IPEC FEDERATION

The International Pharmaceutical Excipients Council

Technically Unavoidable Particle Profile (TUPP) Guide

For Pharmaceutical Excipients

Version 2
2024

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.

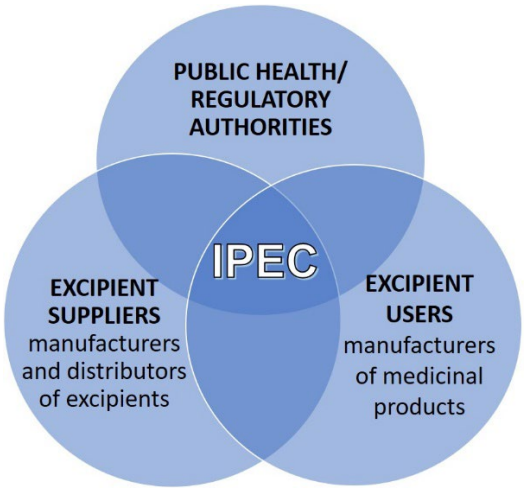
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and end-users. At the current time of 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

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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 to 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 scientific, quality and/or regulatory considerations.

This document offers best practice and guidance on the subject of technically unavoidable particles that may be present in excipients. 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**.*

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ACKNOWLEDGEMENTS

This Guide was reviewed and updated by representatives of the associations which constitute the IPEC Federation (IPEC). The IPEC Federation greatly appreciates the time devoted by the core team of individuals 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.

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1 INTRODUCTION

1.1 Background and Purpose

The subject of visibly different particles in **excipient**s has been and continues to be a topic of great interest and importance to the pharmaceutical industry.

These types of particles have always been present in excipients, but the interest and concern over their presence has escalated. A central cause of the increased concern is the issuance of several US FDA Form 483s (adverse findings from an FDA inspection) to pharmaceutical companies by FDA investigators for insufficient or incomplete investigations of unusual, visible particles. These 483s did not prohibit these technically unavoidable particles but addressed the insufficiency of the investigation process.

IPEC, USP and regulatory authorities have not dealt with this issue and as a result, **material**s are rejected unnecessarily. The consequence is that both excipient users and makers spend valuable resources investigating particles that are technically unavoidable and do not pose a risk to patient safety. In many instances, the identity and origin of these particles are already known and have been investigated extensively by the excipient manufacturer to show they present no risk to the end user. These types of particles are inherent to the product. This **guide** provides a pathway to provide data on the identity and origin of these particles in excipients as a way of fulfilling the investigational component for the identification of unusual visible particles in excipients.

The purpose of this guide is to provide understanding between manufacturers and excipient users on the types of normal, inherent, visibly different and **technically unavoidable particles**. This guide describes the expectations regarding the exchange of information comprising an investigation and leading to the proper disposition of affected excipient.

The concepts presented in this guide should be considered as part of a risk evaluation for use of excipients in drug products. This guide is not meant to deal with foreign **contamination** or adulteration.

1.2 Scope

This guide is applicable to all excipients used in the **manufacture** of **medicinal products**. Information in the guide may also apply to excipients used in veterinary medicines. Not all options discussed in this Guide will be applicable to every excipient, and persons using this Guide should apply the principles of **risk assessment**, and common sense to ascertain what options will apply in their particular circumstances.

This guide is focused on visible particles, not microscopic (sub-visible) particles. Observation of visible particles triggers an investigation requiring extensive resources to be expended in identifying the source of the particles. Technically unavoidable, visibly different particles are

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particles inherent to the excipient and its production, which are of no significant safety risk, which are well characterized / known to the manufacturer and have already gone through prior risk assessment which may include investigation / profiling / evaluation. With current technologies, these particles are technically unavoidable and cannot be eliminated in the finished excipient. This guide encourages communication between excipient makers and users to reduce time, money and resources expended and to ensure adequate investigation.

Excipients used in solid oral dosage forms are the primary focus of this guide. The concepts presented may be applicable to other dosage forms after an appropriate risk evaluation is performed. The use of excipients in parenteral formulations requires additional consideration beyond the scope of this guide [4].

This guide applies to excipients manufactured by either **batch** processing or **continuous** processing, and the use of the term "**batch**" or "**lot**" may refer to either batch or continuous processing.

1.3 Principles Adopted

This guide is internationally applicable, reflecting the diverse nature of excipients, which often have uses other than medicinal applications. As an international guide, it cannot specify legal requirements or consider in detail the characteristics of every excipient or service.

This guide is not intended to condone poor GMPs. This guide assumes full compliance with appropriate GMPs and is not applicable to objectionable particles resulting from contamination or adulteration.

This guide relies on a risk-based approach for evaluating visible particles in excipients. This guide provides for the sharing of information between excipient manufacturers and excipient users, for the purpose of understanding the technically unavoidable particles. Additionally, this guide provides an approach for investigation for those rare occurrences when a previously unobserved particle is found by the end user.

Manufacturers and **distributor**s should consider how this guide may apply to their specific organization's excipient(s). The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The term "should" indicate recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of **quality assurance**. Note that "should" does not mean "must" or "shall*".*

This guide includes notes that offer common examples for interpretation and implementation without adding further requirements. Notes are not intended to contain an exhaustive list. They are presented as indented, italicized blue text.

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2 GENERAL CONCEPTS

This Guide is based on the concept of technically unavoidable particles as was introduced in the European regulation for cosmetics [5]. The concept of “technically unavoidable” assumes minimization of such particles through implementation and application of GMPs and currently available technology, and that the remaining particles pose no risk to the patient.

Some of the particles that are typically described as technically unavoidable are described below, including but not limited to:

- Particles discolored due to heat (e.g., friction, drying or spray drying) resulting in charred particles.
- Particles shed from equipment materials of construction due to normal and reasonably expected wear (the equipment and components should be evaluated in a documented risk assessment).
- Particles consistent with routinely used gaskets, seals, filters, etc. (the equipment and components should be evaluated in a documented risk assessment)
    - Many of these components should be anticipated to experience wear and are routinely replaced on a preventive maintenance schedule. Thus, particle shedding should be considered a normal part of the process.
    - The materials of construction of these items should be food **grade** or food contact approved or otherwise justified and of appropriate construction.
- Particles of the excipient which may be discolored due to traces of lubricants, greases, oils or like materials.
    - Lubricants, greases and oils or like materials should be cleared for use in food grade or food contact or otherwise justified.
- Packaging component particles
    - These particles are small, unavoidable, materials of construction of the packaging, e.g. plastic, cardboard or paper shedding.
- Misshapen or morphologically distinct particles, including but not limited to:
    - Compressions or agglomerations of particles
    - Elongated and/or tangled particles.
    - Flakes
    - Under or over-processed particles
- Color variation inherent to the product
- Intrinsic components carried through from **raw material**s (mined materials or those sourced from natural products)

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3 RISK ASSESSMENT

Excipient manufacturers, who are aware that their products (from raw materials through packaging) may give rise to these types of particles, should have performed a risk assessment around the types of particles that may be present. Various risk assessment models may be used for this purpose, several of which are discussed in ICH Q9 – Quality **Risk Management** [2]**.** Excipient makers should be willing to share TUPP information with excipient users. Where the excipient manufacturer considers this information confidential, the method for sharing this information is negotiated and agreed between the excipient maker and the excipient user and is outside the scope of this Guide.

NOTE: Although "acceptable" TUPs may result from normal equipment wear and tear, a risk assessment should be used to document that they were not formed due to equipment failure or use of inappropriate materials of construction, etc.

4 TECHNICALLY UNAVOIDABLE PARTICLE PROFILE

Excipient users should evaluate the risk to patient safety as it relates to their application.

The **Technically Unavoidable Particle Profile** (TUPP) documents the maker's knowledge of:

- the types of technically unavoidable particles
- their origin from a particular manufacturing process or product.

The TUPP documents are based on prior investigations of visible particles, results of risk assessments, and characterization of raw material, unavoidable particles from excipient packaging (materials of construction), etc. Information such as the following might be included in a TUPP:

- A digital photo, if available
- Particle analysis/composition, if determined
- Typical dimensions/color/texture, etc. of particle(s)
- Origin

The TUPP should exist in a form that can be shared with excipient users, potential excipient users and regulatory agencies. Where applicable and a TUPP has been developed, it should be shared with excipient users during excipient **qualification** to help support any potential investigation and avoid future complications.

Despite the evaluation of the technically unavoidable particles (TUPs) and their origin, **specifications** or limits on such particles and acceptance criteria should not be expected on a **certificate of analysis (CoA).** The small numbers of particles relative to batch size and their random distribution make their detection (based on statistical sampling) and consequently their qualification and setting of a specification unrealistic. However, the levels observed should be consistent with manufacturer's historical levels and may be included in a **composition profile**

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[3].There may be situations in which the excipient manufacturer and excipient user may have a mutually agreed control strategy. Even so, excursions above agreed TUP limits cannot always be prevented due to their distribution in the lot as the low levels and low detectability are beyond the capability of the process.

5 ATYPICAL PARTICLES

NOTE: Atypical particles found before lot release by the excipient manufacturer require investigation prior to release.

Particles not evaluated in the TUPP require further investigation to determine whether they are foreign matter or are inherent to the process or product and should be included in the TUPP, if appropriate. Results of the investigation are to be shared with the excipient user, as appropriate.

Depending on the results of the investigation, and the excipient user's risk assessment, a decision on acceptance of the atypical particle must be made by the excipient user. If the investigation indicates the presence of foreign matter, the material should be placed in quarantine until an appropriate mutually agreed disposition has been determined.

For a successful outcome of an investigation, there must be a cooperative exchange of information between excipient users and makers. The more information provided by the excipient user, the easier and faster an investigation can be completed by the maker, and *vice versa*. It is the excipient user's responsibility to provide as much information as possible about the particle found such as:

- A digital photo, if available
- A sample of the particle, if available.
- Particle analysis/composition, if determined
- Dimensions/color/texture, etc. of particle(s)
- Particle(s) found during incoming inspection or dispensing of the excipient,
- A description of how the sample was taken from the excipient
- A description of cleaning of containers and how containers are opened, particularly for bags.
- Particle(s) found during manufacturing
- A description of where the particles were found e.g. in the excipient itself or from a mixture or during the drug manufacturing process
- Whether information is being gathered from multiple **supplier**s

For those particles that are not consistent with the current TUPP, a full investigation is required. The investigation should conclude that a previously unseen particle has been found, the reason it was not seen before and **justification** for why there is no impact to the excipient quality, safety

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or performance. Such a result should satisfy the requirements for an out-of-trend (OOT) investigation under GMP. However, if a particle type is not included in the TUPP yet (i.e., has not been observed previously) but consistent with materials of construction of the manufacturing equipment, facility, gaskets, lubricants, etc., the finding should be included in a revised TUPP.

6 EXPECTATIONS OF EXCIPIENT MANUFACTURERS

An excipient manufacturer should understand and have available a TUPP, if appropriate. The scope and complexity of the profile depends on the excipient. For those excipients that do not have a history of visible particles, the TUPP is simply a statement that atypical visible particles have not been observed, and that none have been reported. However, for those types of excipients that do have a history of technically unavoidable particles, either through process-related formation, raw material introduction or morphologically distinct particles of product, the TUPP will likely be more comprehensive.

Consistent with GMPs, in-process sources of particles should be identified, and mitigation strategies and technologies employed. Once mitigation technology is implemented, it should be properly maintained to ensure continued effectiveness. In the absence of process failure, any particles not removed should be characterized as technically unavoidable since the manufacturer has met the obligations of GMP. Periodic evaluation of mitigation strategies, technologies and continuous improvement initiatives should be included as part of the GMP quality management system related to technically unavoidable particles.

The excipient manufacturer has an obligation to assist excipient users in understanding the nature of particles observed in the excipient. This assistance could be as simple as an exchange of information indicating that the particle is described in the TUPP, or a more thorough explanation of how particular types of particles arise.

Below are examples of some of the types of information or data that may be considered as inputs for the development of the TUPP.

- Photographs, chemical analysis, physical characterization, and other forms of characterization, as applicable
- Materials of construction of the manufacturing process and components
- Lubricants, gasket materials, sealants, other consumable maintenance items
- Heat sources – frictional and added heat sources (drying, distillation, etc.)
- Discussion of how technically unavoidable particles are minimized and controlled.
- Discussion of and trends in periodic particle types including risk assessment and decisions based on the observed trends.
- Discussion of the preventive maintenance program

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- Discussion of the continuous improvement strategy/processes relating to technically unavoidable particles and their formation
- Discussion of the investigation process for unusual findings

7 EXCIPIENT USER EVALUATION CRITERIA

When a visible particle is encountered by the excipient user, the excipient manufacturer should be contacted to help identify this particle and its source. When the observed particles are within the range of normal or typical particles likely to be observed with the excipient, the disposition should not normally result in the rejection of material. This exchange of information between excipient user and maker may be a TUPP, a report of the result of the maker's evaluation of the particle, or both. This report should provide sufficient information to the excipient user to perform a risk assessment for their product or application. If it is determined that the particle is technically unavoidable, it is important for excipient users to understand that these particles have historically been present in the excipient. The excipient user may evaluate whether these particles are acceptable for their product or process. As the excipient user gains experience with the excipient and its TUPP, the need for evaluation of individual particles may be reduced.

Customer specific TUP issues that may be related to a specific application or dosage form should be discussed with the excipient manufacturer. In addition, any reduced levels of TUPs that may be needed to support the application or dosage form should also be discussed with the manufacturer. Reduced levels of TUPs are usually not achievable without additional processing, potentially resulting in changes to performance characteristics of the excipient, introduction of new or different TUPs, and/or increased costs. In many cases, reduced levels of TUPs may not be technically or economically achievable and/or feasible.

8 REFERENCES

IPEC documents referenced below can be accessed at the following website links:

IPEC-Americas page: https://ipecamericas.org/

IPEC Europe page: https://www.ipec-europe.org/guidelines.html

[1] The International Pharmaceutical Excipient Council General Glossary of Terms and Acronyms.

[2] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Q9 – Quality Risk Management

[3] The International Pharmaceutical Excipient Council Composition Guide for Pharmaceutical Excipients

[4] The International Pharmaceutical Excipient Council – Pharmaceutical Quality Group Good Manufacturing Practices Guide for Pharmaceutical Excipients

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[5] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R1223-20190813)

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