

ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC)

Guidance on Handling of Insoluble Matter and Foreign Particles in APIs

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Disclaimer

This document represents voluntary guidance for API manufacturers and their customers, and the contents should not be interpreted as regulatory requirements. Alternative approaches than those described here may also be used.

Foreword

The CEFIC* Sector Group APIC (the Active Pharmaceutical Ingredients Committee) was founded in 1992 as a direct consequence of the rapidly increasing European regulatory requirements affecting the manufacture of Active Pharmaceutical Ingredients (APIs).

APIC represents producers of APIs and API intermediates in Europe. Its membership consists of more than 60 companies, located all over Europe, and of several national industry associations. For around 2/3 of its members, selling APIs and intermediates is their major business while ca. 1/3 of the members are primarily marketing final medicinal products.

APIC's focus is on worldwide Quality, Good Manufacturing Practice (GMP) and Regulatory matters relating to APIs and intermediates. Through the years APIC has developed into a high-profile industry association with an excellent, worldwide reputation.

APIC has already developed a series of guidance documents and position papers (see <http://apic.cefic.org/>). This document offers best industry practice and guidance for appropriate controls for the unavoidable presence of minute amounts of particles in APIs. The guideline highlights potential factors to minimize patient risk within reasonable limits.

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2. Introduction and Purpose

The subject of particles (sometimes referred to as visible particles, insoluble particles /matter or foreign particles) in Active Pharmaceutical Ingredients (APIs) and related intermediates has been, and continues to be, a topic of great interest and importance to the pharmaceutical industry. Particles have always been present in APIs but the interest and concern has risen due to an increased number of inspectional observations from various Regulatory Authorities concerning visible particles in Drug Products and APIs. The elevated presence of particles as well as inappropriate methods of investigation, controls and preventive and/or corrective actions were all subjects of citations by authorities and observations by API customers.

Currently the guidance from health authorities (EMA, FDA, others) or Pharmacopoeias (e.g. EP, USP) about particles in APIs is very limited¹. This lack of guidance has led to uncertainty of how to deal with insoluble matter, and has sometimes resulted in the unrealistic expectation that no single visible particle should be present in any amount of API, irrespective of its size or the overall amount present in a batch.

Therefore the idea was born to develop such a guidance document as a basis for common understanding regarding the presence of particles in APIs.

2.1 Purpose

This document intends to provide guidance to the API/intermediate industry, API users, API customers, suppliers of raw materials and other stakeholders for a standard approach towards the establishment of acceptable limits for the presence of particles, and guidance on appropriate investigation of any deviations from these limits in Active Pharmaceutical Ingredients (APIs) and API Intermediates.

It is obvious that a detailed guidance document will provide the following **benefits** to the industry and to Health Authorities:

- Provide a basis for a common understanding regarding the presence of particles in APIs;
- Provide current scientific, process, analytical, equipment and engineering knowledge, and proven good practices, to minimize the presence and risk of particles in APIs;
- Provide proven test methods and scientifically based acceptance criteria for particles in APIs;
- Share possible investigation tools to support the systematic and faster identification of root cause, appropriate corrective/preventive actions and risk assessments to enable the Quality Unit to make a solid GMP oriented final product disposition decision.

This guideline suggests the various measures and processes that could be applied to minimize the presence of insoluble matter down to acceptable levels, to establish appropriate controls, and therefore helps to ensure a more reliable supply chain.

This guidance assumes full compliance with relevant GMPs (e.g. good engineering, maintenance, documentation practices).

¹ Remark: Examples of current regulatory expectations include parenteral or ophthalmic drug product applications, e.g. “essentially free from visible particles” e.g. USP <790>, “practically free from particles” (Ph. Eur.), 2.9.20. Particulate contamination: visible particles

2.2 Background

The United States FD&C Act - Subchapter A - SEC.501.[351]^{b)} states that a drug or device shall be deemed to be adulterated -

- (a)(1) if it consists in whole or in part of any filthy, putrid, or decomposed substance; or
- (2)(A) if it has been prepared, packed, or held under insanitary conditions, whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health...

(Remark: only the most relevant part of this subchapter has been copied from FD&C Act)

The presence of particles in API can be considered product adulteration if an absolute interpretation of the FD and C Act is made. However, the regulation and its preamble recognize that manufacturers cannot provide 100 % assurance that all active ingredients manufactured will be free from one form of contamination or another. The preamble also states the procedures must be “designed to prevent” contamination. This implies an acknowledgement that procedures cannot fully guarantee contamination prevention. Moreover, the preamble also states that the level of concern for contamination will be dependent upon the final application of the drug product and the related risk to the patient.

The regulation therefore recognizes the fact that any contact between two different materials results in some physico-chemical interaction, especially when mechanical force or other kind of energy is applied (e.g. stirring, filtering, milling), but also requires that the degree of interaction is minimized by equipment design and selection of materials of construction.

API manufacturers carefully select equipment construction and other materials for their inertness / compatibility with process streams, and on the basis of safety characteristics (e.g. food grade oils, plastics, packaging materials), because the presence of trace amounts of such materials in an API can never be totally excluded, i.e. while not immediately apparent they can be detected if sufficient analytical effort is applied.

Because of these selection criteria, the presence of trace amounts of such inherently safe materials are process related and can hardly be considered as being “filthy, putrid, or decomposed substances”.

To summarize: Such traces of equipment construction materials and process contact materials in products (intermediates or APIs) are:

- Unavoidable;
- Minimized by selection of inherently safe materials with high (but not unlimited) resistance against mechanical / chemical interaction with processed materials;
- Their presence or absence at intermediate synthesis steps is potentially not relevant, as subsequent steps such as filtrations or purifications will remove them;
- Controlled at the level of the API by means of a variety of non-specific tests during routine QC testing which are generally able to detect visible particles in the parts per million range.

3. Scope

This guidance covers solid matter visible to the naked eye² in APIs or API intermediates or raw materials. The scope is mainly small molecule APIs that are manufactured by chemical synthesis, or by extractions as covered by ICH Q7. Insoluble matter or particles (as a general term) also includes larger particles or objects (e.g. pieces of plastic, bolts).

Out of scope are cross-contamination, chemical impurities, airborne or sub-visible particles, heating/cooling agents, oil and other lubricants. This guidance is not applicable for agglomerates of the product itself. This guidance does not cover biotechnological APIs (large molecule) and excipients³. However, parts of this guidance document could also be applied for other materials that are used in drug product manufacturing.

This guidance assumes that any particles are homogeneously distributed throughout a batch; if there is any indication whatsoever that the particles may not be homogeneous an investigation must be initiated.

4. Definitions of particles

4.1 Particles in final APIs

In the production of final APIs a variety of types, sizes, and shapes of particles from multiple origins can be observed by different analytical and inspection methods. The presence of these particles should be appropriately controlled, and many API manufacturers have implemented QC controls for particles in their products. Also visual examination at various points of the API manufacturing process might be performed either in production or in the QC lab.

In the following the different types of particles are listed and explained.

Technically unavoidable particles should be seen as particles which do not harm the health or safety of the final consumer. They should not affect the efficacy and quality of the related Drug Product due to the (chemical) harmlessness of the material and / or their mechanical attributes and low amount.

The technically unavoidable particles are intrinsic to the manufacturing process, the production equipment and processing aids. The construction materials and equipment were designed and intended to be in contact with the product/product solution. Typically these materials are inert and compatible with the process and cleaning conditions. Generally safe materials and appropriate equipment design with high (but not unlimited) resistance against mechanical / chemical interaction with processed materials should be selected to minimize the potential to release particles into the product.

The tolerable amount should not exceed predefined limits based on the presupposition of homogeneously distributed small particles. These minute amounts originate from “normal wear and tear” and not from equipment breakdown, damage, human error or other non-equipment related issues. The predefined limits should be based on regular process/equipment capabilities and documented risk assessments. If the results are

² Minimum size that can be seen by naked eye is about 40 to 200 micro metres, see also section 6.2.2

³ See also “Technically Unavoidable Particle Profile Guide 2013” [see Ref.^{b]}]

within the predefined limits an investigation is not required. However for any abnormal occurrence (even within predefined limits) an investigation should always be instigated.

Examples of **process and equipment related particles**: charcoal, fibers from filters, fibers from centrifuge bags, inorganic salts used or formed, seal/gasket materials, construction material of equipment (stainless steel, glass from glass lined reactor, enamel, PTFE).

Fibers have typically diameter of less than or equal to 40 microns (size is based on experience), and a length: diameter ratio larger than 3:1⁴. Examples are fibers from centrifuge bags and/or, filters.

Support equipment should also be selected for their inertness and compatibility with the process and cleaning conditions (e.g. scoops, cleaning tissues, personal protective equipment like gloves, clothing, textiles, gowning gear or filter masks).

Atypical particles are particles that should not be present in final API and their presence should always trigger an investigation. These particles consist of foreign matter which is not intended/designed to be in direct contact with the product/manufacturing process. These atypical particles commonly originate from materials which accidentally or unintentionally came into contact with the product or a process stream.

Examples are operator's pencil, cable binders, nametags, or duct tape.

Risk assessments might identify that a product is acceptable in cases where foreign matter was dropped in and immediately removed as a whole, or with the assurance that all the foreign matter was removed, while maintaining the integrity of the product.

Hair, human skin particles, and insects should be GMP controlled by appropriate gowning procedures or pest control.

4.2 Particles in API intermediates

It is not general practice to determine and quantify the presence of particles during the manufacture of API intermediates. However, a general visual appearance test is in most cases performed as a regular QC test, or a visual examination is performed during operator handling of an intermediate in production or in the QC laboratory. Therefore elevated or abnormal (i.e. out-of-trend) presence of insoluble matter, e.g. generated by equipment failure or other incidents, can be observed during QC testing or during manufacturing activities. Any limits and controls for particles in API intermediate steps can be different from those at the final API step if there are appropriate filtrations in subsequent process steps.

Measures should be in place to minimize the presence of particles in API intermediates, unless it is intended to remove them in the downstream process. Abnormal presence of particles in API intermediates might be an indication of equipment, process or operator failure and an investigation should be initiated.

In principle the definitions for technically avoidable and atypical particles in API intermediates are the same as described for APIs.

⁴ Other definition of fibers: Definition of fibers, evaluated by microscope: a countable fibre, as defined by WHO (1996), is any particle that has a length > 5 µm, a length:diameter ratio larger than 3:1 and a fibre diameter < 3 µm (often referred to as WHO fibres) Ref. ^{c)}
Also of interest: Ref ^{d)}

4.3 Particles in raw materials (including packaging materials) for APIs

Suppliers for raw materials or packaging material should have measures in place to avoid particles caused by equipment failures and/or other abnormal occurrences. The supplier should have an appropriate maintenance and equipment checking program, and a system to detect technical or other failure, and, if this was to occur, to bring the equipment back into normal operation. It is also desirable to incorporate physical removal of potential particles, such as filtration or sieving, into the later stages of the manufacturing process. Nevertheless, equipment failure, human error, or the like, can lead to an increase in the presence of particles in the raw material. The raw material supplier should always notify the API manufacturer in the event of any incident in their manufacturing process that could lead to the presence of particles in material supplied.

The supplier qualification program of the API manufacturer should emphasise these expectations and perform proactive and regular communication to the suppliers to make them aware of issues that might be caused by particles.

Raw materials for API manufacturing and packaging material for API packaging are in many cases not specifically tested for foreign matter. However the standard checks “appearance of sample”, “shape and appearance” (integrity) of the packaging (secondary) and primary packaging performed during incoming QC tests are likely to detect visible particles if present. Especially, it is expected that raw materials do not contain particles in a size which might damage process equipment (e.g. glass lined reactors, valves) in further manufacturing activities. They should not contain any foreign matter that could be dissolved in the downstream API chemical processing step(s). Raw materials and/or packaging materials should not contain particles caused by insufficient plant hygiene (insects, other human or animal matter, hairs etc.). In the event of any abnormal findings the API manufacturer should initiate an investigation.

5. Good practices to minimize the presence of particles in APIs

The API manufacturer should consider preventive measures, removal methods and inspection methods in order to minimize the presence of particles in their API products.

The following lists give examples of good practice that API manufacturers may consider, they are not intended to be exhaustive.

5.1 Key preventive measures

- Design of plant, process, and equipment:
 - Selection of suitable construction materials; e.g. elimination of metallic particles due to attrition between metal-to-metal contact moving parts;
 - Minimize or eliminate open handling;

- Pre-conditioning of the equipment with first solvent to be used in the process (e.g. “dry run”);
 - Polish (final) filtration of a product solution prior to final crystallization;
 - Filtration of product/equipment contact utilities (e.g. gases), solvents or other liquids as close as possible to the point of use;
 - Use of appropriate rooms and/or other methods of protection according to the nature of the process step;
 - Appropriate environmental conditions during open handling in the final stages of API manufacturing.
- Plant and equipment maintenance and cleaning:
 - Preventive maintenance program and schedule for all equipment parts that are intended to be in direct contact with the product and process stream;
 - Effective cleaning and inspection procedures;
 - Cleaning after maintenance (e. g. repairs),
 - Rinsing of equipment after cleaning/prior to manufacturing through a filter, and visual examination of that filter to identify equipment issues.
 - Inspection of equipment prior to production;
 - Use of risk assessment to identify potential sources of particles during process manufacturing, sampling and analysis e.g. FMEA;
 - Gowning of operators – to protect exposed product (gloves, hair cover, Tyvek suits, etc.);
 - Effective training of operators and maintenance staff;
 - Written procedures in place;
 - Appropriate storage/dispensing/sampling for packaging materials, raw materials and intermediates.

5.2 Removal/detection methods

- In-line filters/sieves (e.g. bag filters, cartridge filters, monoplate filters, etc.)
- In-line detectors (e.g. metal detectors, magnets);
- Final polishing filtration;
- In-line separators (mainly used in continuous process and charging of raw materials);
- Use of sampling and/or in process control tests whenever a higher risk is perceived.

5.3 Inspection methods

- Inspection of raw materials (including packaging), in-process, intermediates and final product by:
 - Visual inspection, during processing and/or QC tests;
 - Filter testing;
 - Automated and/or computerized inspection techniques.

6. Analytical controls and acceptance criteria

6.1 General rules for APIs

The amount, shape and type of particles should not affect the potency, efficacy or safety of the API. Particles are generally inert and biologically non active materials. Traces of technically unavoidable particles are minimized by selection of inherently safe materials with high (but not unlimited) resistance against mechanical / chemical interaction with processed materials. Various compendial or pharmacopoeial tests might detect insoluble matter, and a batch of API must pass all of these (e.g. appearance, appearance of solution, clarity of solution, heavy metal test or residue on ignition). Also any other pharmacopoeial or ICH requirements that are applicable for APIs must be fulfilled.

6.2 Analytical methods for APIs

This chapter describes a number of QC tests that are used for particle determination in API release testing. This list is not intended to be mandatory or exhaustive, i.e. there might be other tests that are also suitable for the determination of particles in final APIs. The specific test application and test execution frequency can be based on a risk assessment.

6.2.1 Appearance Test

Visual examination of a powder with a defined sample size. The typical sample size is several grams. The test procedure should detail how the sample has to be examined (e.g. how to spread out on paper).

Some details about the detectability by naked eye, preventative measures and sample size that are described in the following chapters for the Filter Test do also apply in general for the Appearance Test.

6.2.2 Filter Test

In general the company and/or product specific limits for insoluble matter have to be based on normal process performance without equipment failure or other issues (e.g. filter breakthrough, human error). The acceptance criteria may differentiate between metal, glass and/or other materials / particles.

The naked eye can detect particles with a minimum size of about 0.04 – 0.2 mm (see also Ref.^o).

6.2.3 Sampling and sample size

Preventive measures for “Sampling”.

To prevent false positive results from the filter test, which would take a lot of time and effort to investigate, the following measures should be considered:

1. Sampling containers:
 - a. sampling containers/bags should be clean (e.g. bought with certificate or, if re-used, cleaned via a qualified / validated procedure);
 - b. sampling containers are often made of plastic, with screw caps. Especially if the sampling containers are reused, the screw threads of both the container and the

- screw cap should be inspected before use. Friction on the thread can lead to (white) particles (may appear as fibers or twisted white particles) on the filter;
- c. disposable containers/bags can be used.

- 2. Environmental conditions of the sampling point:
 - a. Samples should be taken with appropriate protection, with special care to avoid introduction of particles e.g. within the filling area of the product or using an automatic sampler, minimising any contact between sample and the environment.

Quantity of the sample may vary in relation to batch size (e.g. especially for very small batch size, highly potent or toxic substances). A representative sample of the batch has to be taken for release testing; typically 5 to 100 g, to ensure that clear differentiation of filter coloration can be achieved.

6.2.4 Preventive measures for the test execution

Laboratory equipment

- a. Both sampling equipment and laboratory equipment has to be clean and free from particles and fibers; the cleaning procedures should be suitable and should be documented;
- b. Cleaning of lab-equipment used (e.g. glassware) and sampling devices should be done directly before usage. The cleaned equipment should be stored under appropriate conditions.

Solvents

- a. If a filter test is performed the solvents have to be free from particles; the solvents should be filtered before usage; if special equipment is use (e.g. a Milli-Q-System) it should be cleaned and maintained appropriately.

Environmental conditions during execution of the filter test:

- a. The filter test should be performed under particle free environment; for example in a ventilated hood in the laboratory.

6.2.5 Test execution:

For example:

1. Dissolve sample – typically 5 to 100 g – in a suitable solvent and filter (typically a solvent resistant microfilter - e.g. 10, 5, 0.45 micro meter pore sizes - is used) off the solution; note that a black colored filter for analysis of white particles might be used.
2. Dry the filter.
3. Visual examination of filter by naked eye.
4. Comparison with a blank solution to ensure no false positive results.
5. Comparison with a reference filter loaded with charcoal, ferrous oxide and/or other applicable reference substance.
Test is passed if no particles are visible by naked eye and the comparison with the reference filter showed that the filter coloration is not darker than the reference filter.
6. If particles are visible by naked eye an evaluation by microscope has to be performed.
7. Test is passed if number and size of particles identified fulfill the predefined specified values.

Remark: Additional specific investigational tests might be required for further

characterization or identification of the specific particles, i.e. in case abnormalities are detected.

8. If test is not successfully passed an investigation has to be initiated to identify root cause, product impact and any related CAPAs.

Remark: Also weighing, scanners and other recognition technologies combined with automated evaluation can be applied instead of examination with naked eye and/or microscope

6.3 Acceptance criteria for APIs

The acceptable limits for particles should be based on the knowledge and history of regular process and equipment performance. Any equipment, process or human failure can lead to increased level of particles in the API. If there is no indication of such a failure and the testing results of the API are within the predefined acceptable limits the batch can be considered acceptable and there is no need to further investigate. Specific action and alert limits might be applied to ensure that any evolving process and/or performance issues can be detected and mitigated prior to exceeding the predefined action limits.

6.3.1 Dosage forms & route of administration

APIs are used for different drug product dosage forms. The limits for particles might also take into account the route of administration, e.g.

- Tablets, capsules for oral applications: minute amounts of particles pass the gastrointestinal tract unchanged;
- Solutions for parenteral, inhaler, ophthalmic applications: normally the solutions are filtered by the drug product manufacturer via very small pore size. Minute amounts of particles are generally removed by that filtration step. Related Drug Product (vials, ampules, syringes, solutions) are tested for particulate matter during QC release testing;
- Inhalers (dry form): a tighter limit might be applicable due to this specific dosage form;
- Ointments, creams, shampoos, powders: minute amounts of particles normally do not pass the skin or mucous membrane and therefore do not enter the body.

6.3.2 Proposal for limits:

Typical limits for particle size seen via a filter test:

- Upper limit for particle size (except fibers) is in the range of up to 1 mm, i.e. acceptance criteria: No particles in the analytical sample that are larger than 1 mm.⁵ For metal particles acceptance criteria of 0.5 mm is often applied.⁶

⁵ **Justification:** According to FDA Compliance Policy Guide (Ref.⁹) for foods (ready-to-eat) that contain hard or sharp particles 7 mm to 25 mm, in length should be considered adulterated within the meaning of 21 U.S.C. 342(a)(1). An upper limit of 1 mm fulfils this requirement for APIs that are used for an oral application of the related drug product. APIs that are used for parenteral use are normally dissolved and filtered applying a sterile

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- Limit for all particles less than 1 mm in size should be set based on normal process performance⁷.
- Normal process performance should be defined by the individual API manufacturer based on historical data.

Separate limits may be set for fibers, again based on normal process performance.

A limit between 10 and 100 ppm is proposed for the maximum amount of particles allowable.

A specific limit between 2 and 10 ppm is proposed for very small particles (e.g. <0.04 to 0.2 mm coming from charcoal treatment etc.) if applicable.⁸

This is proposed as a general guidance based on normal process performance; all abnormal or out of trend occurrences should be investigated.

This limit can be applied individually for the different sizes and specific weight of the particles.

Since metal has a much higher density compared to other material separate limits for metals and other particles can be applied.⁹

It is recommended to align the specification with API user /customer.

The following table provides an overview of typical materials used as construction materials in API manufacturing plants (Ref.^f): these are average densities and can vary

Construction material	Density
	[g/cm ³]
Rubber Stopper	1.2
Polypropylene	0.9
Nylon	1.15
Paper	1.15
Teflon	2.2
PVC	1.4
Polyester	1.4
Glass	2.5
Stainless steel	8

filtration step. The related drug product is tested for particulate matter (e.g. USP <788> Particulate matter in injections).

⁶ Background: The acceptance criteria of 0.5 mm for metal particles is also often applied at drug product manufacturers for in-line metal detectors/metal separators.

⁷ Justification for very small particles: see Ref.^b; for inert particles >0,2 mm, as they are not dissolved and not absorbed in the gastrointestinal gut: see Ref.ⁱ

⁸ Justification: limit is based on experience and practicality of this test to detect about 2 ppm charcoal on a filter with about 25 to 50 mm diameter

⁹ Remark: It is recognized that particles might only be identified as metals by applying specific analytical techniques

An example table for max number of particles is shown below:

For simplification purposes 2 different categories of particles were applied:

Metal (density: 8 g/cm³) and other particles (density: 2.5 g/cm³).

For calculation purposes a sphere model was used and a base limit of 10 ppm was applied for both ranges individually¹⁰.

100 g sample	0.2-0.5 mm	0.5-1 mm
Max # of particles Metal	2	0
Max # of particles Other Materials	6	1

6.4 (In-)Process controls for intermediate process steps

(In-)process controls are intended to help detect particles during the manufacturing of the API and at the same time identify the possible sources, thus allowing measures to be implemented to minimize the presence of these particles.

The controls described in this chapter are examples that could be used by API manufacturers as appropriate.

General conditions:

- In process control points should be defined based on an assessment regarding equipment, materials flow, process etc.;
- Sampling: a sampling process has to be designed in a way that both the product as well as the sample is not adulterated (clean containers, clean sampling devices, control of the sampling environment etc.).

In process controls:

- Sampling and inspection of the samples (by different techniques like filter test, visual inspection, others);
- Implementation of security sieves or filters and appropriate periodic review of these devices during production (for presence of particles);
- Installation of metal detectors and / or metal separators / permanent magnets (applicable for ferromagnetic particles only) and appropriate periodic review of these devices during production (for presence of metal particles);
- Visual inspection of the product during handling e.g. charging & discharging;
- Visual inspection of the equipment and utensils before and after use, including e.g. integrity check of sieve screens;
- Weighing and/or visual inspection of pieces of equipment before and after the process (e.g. Gaskets, Teflon valves etc.);
- Equipment clearance/counting/reconciliation of equipment parts.

¹⁰ Calculation example: 100 g sample: 10 ppm corresponds to 1 mg. 1 metal particle with density 8 g/dm³ and 0.5 mm diameter of sphere: $m = \frac{4}{3} \pi r^3 \cdot \rho = \frac{4}{3} \pi (0.00025\text{m})^3 \cdot 8000\text{kg/m}^3 = 5.24\text{E-}07\text{ kg} = 0.524\text{ mg}$, i.e. 2 metal particles correspond to 1 mg

Remark: Also alternative calculation models might be applied based on observed particle shapes, e.g. flakes, rod-shaped particles

Prevention measures:

- Visual inspection of the equipment and utensils before use;
- Visual inspection of a filter test of the last rinse (after cleaning and conditioning the equipment);
- Inspection and clearance of the work;
- Use of engineering controls, additional levels of protection e.g. charging booths, glove box;
- Effective preventative maintenance procedures;
- Effective training of operators & technicians;
- Minimize open operations after final filtration step. Perform closed operations wherever possible after final filtration, use closed centrifuges, continuous liners for packaging operations etc.;
- Appropriate gowning of operators and technicians – gowning gear and materials used for personnel protection should be selected to avoid the release of particles and fibers.

7. Incident management

Equipment failure, human error, or the like, can lead to an increase in presence of insoluble matter in an API above the defined limit. The following provides general guidance on what actions a manufacturer must take in the event of an abnormal occurrence.

An investigation should be carried out in the event of particles being present in the API product at levels above the established limits; also in the event of an abnormal occurrence e.g. presence of particles in raw materials, intermediates, in process control samples. In the event of an "out of trend" event (e.g. presence of abnormal coloured particles) an investigation should also be carried out.

- The investigation should concentrate on the identification of the source of insoluble matter, identification of the type of matter e.g., glass, metal, plastic; an assessment of the extent of insoluble matter present, and an assessment by the Quality Unit of its impact on product quality, safety and efficacy of the final API.
- The evaluation of other batches, equipment, processes where there could be an impact should also be considered as part of the investigation.
- Include an assessment of material compatibility (material should not be additive, absorptive or reactive).
- Justify appropriateness of filter for particle size present, or other process unit operations which will remove the insoluble matter
- In case of reprocess to remove particles, the investigation should explain why the filtration in the original process did not remove the insoluble matter.
- The reprocess/rework method should be justified or validated as appropriate.

For raw materials (including packaging) and API intermediates particle testing is not routinely required, however, if any abnormal findings occur during material handling, cleaning, maintenance etc.

- An assessment of material compatibility (material should not be additive, absorptive or reactive) and impact/removal in subsequent steps must be performed.
- If particles are found in sourced raw material exceeding defined limits or general expectations, a thorough investigation should be completed and corrective action involving the supplier should be performed where applicable.

7.1 Determination of identity of particles

Technologies that may be employed:

- Microscopy
- Scanning Electron Microscopy
- Energy dispersive X-ray analysis
- Infrared spectroscopy (including n attenuated total reflection technology)
- elemental analysis
- inductively coupled plasma optical emission spectrometry (ICP-OES)
- comparison with specimen samples or databases
- X-ray fluorescence spectroscopy
- Particle counter for liquids and solids
- Micro Raman

7.2 Identify source/root cause – examples of investigation techniques and aids

- 5 whys
- Cause tree analysis
- Knowledge/database of construction materials of equipment train
- Ishikawa diagram (fishbone)
- Is-Is not
- Kepner Tregoe

7.3 CAPA / course of action to avoid reoccurrence

Corrective actions and preventative actions must be defined and implemented to demonstrate that the correct root cause has been identified and that the problem has been eliminated or reduced to an acceptable tolerance level where applicable.

7.4 Risk assessments: topics to be considered during the investigation/disposition decision

- Prerequisite: Identification of the particle(s), size/range of size, amount, distribution/homogeneity in the batch;
- Identification of the source/root cause;
- An assessment of material compatibility (material should not be additive, absorptive or reactive) and its impact in the product;
- Consider whether removal in subsequent steps can be/should be performed;
- Justify appropriateness of filter capabilities versus particle size present, or other process unit operations which will remove the particles (e.g. distillation);
- If during investigation it is determined that the material is foreign matter (not intrinsic to the process or equipment), or not compatible with the product then consideration should be given to rejection of the lot or lots;
- For an atypical particle or foreign matter dropped into the batch briefly (e.g. a pen), which is immediately removed with the assurance that the complete foreign matter is

removed, while maintaining the integrity of the product, a risk assessment should be written to determine the impact and a path forward;

- Particles may also be removed by further downstream processing when a filtration step is already included or when a filtration step can be easily introduced without altering the process (e.g. passing a liquid raw material or solvent over a filter before charging to a vessel or reactor). An assessment should be performed to demonstrate that the particles are inert (insoluble, not reactive, not additive) under the process conditions of the proposed removal method (solvents, reagents, temperatures, pH, etc.);

While inertness and compatibility of these particles might not be an issue, there may be a concern on secondary impact (e.g. damage to glass lined coating may expose carbon steel of reactor wall to corrosive or abrasive product streams). Any potential secondary impact should also be evaluated as part of technical assessment.

The insoluble matter might be removed in the Drug Product Formulation process.

8. References

- a) “Technically Unavoidable Particle Profile Guide”, IPEC 2013 Draft , permission received on 10 Nov 2014 from Kim Beals, Executive Director, IPEC-Americas
- b) United States FD&C Act - Subchapter A - SEC.501.[351]
<http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec351.pdf> c)
<http://monographs.iarc.fr/ENG/Monographs/vol81/mono81.pdf> (WHO IARC monograph volume 81), see page 61, also Glossary on page 379.
- d) 16 CFR Part 303 (RULES AND REGULATIONS UNDER THE TEXTILE FIBER PRODUCTS IDENTIFICATION ACT); § 303.7 Generic names and definitions for manufactured fibers <http://www.law.cornell.edu/cfr/text/16/part-303>
- e) <http://sciencefocus.com/qa/how-small-can-naked-eye-see>, <http://www.tbh-online.com/needtoknow/particlesizes.html>,
<http://www.muellerenvironmental.com/documents/200-055.pdf>
AAPS PharmSciTech, Vol. 12, No. 1, March 2011f)
http://www.engineeringtoolbox.com/density-solids-d_1265.html
- g) FDA. 1999. Foods - Adulteration Involving Hard or Sharp Foreign Objects.
<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074554.htm>, other references:
<http://seafood.oregonstate.edu/.pdf%20Links/Compendium/Chapter-28-Hard-or-Sharp-Objects.pdf>
Lehman H. Glass and metal fragments in food and beverages. Quarterly Bull. Assoc. Food and Drug Off. 1958, 22(1) 24-26
CPG Sec. 555.425 Foods. (2005). Adulteration Involving Hard or Sharp Foreign Objects
- h) Hussain N, Jaitley V, Florence AT. Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics. Adv Drug Deliv Rev 2001. 50(1/2):107-142
- i) Volkheimer G. The Phenomenon of Persorption: Persorption, Dissemination and Elimination of Microparticles. In: Old Herborn University Seminar Monograph 14 (p. 7-15), Editors: Heidt PJ, Nieuwenhuis P, Rusch VD, van der Waaij D, Verlag wissenschaftlicher Schriften und Bücher, Herborn-Dill (Germany), 2001

9. Glossary

Note: For all other GMP-relevant terms it is referred to the glossary of the ICH Q7 Guideline