IPEC FEDERATION

The International Pharmaceutical Excipients Council

Technically Unavoidable Particle Profile (TUPP) Guide

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

FOREWORD

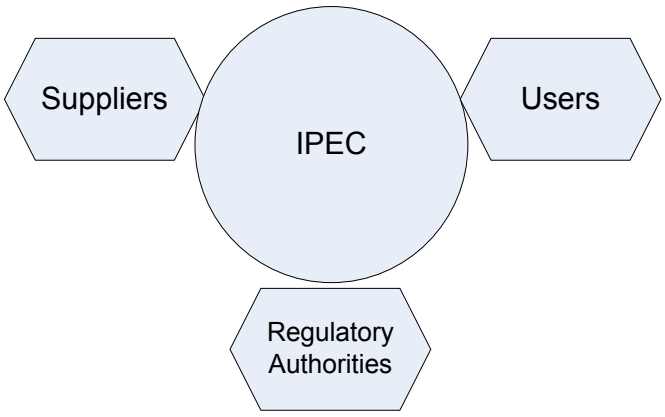
IPEC is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association comprising four regional pharmaceutical excipient industry associations covering the United States, Europe, China and Japan (which are known respectively as IPEC-Americas, IPEC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

IPEC has three major stakeholder groups;

Excipient manufacturers and distributors, who are considered suppliers in this document,

Pharmaceutical manufacturers, who are called users, and

Regulatory authorities who regulate medicines.



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

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ACKNOWLEDGEMENTS

This guideline is the result of the hard work and substantial resources of IPEC member companies. IPEC greatly appreciates the many hours the following individuals devoted to develop this guide and the generous support of their employers for providing the necessary time and resources.

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Technically Unavoidable Particle Profile Guide

Background and Purpose

The subject of visibly different particles in excipients is a topic of great 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) (483) 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, materials are rejected unnecessarily. The consequence is that both 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 of the identification of unusual visible particles in excipients.

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 which can result from a failure of Good Manufacturing Practices.

Scope

This Guide is applicable to excipients used in the manufacture of pharmaceutical products. However, 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. Visible particles are often known to the excipient manufacturer, have been previously investigated, and pose no risk to patient safety. 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.

General Principles

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 encourages a risk-based approach to the evaluation of visible particles in excipients. The sharing of information between the excipient manufacturer and user, for the purpose of understanding the technically unavoidable particles is encouraged. Additionally, this guide provides an approach for investigation for those occurrences when a previously unobserved particle is found by the end user.

General Concepts

This Guide is based on the concept of technically unavoidable particles as was introduced in the European regulation for cosmetics. The concept “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 typically described as technically unavoidable are described below, including, but not limited to:

- Particles discolored due to heat (e.g. charred particles)
- Particles shed from equipment materials of construction due to normal and reasonably expected to wear (these components should be evaluated in a documented risk assessment)
- Particles consistent with routinely used gaskets, seals, filters, etc.(these components should be evaluated in a documented risk assessment)
    - Many of these components are expected to wear and are routinely replaced on a preventive maintenance schedule. Thus particle shedding should be considered an unavoidable and 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, oils and 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:
    - Compacted or agglomerated particles
    - Elongated or tangled particles
    - Flakes
        - Under processed product
- Color variation inherent to the product
- Intrinsic components carried through from raw materials (mined materials or those sourced from natural products)

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.[1] Excipient makers should be willing to share the results of their risk assessment. Where the excipient manufacturer considers this information confidential, the method for sharing this information is negotiated and agreed between the maker and the user, and is outside the scope of this Guide.

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, and
- their origin from a particular manufacturing process or product.

The TUPP documents results from prior investigations of visible particles, results of risk assessments, and characterization of raw material, unavoidable particles from excipient packaging, etc. The TUPP should exist in a form that can be shared with users, potential users and regulatory agencies. Where applicable and a TUPP has been

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002873.pdf (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002873.pdf).

developed , it should be shared during excipient qualification to 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. The small numbers of particles relative to batch size, and their non-random distribution throughout the lot, make the setting of a specification unrealistic. However, the levels observed should be consistent with manufacturer's historical levels.

Where the TUPs are aesthetically unacceptable in the solid oral dosage form, limits and methods may be a matter for agreement between the user and excipient maker. Even so, excursions above agreed TUP limits cannot always be prevented due to their distribution in the lot and as the low levels and low detectability are beyond the capability of the process.

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 user, as appropriate.

Depending on the results of the investigation, and the user's risk assessment, a decision on acceptance of the atypical particle must be made by the 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 users and makers. The more information provided by the user, the easier and faster an investigation can be completed by the maker, and *vice versa*. It is the 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,

    - A description of how the sample was taken from the excipient
    - A description of the 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 suppliers

For those particles that are not consistent with the current TUPP, a full investigation is required. However, if a particle is not included with the TUPP (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. The investigation should conclude that a previously unseen particle has been found, the reason it was not seen before and why it poses no risk to the end user. Such a result should satisfy the requirements for an out-of-trend (OOT) investigation under GMP.

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

User Evaluation Process

The purpose of this guide is to provide understanding between manufacturers and users of the types of normal, inherent 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. 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.

When a visible particle is encountered by the user, the excipient manufacturer should be contacted to help identify this particle and its source. This exchange of information between 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 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 users to understand that these particles have historically been present in the excipient, and pose no risk to the end user. The user may evaluate whether these particles are acceptable for their product or process. As the 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 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.