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Commentary

Foreign Particles Testing in Orally Inhaled and Nasal Drug Products

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The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) presents this paper in order to contribute to public discussion regarding best approaches to foreign particles testing in orally inhaled and nasal drug products (OINDPs) and to help facilitate development of consensus views on this subject. We performed a comprehensive review of industry experience and best practices regarding foreign particles testing in OINDPs, reviewed current guidances and techniques, and considered health and safety perspectives. We also conducted and assessed results of an industry survey on U.S. Food and Drug Administration requirements for foreign particles testing. We provide here a result of our review and survey: a summary of industry best practices for testing and controlling foreign particles in OINDPs and proposals for developmental characterization and quality control strategies for foreign particles. We believe that clear consensus-based recommendations and standards for foreign particles testing and control in OINDPs are needed. The proposals contained in this paper could provide a starting point for developing such consensus recommendations and standards.

KEY WORDS: characterization; foreign particles; foreign particulates; quality control techniques; testing.

INTRODUCTION

Foreign particles (also known as "foreign particulates" or "foreign particulate matter") in orally inhaled and nasal drug products (OINDPs) are contaminant particles that may be derived from the active, excipients, container/closure components, formulation, environment, the process of manufacturing the drug product, and/or the process of actuating the drug product device.

Testing for foreign particles is currently of great interest to the pharmaceutical industry, regulatory bodies, and the scientific community, as evidenced by a growing number of seminars and conferences addressing this issue, such as the 2002 AAPS/U.S. Food and Drug Administration (FDA) Workshop on Drug Substance and Drug Product Specifications and the 2004 Respiratory Drug Delivery IX. The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), an association of pharmaceutical companies that develop, manufacture, or market OINDPs, supports the development of science- and experience-based regulatory guidance in this area. IPAC-RS understands that regulation must evolve with scientific advancements and believes that the time is right for public comment to facilitate development of regulatory recommendations addressing control of foreign particles in OINDPs.

We present a review of current industry best practices and recent regulatory recommendations regarding foreign particles testing in OINDPs. Based on this review, we believe that there exists significant need for further discussion of this topic by regulators, industry, and the scientific community in order to develop consensus-based recommendations on the most appropriate testing approaches and specifications.

To contribute to this discussion, we also present in this paper proposals for these stakeholders to consider in developing appropriate approaches to foreign particles testing. We first identified aspects of the testing and regulation of foreign particles that might benefit from further examination. These include agreement on a general paradigm for assessment of foreign particles in OINDPs, appropriate approaches to sampling, understanding of current techniques for foreign particles testing, and safety and quality considerations in development of controls for foreign particles. We then developed specific proposals addressing these topics based on IPAC-RS company experiences. These points are summarized below:

- Sampling should be tailored to the specific dosage form and manufacturing process. Specific recommen-

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dations for sampling are not addressed in this paper but could be addressed in a USP test chapter.

- Full characterization of foreign particles (which may include identification, understanding of source, enumeration, and determination of batch-to-batch consistency, shape, and size) should be conducted during development studies in order to develop strategies for control of product manufacture. Full characterization need not be performed for routine quality control on commercial batches during release or stability testing. For those products where foreign particles testing during routine quality control will be performed, testing should be limited to enumeration.

A specific strategy might be the following:

During development, the extent to which foreign particles are characterized should be maintained at a level of detail that enables the likely source of the contamination to be identified and that provides a basis for the sampling and testing approach used in product quality control.

For development batches, enumeration of foreign particles should be done during stability studies.

For development batches, if no stability trends for the levels of foreign particles are present, it is reasonable to limit quality control of foreign particles to enumeration on release of commercial batches. If foreign particle levels are low and stable, such enumeration assessments should be phased-out.

- For OINDPs, the U.S. Environmental Protection Agency (EPA) National Ambient Air Quality Standard (NAAQS) for particulate matter $\leq$10 μm may be considered the relevant particle standard. Safety considerations based on this EPA standard can be used to develop an upper limit for levels of foreign particles $\leq$10 μm. We believe that it is inappropriate to develop particle level limits for foreign particles >10 μm or >25 μm based on *safety* concerns. Instead, for these larger particles, it is more appropriate to establish enumeration controls based on quality concerns.
- Specified lower size limits should be established, based on the properties of the materials involved and the technologies required.
- Standards for nasal products should be less stringent than those for inhalation products. For instance, particle level limits can be based on quality considerations only.
- Specifications for particle size ranges and particle level limits based on quality control considerations should be drug product specific.
- USP standards established for injectables are not necessarily appropriate for OINDPs.

MATERIALS, METHODS, AND DISCUSSION

Review of Regulatory Guidance for Foreign Particles in OINDPs

FDA Draft and Final Guidances

IPAC-RS commends FDA for development of the *Draft Guidance for Industry, Chemistry, Manufacturing and Controls Documentation for Metered Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs)* and the final *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products–Chemistry, Manufacturing and Controls Documentation* (referred to throughout this paper as the "draft guidance for MDIs/DPIs" and the "guidance for nasal sprays," respectively). These guidances provide regulatory recommendations for foreign particles testing, which also serve as a starting point for further discussions regarding best approaches to this testing requirement. We therefore review FDA's current recommendations for foreign particles testing as described in the draft and final guidances.

In 1998 and 2002, the FDA issued the draft guidance for MDIs/DPIs and the final guidance for nasal sprays, respectively. The guidance for nasal sprays represents a finalization of the draft guidance for nasal sprays originally issued in 1999.

The draft guidance for MDIs/DPIs addresses testing for foreign particles in MDIs and DPIs under *Specifications for Drug Product*, *Microscopic Evaluation*. For MDIs, the draft guidance states that:

> . . . microscopic examination of the formulation has certain merits and, therefore, should be retained for release and stability purposes. For example, the examination provides information on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, crystal growth, and foreign particulate matter (Section III.F.1.l, lines 645–649, pp. 21–22).

For DPIs, it states:

> Appropriate acceptance criteria should be instituted for the appearance of the drug product formulation using a microscopic test approach. This test is useful for detection of large particles and agglomerates of the drug substance, can define morphology of drug substance and carrier particles, and can detect foreign particulate matter. The type, origin, and profile of foreign particulates, including fine particulates, should be controlled (Section III.F.2.k, lines 796–802, p. 25).

The guidance for nasal sprays states the following regarding foreign particles in nasal sprays:

> For both solution and suspension nasal sprays, there should be validated tests and associated acceptance criteria for particulate matter. Particulate matter can originate during manufacturing, from formulation components, and from the container and closure components. Levels of particulate matter in the drug product can increase with time, temperature, and stress. If stability data generated in support of the application demonstrate that levels of particulate matter do not increase with time, this can be sufficient to justify testing of this attribute only on batch release (Section III.F.1.k, p. 16).

For inhalation solutions, suspensions, and sprays, the guidance refers to the above language for nasal sprays, but adds the following:

> The acceptance criteria should include limits for foreign particulate matter less than 10 micrometers (μm), greater than 10 μm, and greater than 25 μm (Section III.F.1.g, p. 18).

In March 2002, at the *AAPS/FDA Workshop on Drug Substance and Drug Product Specifications*, industry and FDA identified and focused discussion on several topics of primary importance to particulate matter: appropriate size ranges for reporting, technologies for testing, toxicological

and safety assessment strategies, and components and/or drug product controls. After extensive discussions, the participants reached no conclusion on any of these topics at this meeting. The meeting summary states that FDA and industry are still in the "information gathering stage" (*AAPS/FDA Workshop on Drug Substance and Drug Product Specifications*, 2002, *Workshop Final Summary,* p. 8).

Industry Survey

As regulators and industry continue to explore appropriate approaches to foreign particles testing, regulatory guidance evolves and is implemented. Such guidance may or may not be reflected in currently available guidance documents. Anecdotal evidence from companies has suggested that regulatory requirements for foreign particles testing in OINDPs has evolved since issuance of the draft guidance for MDIs/DPIs and may include more specific requirements than are outlined in the final guidance for nasal sprays.

Therefore, to better understand the current requirements for foreign particles testing, IPAC-RS initiated a confidential survey of member companies in 2002. The survey asked for FDA's requests on foreign particles testing made to companies in the past several years. Recent survey submissions address FDA requests made in 2003.

The results suggest that since 1994, FDA has come to recommend, for some products, enumeration and identification of particles in specific size ranges. For instance, for suspension MDIs, FDA comments have changed from general requests for size distributions to more specific requests for control, enumeration, and identification of foreign particles of less than 10 μm, greater than 10 μm, and greater than 25 μm. These size limits are not mentioned in the 1998 draft guidance for MDIs/DPIs, although they are recommended for inhalation solutions, suspensions, and sprays in the 2002 final guidance for nasal sprays.

Additionally, the survey results suggest that FDA currently recommends identification and enumeration of foreign particles as part of routine release testing and stability testing. As an example, for a suspension MDI, FDA requested this approach for foreign particles in the size ranges described above. For a nebulizer, the FDA has requested identification and "control" of foreign particles at release and on stability, for the size ranges less than 1 μm, 1 μm $\leq x <$ 10 μm, 10 μm $\leq x <$ 100 μm, and so forth. The requests associated with an MDI solution recommend that "qualitative and quantitative" testing of foreign particles be performed on stability and that foreign particles "should be fully characterized as to their origin . . . and what the proportions are." The recommendation for full characterization and enumeration of foreign particles on release and stability is not described in the draft guidance for MDIs/DPIs.

The survey results do not indicate that FDA is recommending particular techniques for performing identification or enumeration. Additionally, neither the survey results nor existing guidance explains whether foreign particles should be measured in the emitted dose or in-product (i.e., in the canister for MDIs). IPAC-RS agrees with FDA that these issues need not be addressed in regulatory guidance. These topics are nevertheless important aspects of a comprehensive approach to control of foreign particles, and we therefore address them in Section IV of this document, in order to enhance understanding of the capabilities, limitations, and complexities of current techniques.

Survey results demonstrate that duringthe past 5 years, FDA's approaches to regulation of foreign particles have, in some areas, evolved significantly. For instance, results suggest that during the last 5 years, regulatory recommendations for foreign particles testing have become more expansive and specific. This change is most apparent in regard to recommendations for appropriate size ranges, as detailed above.

Survey results are less clear regarding regulatory recommendations for *when* certain types of particles assessments should be performed. For instance, results appear to suggest that FDA recommends full particle characterization (i.e., complete identification and enumeration) of foreign particles during routine quality control testing of commercial batches. However, recent feedback from some companies suggests that FDA now recommends that full characterization be conducted only during development, with quality control studies limited to enumeration.

We agree with and support the approach that full characterization be conducted only during development, with quality control studies limited to enumeration. Current commonly used techniques and methods for full characterization of foreign particles could be applied on a routine basis only with great difficulty (see Section III). Such characterization is time and labor-intensive and inefficient. For example, a recent industry-wide assessment by IPAC-RS demonstrates that full characterization of a single OINDP unit (e.g., a single MDI canister or DPI container) could require up to 5 different analysts and up to 130 scientist hours. Additionally, such characterizations would require specialized and extensive instruction of clean-room technicians—expertise that pharmaceutical companies typically do not possess. Such expertise is often contracted out to highly sophisticated, dedicated laboratories. The assessment suggests that full characterization provides little benefit at high cost and therefore is inappropriate as a routine quality control tool. A more efficient and value-added approach that would afford better quality control would be to conduct full characterization in development studies, identify the source of the particles, and develop an understanding of the manufacturing process and areas of high risk for foreign particles contamination. Finally, development and stability data would be monitored for trends. All this collected experience and information could then be used to control levels and types of particles to a stable minimum population. These ideas are explored further in Section II.B.3.

In general, the survey results serve to highlight two principal areas where regulatory discussion has developed since issuance of the draft CMC guidances for OINDP in 1998–1999: i) development of size cutoffs and ii) appropriate implementation of full foreign particle characterization. We support further discussion of these important topics. We therefore address these in more detail in Section II.B below.

Sampling and suitable testing techniques, while appropriately not addressed in regulatory guidance, impact development of size cutoffs and the question of full characterization. As such, industry and regulators would benefit from further public discussion and development of consensus views on the appropriate approaches to sampling, and clear understanding of suitable testing techniques. In Section II.B, we also address sampling and testing techniques. Additionally, we discuss in further detail how the capabilities of current

testing technologies support limiting full characterization of foreign particles to development studies.

Approaches to Foreign Particles Testing in OINDPs

Sampling

Sampling of foreign particles from product is of fundamental importance to foreign particles testing. Therefore, industry and regulators would greatly benefit from public discussion and development of appropriate approaches to sampling.

We suggest that a *general* approach to sampling is difficult and probably not feasible. We therefore propose that the sampling strategy be tailored to the specific dosage form and manufacturing process. Sampling should not mask or remove foreign particles.

Specific recommendations for sampling could be addressed in a USP test chapter.

Capabilities of Current Technology

Table I contains commonly used techniques for foreign particles analyses and the capabilities and limitations of each. Details of typical methods associated with these techniques are contained in Section II.C.

General Approaches to Control of Foreign Particles

In this section, we discuss general considerations that should be included in any approach for developing and establishing effective quality controls for foreign particles in OINDPs, in the context of the capabilities of current techniques and methods. Control of foreign particles should start with assessments from development studies and, when appropriate, should be maintained through routine quality control testing.

Development Studies and Routine Quality Control Testing. Given the capabilities of the techniques shown in Table I, we recommend that full characterization of foreign particles be performed during development only. Full characterization

Table I. Common Techniques for the Analysis of Foreign Particles in Inhalation Products Including Foreign Particle Count and Identification

Technique	Capabilities	Limitations
Optical microscopy	1. Positive observation: • Morphology • Birefringence • Refractive index • Color • Size • Number 2. Individual particles may be harvested for analysis by other methods (i.e., FTIR, SEM/EDX). 3. May be amenable to automated counting with some newer technology (e.g., computer controlled stages coupled with image analysis could allow counting high number of particles in short periods of time, improving statistical confidence limits).	1. Very labor intensive and therefore a significant time investment. 2. Limited practical utility in lower particle size ranges. For instance, counting particles less than 5 μm using this method is extremely labor intensive and may lead to inaccuracies. 3. Most useful for counting—limited utility for identification.
Scanning electron microscopy with energy dispersive X-ray (SEM/EDX)	1. Excellent utility to submicrometer levels due to use of electron beam. Provides improvement over optical microscopy methods, which use visible light and have lower limits in micrometer range. 2. Some automated counting capabilities available. 3. Particle identification *in situ.* 4. EDX provides elemental identification.	1. Particle identification of limited utility for organics and polymers, as EDX will usually only classify these materials according to their carbon content. Differentiation among chemicals is not provided. 2. Labor intensive for manual analysis. 3. Long instrument run-times even when on automated counting/analysis. 4. Analysis limited to small sample sizes.
Fourier-transform infrared (FTIR) microscopy	Identification of organics, polymers, and inorganics.	1. Not practical for particle counting. 2. Particles for identification must be harvested individually. 3. Labor intensive.
Raman microprobe	1. Identification of organics, polymers, and inorganics. 2. Offers capability for automated chemical characterization of individual particles.	Cannot analyze fluorescent materials, metals.
Light obscuration–Particle Counting	1. Particle counting capability from approx. 2 μm and larger. 2. Relatively simple technique. 3. Short analysis times.	1. Particles counted are not available for further analysis (i.e., identification).

may include identification, understanding of source, enumeration, and determination of batch-to-batch consistency, shape, and size. Further, we suggest that during development, the extent to which foreign particles are characterized be maintained at a level of detail that enables the likely source of the contamination to be identified and that provides a basis for the sampling and testing approach used in product quality control.

For development batches, enumeration of foreign particles should be done during stability studies. During development stability studies, if an upward trend in particle number is detected, then full characterization of particles can be performed. For these development batches, if no stability trend for the amount of foreign particles is present, it is reasonable to limit quality control of foreign particles to enumeration on release of commercial batches. If foreign particle levels are low and stable, we suggest that such enumeration assessments be phased out. However, if during routine quality control stability studies, unexpected results are observed, then further characterization information such as identity and origin of particles can be collected.

Because of the great variety of OINDPs, we recognize that the scheme for routine testing of commercial batches outlined above may not be appropriate for all OINDPs. For instance, for certain products, where foreign particles are eliminated as part of the manufacturing process, any foreign particles testing on release of commercial batches is neither useful nor meaningful.

In general, manufacturers should establish a thorough understanding of the manufacturing process, specifically areas that could contribute to foreign particle contamination. Ultimately, all data and information should be used to reduce the number of particles to a minimum and stable population.

Techniques for Use in Development and Routine Quality Control. Use of complementary techniques such as scanning electron microscopy/energy dispersive X-ray (SEM/EDX), Raman microscopy, and IR microscopy in the one-time characterization study on development batches, together with enumeration data, will provide good insight into the expected numbers and nature of the foreign particles. Although good for characterization, SEM/EDX, Raman microscopy, and IR microscopy are not well suited for quality control, because these methods are exceedingly time consuming and more applicable to research studies. (See also the discussion below regarding analyses of only minor sections of a surface that contains sample.)

Microscopic techniques are generally regarded as most applicable to larger particle size ranges. Furthermore, only a minor part of a sample can be covered in an analysis. As an example, counting particles on 1% of a surface covered with 1000 particles randomly distributed over the whole surface (assuming no edge effects) will, for statistical reasons, give a relative standard deviation of 32% in the found number, due only to this sampling procedure. Even with the restriction of looking only at small sample surfaces, microscopic methods are not well suited for quality control when analyzing samples at very low micrometer levels. The particles should not only be counted but also size-classed, which are procedures dependent on the subjective judgment of the analyst. (Note: Techniques such as stereology, used in geology and biology applications, may be considered for particle counting in OINDP.)

Light obscuration is a technique well suited for routine quality control testing because, of the discussed enumeration techniques, light obscuration is the only readily available technique that covers a relevant size range, that is, 2–400 μm. (Note that for measurements on delivered dose, 2 μm can be too low, because the pressure drop over a collection filter might be a limiting factor, not allowing use of filters with pore sizes that can catch particles of this size.) This high-throughput technique is the basis for USP methods for quality control of other, non-OINDP products. Light obscuration therefore may be considered as a method for routine quality control testing of foreign particles in OINDP.

Reasonable size ranges to include in acceptance criteria for quality control purposes could be 2–10 μm, 10–25 μm, and 25–100 μm (1). Furthermore, acceptance criteria on the numbers of foreign particles should be data driven with reasonable safety limits. As will be discussed below, an upper limit based on safety concerns could be derived from, for instance, the National Ambient Air Quality Standards (NAAQS). However, final specifications for particle size ranges and particle level limits would necessarily be drug product specific.

Assessing Safety of Foreign Particles in Specified Size Ranges

Introduction. Size range specifications and foreign particle levels are of primary importance in a coherent approach to control of particulate matter in drug product. The FDA guidance for nasal sprays recommends that for inhalation solutions, suspensions, and sprays, "the acceptance criteria should include limits for foreign particulate matter less than 10 micrometers (μm), greater than 10 μm, and greater than 25 μm."

Limits for foreign particle levels can be established based on factors related to particle safety, drug product quality, or both. In this section, we present considerations for developing upper limits for foreign particle levels based upon the *safety* of foreign particles in given size ranges. Such considerations can be included in approaches to developing safety controls for foreign particles in OINDPs. The drug product sponsor may further refine these limits through consideration of quality issues. Quality considerations are discussed above in Section II.B.3.

We emphasize that the approaches and considerations contained in this section *do not constitute a proposal* for a standard for particle levels. Rather, we only present these considerations as an *example* of how manufacturers might use available information for understanding particle level limits from a safety perspective.

Safety Considerations when Establishing Foreign Particle Limits.

Safety considerations for foreign particles ≤10 μm.

Inhaled particles with aerodynamic diameters ≤10 μm are sufficiently small to penetrate beyond the upper airways and deposit substantially in the lungs (i.e., airways and alveoli) (2,3). Therefore, these particles do pose safety concerns, and the implications of inhaling these particles should be considered during development studies. During drug product development, the safety of foreign particles ≤10 μm may be evaluated during toxicological studies on the formulation, provided that the lung surface of the test species receives an adequate dose of these foreign particles (note that it may be

problematic to achieve an adequate lung dose in animal species that are obligate nose breathers, e.g., the rat, as large fractions of particles ≤10 μm deposit in the nose) (4). Further, if any nonroutine foreign particles are detected, then attempts should be made, on a case-by-case basis, to characterize the material and conduct a risk assessment on the detected material.

The safety of foreign particles ≤10 μm may also be assessed based on comparison to the allowable exposures to ambient particles. The EPA has established National Ambient Air Quality Standards (NAAQS) that are considered to be protective of public health with an ample margin of safety even for sensitive subpopulations, such as children, the elderly, and those with disease (*National Ambient Air Quality Standards for Particulate Matter*, *Federal Register*, **62**, no. 138, 1997). The NAAQS for particles are mass-based standards without regard to the chemical composition of the particulate matter. This assumes that the particulate matter on a weight basis is of equal toxicity irrespective of the chemical form (i.e., it has the same potential to cause harm).

For particles with aerodynamic diameters ≤10 μm (PM_{10}), the NAAQS limit is 50 μg/m^3 (annual arithmetic mean). The EPA assumes that a person breathes 20 m^3 of air per day, so the total allowable mass for PM_{10} is 1 mg per day (*Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry,* EPA/600/8-90/066F, National Technical Information Service). Because patients may have substantial exposure to ambient particles, our proposed limit for OINDP foreign particulate matter ≤10 μm would need to be a small percentage (e.g., 1–5%) of the allowable PM_{10} mass so as not to appreciably increase a patient's exposure to particles from all sources. A foreign particles limit that is 1% of the allowable PM_{10} mass would be 10 μg/day for particles ≤10 μm/day. [Note that patients with lung disease generally breathe <20 m^3/day (5), so their daily exposure to ambient particles tends to be lower than for active healthy adults.]

To relate the number of foreign particles measured in a drug product to the proposed 10 μg/day limit, one must measure or estimate an aggregate particle density so that particle number can be converted into particle mass. To do this, one option is to use analytical methods (e.g., SEM/EDX and FTIR/Raman) to compute an aggregate mean density for all particles in each size range. Another option is to assume a worst-case maximum density for all foreign particles. In many cases, stainless steel (density = 8 g/cm^3) would be the most dense material that contacts a formulation during processing and filling, so it could be assumed that all foreign particles have a worst-case density of 8 g/cm^3. If the mass of the particles within a size range were found to be below the proposed limit, then no further chemical analysis would be necessary for safety purposes. Furthermore, if it can be shown that the formulation has no contact with stainless steel, then a more appropriate lower worst-case density could be used.

Table II shows the number of foreign particles ≤10 μm that would be allowable per day with a limit of 10 μg/day for various sizes and densities, assuming that all particles are of the stated size and density. It can be seen that if all the particles had a diameter of 1 μm and density of 1 g/cm^3, then up to 19 million particles per day would be allowed. Conversely, if all the particles were 10 μm in diameter with a worst-case density of 8 g/cm^3, up to 2400 particles per day could be allowed.

Table II. Number of Allowable Foreign Particles ≤10 μm per Day with a 10 μg/Day Limit[a]

Size (μm)	Density (g/cm^3)			
	1	2	4	8
0.5	1.5×10^8	7.6×10^7	3.8×10^7	1.9×10^7
1	1.9×10^7	9.6×10^6	4.8×10^6	2.4×10^6
2	2.4×10^6	1.2×10^6	6.0×10^5	3.0×10^5
3	7.1×10^5	3.5×10^5	1.8×10^5	8.8×10^4
4	3.0×10^5	1.5×10^5	7.5×10^5	3.7×10^4
6	8.8×10^4	4.4×10^4	2.2×10^4	1.1×10^4
8	3.7×10^4	1.9×10^4	9.3×10^3	4.7×10^3
10	1.9×10^4	9.6×10^3	4.8×10^3	2.4×10^3

[a] Assumes all the particles are of stated size and density.

The EPA has also established NAAQS for particles with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$), however the very conservative approach of taking 1% of the PM_{10} standard to give a limit of 10 μg/day exposure is adequately protective, and therefore we believe that a separate safety consideration of the $PM_{2.5}$ limit is not needed.

We do recognize that there exists significant evidence that particle toxicity is dependent on size, due to differences in particle surface area and solubility (1,6–13). It is also the case, however, that for ambient air, differences in actual chemical composition between smaller and larger particles adds a further safety concern that is not as relevant for inhalation drug products. In ambient air, particles ≤2.5 μm generally have a different origin and chemistry than particles >2.5 μm. Specifically, particles ≤2.5 μm in ambient air tend to be derived from coagulation of smaller particles from photochemical smog and gas-to-particle conversion as well as directly from combustion; in contrast, particles >2.5 μm tend to originate from mechanical dispersion and dust re-suspension (14). Because particles <2.5 μm have different chemical compositions than larger particles, they also have different toxicological profiles. Furthermore, the EPA created the $PM_{2.5}$ standard in large part due to the increased mortality observed in cities with higher average $PM_{2.5}$ levels (see NAAQS for Particulate Matter and Refs. 15, 16).

The situation is different for inhalation drug products because the sources and therefore chemical composition of foreign particles ≤2.5 μm and ≤10 μm are essentially the same. For instance, in an inhalation drug product, a particle ≤2.5 μm and a particle ≤10 μm can originate from the same source, such as a valve or a can (e.g., plastic or metal shaving), and therefore would have the same chemical composition. Thus, for inhalation drug products, differences in surface area and solubility would likely be the main size-related safety considerations. However, a 1% PM_{10} limit of 10 μg/day should be sufficiently conservative to account for these two factors and should not compromise patient safety.

Safety considerations for foreign particles >10 μm and >25 μm.

In general, inhaled particles with aerodynamic diameters >10 μm or >25 μm deposit predominately in the extrathoracic region of the respiratory tract (i.e., nose and oropharynx), being too large to penetrate substantially into the lungs (i.e., airways and alveoli) (2,3).

In view of this low lung exposure, the EPA has no NAAQS for particles >10 μm or >25 μm. If the particles are relatively insoluble, they will be cleared to the throat and swallowed, resulting in gastrointestinal exposure (3). If they are soluble, they will be absorbed from the extrathoracic region and GI tract, resulting in systemic exposure (3).

From a toxicological perspective, once particles are in the GI tract, they can be treated in the same way as ingested food. That is, there is no upper limit on the amount of particles that can be ingested; a toxicological concern would exist only if any of these ingested particles were intrinsically toxic. The same concern holds for soluble particles that would be absorbed from the extrathoracic region and GI tract. For a drug product, any particle-related toxicity should have been identified during the toxicology studies on the formulation. Thus, we think that it is inappropriate to establish an enumeration limit for foreign particles >10 or >25 μm based on *safety* concerns. Instead, for these larger particles, it is more appropriate to establish controls based on quality concerns. Approaches to quality control are discussed in Section II.B.3. Such an approach is consistent with the regulatory status of foreign particles in other drug products. For example, the USP has no limits for foreign particles in oral drug products (e.g., syrups or tablets), however, there are limits for solutions for injection (see below), as these particles could occlude blood vessels.

Comparison of a Given Particle Level Limit with Foreign Particles in Typical Drug Products. For a perspective on a particle level limit for foreign particles ≤10 μm, this limit can be compared with the particle levels in typical drug products such as MDIs (Table III). The levels of particles 2–10 μm in the two represented products are well below the proposed limit of 10 μg/day, and multiple doses of each product can be administered each day without exceeding the limit. (Note that this comparison omits the mass of foreign particles <2 μm in the drug products, whereas the proposed particle level limit for foreign particles ≤10 μm includes this mass. Because the relative mass of particles <2 μm is much less than the mass for particles in the range 2–10 μm, the actual number of doses per day would only be modestly lower than shown.)

We emphasize that a limit of 10 μg/day is set with the very conservative criterion that the foreign particle mass would comprise only 1% of the total allowable ambient mass. Table IV shows that the levels of particles between 2 and 10 μm in the two drug products are actually ≥100 times smaller than the daily allowable levels under the NAAQS for PM_{10}, even when assuming a maximum recommended dosing regimen of 16 doses/day. Thus, any modest exposures above the proposed limit should not compromise patient safety.

Table III. Comparison of a 10 μg/Day Limit with Foreign Particle Levels in Two Typical Drug Products (for Foreign Particles ≤10 μm)

Product	Product (μg/dose)[a]	Limit (μg/day)	Number of doses/day
A	0.50	10	20
B	0.63	10	16

[a] Particles between 2 and 10 μm.

Table IV. Comparison of Foreign Particle Levels in Two Drug Products with NAAQS for PM_{10}

Product	Product (μg/dose)[a]	Product daily dose (μg/day)[b]	NAAQS for PM_{10} (μg/day)	Safety factor[c]
A	0.50	8.0	1000	125
B	0.63	10	1000	100

[a] Particles between 2 and 10 μm.
[b] Assumes 16 doses (actuations) per day.
[c] Safety factor is NAAQS daily dose/product daily dose.

Establishment of Lower Size Limits

The choice of method or methods for counting, size measurement, and material identification is based on:

1) the need to analyze a statistically significant number of particles;
2) the analytical technology required to determine the identity of the particle;
3) the spatial resolution necessary to distinguish individual particles; and
4) the need to accomplish analysis in a time period that makes the information gained useful (see, e.g., Section II.A.2).

In choosing a strategy to analyze foreign particle materials, these sometimes conflicting needs will have to be balanced. For example, if complete chemical specificity is required, it may be necessary to analyze larger particles; if it is necessary to characterize smaller particles, it may be necessary to use an analytical technology with less chemical specificity.

Consequently, we support the concept of a specified lower size limit based on the properties of the materials involved and the technologies required.

If manufacturers desire, for safety purposes, an understanding of the mass of particles below the lower limit, which are not directly characterized, an upper limit mass could be estimated and compared to a mass per day limit. This estimate could be performed by determining the difference between the estimated mass of particles between the lower limit and 10 μm, and a given mass per day limit for particles less than 10 μm.

As an example, we might have a lower size limit for characterization of 1 μm, and a 10 μg/day mass limit. If the measured mass of foreign particles between 1 and 10 μm is 1 μg, the mass of particles <1 μm could be up to 9 μg and still be within a 10 μg/day limit. It is unlikely that a foreign particle size distribution having only 1 μg between 1 and 10 μm would have greater than 9 μg of particles of size less than 1 μm. For instance, because mass increases as the cube of the radius of a particle, it takes 1000 particles of 0.1 μm diameter to equal the mass of one particle of 1.0 μm diameter assuming the particles all have the same density. Therefore, it would require 9000 times as many particles between 1.0 μm and 0.1 μm to equal a mass of 9 μg. Consequently, it is highly likely that the total mass <10 μm would be <10 μg.

Standards for Other Dosage Forms

For contrast, we examine the standards established by the USP and documented in USP chapter <788> *Particulate*

Matter in Injections (USP 27–NF 22, 2004), which contains enumeration standards for foreign particles in injection dosage forms. The USP recommends that enumeration of foreign particles in injections be performed in two steps. First, injections should be tested via light obscuration, with a given set of limits. If the injection does not pass these limits, then the sample should be tested via microscopy, for which a different set of limits is recommended. The USP recommends enumeration of particles ≥10 μm and ≥25 μm.

For light obscuration, the USP limits are:

Injection	≥10 μm	≥25 μm
Small volume (≤100 ml)	6000 per container	600 per container
Large volume (>100 ml)	25 per ml	3 per ml

For microscopic analysis, the USP limits are:

Injection	≥10 μm	≥25 μm
Small volume (≤100 ml)	3000 per container	300 per container
Large volume (>100 ml)	12 per ml	2 per ml

It is generally understood that these limits for size and number are based on safety and quality considerations for exposure to foreign particles of human capillary and vein systems and on injection configurations. Because the route of administration for injections is fundamentally different than for that for OINDPs, safety considerations would necessarily be different for these dosage forms. The USP standards established for injectables are therefore not necessarily appropriate for OINDPs.

For OINDPs, appropriate particle size ranges and particle level limits based on quality control considerations should be drug product specific.

Review of Common Techniques and Methods

This section provides a summary of several common state-of-the-art techniques and methods used to assess foreign particles in OINDPs: optical microscopy, scanning electron microscopy/energy dispersive X-ray (SEM/EDX), Fourier-transfom infrared (FTIR) microscopy/Raman microprobe, and light obscuration. These are also outlined briefly in Table I. The following review is not exhaustive and is only meant to highlight those techniques that are currently in common use in the industry. We also provide several textbook and literature references that provide further information on the techniques and methods discussed (17–23).

The following general concepts can be considered for each of the techniques:

- Environment: Ideally, samples should be prepared in a particle-controlled environment e.g., Class 100 room or enclosure) to reduce the contribution of ambient particles. This contribution is certainly nontrivial especially in the lower particle size range (e.g., <10 μm). In the absence of this type of room, it is common to use a certified laminar flow hood of the same class rating.
- System suitability: A blank should be run under the same conditions as those intended for the sample analysis. This serves to ensure that the total particulate matter burden of the system components (e.g., filter, filter holder, solvent, etc.) do not contribute in a manner that could preclude an accurate determination of the foreign particles present. Obviously, every additional step in the preparation of the equipment, materials, and sample are potential contributors to the total particles.

Optical Microscopy

Principles of Operation. Particles from an inhaler are collected on a solid support and analyzed with suitable magnification using a microscope and reflected light. Typically, the solid support is a membrane filter with a pore size no greater than 1 μm. With proper lighting, contrast, and magnification, foreign particles can be routinely, if tediously, counted. Note that if the sample is acquired from the delivered dose, then it is often not possible to use an adequate flow rate if 1-μm filters are used.

If particle counting and analysis are performed using transmitted light, a glass microscope slide would be used as the solid support. The particles could also be analyzed using polarized light microscopy (PLM), which would give sample information not obtainable by reflected light microscopy (e.g., birefringence of the particles).

Sampling Considerations. In the case of MDI solutions, the membrane filter is viewed at suitable magnification until all foreign particles have been counted. Alternatively, the MDI could be actuated onto a glass slide and viewed using PLM.

When collecting a sample from either a DPI or an MDI suspension, the filter with the collected sample must be washed with a suitable solvent to remove all active pharmaceutical ingredients and excipient particles, as these will obscure the viewing field. The particles on the filter are counted using reflected light.

Whether using a membrane filter or glass slide, particles may be harvested for further examination using PLM, FTIR microscopy, Raman microprobe, or SEM/EDX as described below.

Equipment Considerations.

- The microscope may consist of a mono- or stereomicroscope with magnifications ranging from 2× to 1000×.
- Microscopes may be the simple "inspection" type used mainly for reflected light applications or advanced polarizing microscopes equipped with cross-polarization capability, various types of objectives, and filters.
- Photographic and/or digital imaging equipment for image archiving.

Frequency of Use by Industry. Optical microscopy is commonly used in both development and in quality control settings.

Scanning Electron Microscopy/Energy Dispersive X-ray

Principles of Operation. Unlike optical microscopy, in which a viewable image is the result of the interaction of a sample with visible light, SEM uses an electron beam, which scans the surface of the test article. This electron beam causes low-energy secondary electrons to be generated, some of

which escape the surface. The incident beam also causes X-rays to be generated. When an incident electron excites an inner, non-valence electron in the test article to a higher energy level, the excited electron will emit the additional energy as an X-ray photon and return to the unexcited state. The energy of the emitted photon is characteristic of the atom from which it came. The secondary electron emission and the X-ray photon emission provide information about both the surface of the object and the atomic number, or elemental identity, of the spot being analyzed.

The EDX analysis provides elemental identity information. Metal and other inorganic particles can usually be identified, and organic materials such as polymers, elastomers, and fibers also can be classified based on their carbon content. In some cases, where the organic material also contains elements such as chlorine or phosphorus, or inorganic materials such as talc, additional information useful for identification may be obtained. However, in general, detailed molecular information, for instance identification of polyethylene *versus* polypropylene, cannot be obtained.

Sampling Considerations. Sample preparation and precautions are similar to those for optical microscopy with two additional cautions:

- Samples must be electrically conductive and mounted on an electrically conductive support (e.g., a metal or carbon stub). If the particles are not conductive, they must be coated with a thin conductive layer. If elemental analysis, or EDX, will be performed, the effects of adding a conductive coating must be taken into account in the analysis.
- Because of the much greater resolution of the SEM relative to the optical microscope, lower size range particles, invisible with light microscopes, will be imaged by SEM. System suitability and system backgrounds for the SEM are vital to the interpretation of the sample data.

Equipment Considerations.

- The scanning electron microscope may be either the high vacuum type or the type that can operate at high near-atmospheric pressure.
- The EDX unit is an accessory to the scanning electron microscope and is available from a variety of sources including major manufacturers.
- The system requires sophisticated computer software for simultaneous SEM image capture and EDX analysis. Also available are automation routines to count and categorize particles by size, elemental composition, aspect ratio, and so forth.

Frequency of Use by Industry. SEM/EDX is commonly used in product development.

Fourier-Transform Infrared Microscopy and Raman Microprobe

Principles of Operation. These techniques use a combination of spectrometer, infrared or Raman, coupled to a suitable microscope to allow focusing of the source energy onto the smallest possible sample area. Depending on the species being analyzed, the exposure to the energy source gives rise to a unique spectral pattern consistent with the structure of the material (e.g., functional groups, electronic state, dipole, etc.).

Sampling Considerations. Typically, the effective lower limit in particle size is about 10 μm for FTIR microscopy and about 5 μm for Raman microprobe. Because glass slides are used in Raman, a sample may be collected directly onto a glass slide (e.g., one actuation from a MDI) and analyzed directly.

FTIR microscopy usually requires actuation onto a slide or filter, followed by harvesting of individual particles and placement of the particles onto salt plates (potassium bromide or barium fluoride). These particles may often be analyzed via Raman microprobe, SEM/EDX and optical microscopy as well, in separate tests.

A laminar flow hood is useful. Clean-room conditions are usually not necessary.

Equipment Considerations for FTIR Microscopy.

- FTIR spectrometer and microscope: For the FTIR microscope, the optics, except for the eyepieces, consist of highly polished reflective metallic surfaces and not glass. Glass is not used because of its very high absorbance in the infrared region, which would make it impossible to analyze the sample of interest.
- The FTIR spectrometer requires use of minimally absorbing support media such as salt plates made of potassium bromide or barium fluoride to support the sample in transmittance mode. In reflectance mode, metal-coated surfaces, such as aluminum or gold, are used.

Equipment Considerations for Raman Microprobe.

- Raman spectrometer and microscope: The Raman spectrometer is available with different laser sources, depending on the spectral range of interest, determined by the functional groups to be analyzed.
- The Raman usually operates in the visible region, where glass is transparent, so standard glass optics are used. Also, regular glass microscope slides may be used to support the sample.

Frequency of Use by Industry. FTIR and Raman microprobe are commonly used in product development.

Particle Counting by Light Obscuration

Principles of Operation. Particle counting by light obscuration uses a laser light source aimed at a detector through a sample volume. As a particle passes through the sample volume between the source and detector, it absorbs or scatters the laser light. The detector thus requires an additional voltage to maintain the same signal level. The larger the obscuring particle, the higher the voltage. Systems are calibrated using certified, traceable particle sizing standards by establishing a linearity plot of detector voltage *versus* known particle size.

This technique is purely a counting technique. Particles counted are not recoverable for analysis by microscopic or spectroscopic techniques.

The light absorbing and scattering properties of the uniform standards used for calibration may not match the properties of the contaminant particles, which may vary in shape and optical properties.

Sampling Considerations. Samples for analysis are prepared in precleaned containers or glassware in an appropriate liquid suspending medium or solvent where appropriate. For example, a dose or doses from an inhaler are actuated into an

appropriate container. The container is then filled with a measured volume of liquid. Aliquots of liquid are then drawn into the counter, and the number of particles are counted in the predefined size ranges.

Equipment Considerations.

- Volume sampler and particle counter: This unit is set to draw a predefined volume and to measure predefined size ranges (or channels). For example, the system can be set to draw 5 aliquots of 10 ml and to count the number of particles greater than 10 μm and greater than 25 μm.
- Sensor: This unit is selected based on its effective minimum and maximum size ranges.

Frequency of Use by Industry. Light obscuration techniques are commonly used in both development and in quality control settings.

CONCLUSIONS

IPAC-RS appreciates the guidance and recommendations put forth by FDA and recognizes that regulators, like industry, are still in the process of developing the most appropriate approaches to foreign particles testing. With this document, we hope to highlight key issues regarding this important topic and to contribute to the development of appropriate, effective, and practical guidance regarding foreign particles testing that will be of benefit to patients, regulators, and industry. The proposals of IPAC-RS are summarized below:

- Sampling should be tailored to the specific dosage form and manufacturing process. Specific recommendations for sampling are not addressed in this paper, but could be addressed in a USP test chapter.
- Full characterization of foreign particles (which may include identification, understanding of source, enumeration, and determination of batch-to-batch consistency, shape, and size) should be conducted during development studies in order to develop strategies for control of product manufacture. Full characterization need not be performed for routine quality control on commercial batches during release or stability testing. For those products where foreign particles testing during routine quality control will be performed, testing should be limited to enumeration.

A specific strategy might be the following:

During development, the extent to which foreign particles are characterized should be maintained at a level of detail that enables the likely source of the contamination to be identified and that provides a basis for the sampling and testing approach used in product quality control.

For development batches, enumeration of foreign particles should be done during stability studies.

For development batches, if no stability trends for the amount of foreign particles are present, it is reasonable to limit quality control of foreign particles to enumeration on release of commercial batches. If foreign particle levels are low and stable, such enumeration assessments should be phased out.

- For OINDPs, the U.S. EPA National Ambient Air Quality Standard (NAAQS) for particulate matter ≤10 μm may be considered the relevant particle standard. Safety considerations based on this EPA standard can be used to develop an upper limit for levels of foreign particles ≤10 μm. We believe that it is inappropriate to develop particle level limits for foreign particles >10 μm or >25 μm based on *safety* concerns. Instead, for these larger particles, it is more appropriate to establish enumeration controls based on quality concerns.
- Specified lower size limits should be established, based on the properties of the materials involved and the technologies required.
- Standards for nasal products should be less stringent than those for inhalation products. For instance, particle level limits can be based on quality considerations only.
- Specifications for particle size ranges and particle level limits based on quality control considerations should be drug product specific.
- USP standards established for injectables are not necessarily appropriate for OINDPs.

IPAC-RS believes that public discussion and achievement of consensus approaches will significantly contribute to FDA's current vision for implementing efficient risk management in both industrial and regulatory settings, as outlined in the August 2003 *Food and Drug Administration's Strategic Action Plan*. This is especially true in situations where efficient risk management "requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry" (*The Food and Drug Administration's Strategic Action Plan, Protecting and Advancing America's Health: Responding to new challenges and opportunities*, 2003, p. 9). Additionally, such discussion and consensus-based approaches will support more efficient development and review processes for production of safe and efficacious new medicines for the public.

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