	<b>7</b>
1.1 Purpose.....	7
1.2 Scope .....	7
1.3 Principles Adopted.....	7
<b>2 GENERAL CONSIDERATIONS</b> .....	<b>8</b>
2.1 Excipient Composition.....	8
2.2 Differentiation of Excipient Manufacture .....	8
2.3 Excipient GMP .....	8
<b>3 SIGNIFICANT CHANGE</b> .....	<b>9</b>
3.1 Definition of Significant Change .....	9
3.2 Change Risk Levels.....	9
<b>4 DETERMINATION OF SIGNIFICANCE / RISK ASSESSMENT</b> .....	<b>10</b>
4.1 General.....	10
4.2 Guiding Principles.....	10
4.3 Change Management Documentation.....	11
4.4 Justification for Level 1 Change.....	11
4.5 Data Analysis.....	11
<b>5 NOTIFICATION REQUIREMENTS</b> .....	<b>12</b>
<b>6 POST IMPLEMENTATION</b> .....	<b>12</b>
<b>7 SPECIFIC CHANGES</b> .....	<b>13</b>
7.1 Types of Changes.....	13
7.1.1 <i>Manufacturing Site</i> .....	13
7.1.2 <i>Scale</i> .....	13
7.1.3 <i>Production and Packaging Equipment</i> .....	14
7.1.4 <i>Raw Materials</i> .....	14
7.1.5 <i>Manufacturing Process</i> .....	17
7.1.6 <i>Packaging</i> .....	18
7.1.7 <i>Labeling</i> .....	19

<b>7.1.8</b>	<b><i>Excipient Specifications and Test Methods</i></b> .....	<b>19</b>
<b>7.1.9</b>	<b><i>Supply Chain</i></b> .....	<b>20</b>
<b>7.1.10</b>	<b><i>Discontinuation of an Excipient</i></b> .....	<b>20</b>
<b>7.2</b>	<b>Criteria used to Evaluate the Impact of Changes on Excipient</b> .....	<b>20</b>
<b>7.2.1</b>	<b><i>Introduction</i></b> .....	<b>20</b>
<b>7.2.2</b>	<b><i>Physical Properties</i></b> .....	<b>21</b>
<b>7.2.3</b>	<b><i>Chemical Properties</i></b> .....	<b>21</b>
<b>7.2.4</b>	<b><i>Microbiological Properties</i></b> .....	<b>22</b>
<b>7.2.5</b>	<b><i>Composition Profile</i></b> .....	<b>22</b>
<b>7.2.6</b>	<b><i>Stability</i></b> .....	<b>22</b>
<b>7.2.7</b>	<b><i>Intended Performance based on the Manufacturer 's Marketed Use</i></b> .....	<b>23</b>
<b>7.2.8</b>	<b><i>Regulatory Status</i></b> .....	<b>23</b>
<b>7.3</b>	<b>Multiple Changes</b> .....	<b>23</b>
<b>8</b>	<b>REFERENCES</b> .....	<b>24</b>
	<b>ANNEX 1: CASE STUDIES</b> .....	<b>26</b>
	<b>ANNEX 2: DECISION TREES</b> .....	<b>28</b>