Pharmaceutical Research, Vol. 24, No. 3, March 2007 (© 2007)
DOI: 10.1007/s11095-006-9172-5

Commentary

Best Practices for Managing Quality and Safety of Foreign Particles in Orally Inhaled and Nasal Drug Products, and an Evaluation of Clinical Relevance

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Received July 4, 2006; accepted September 26, 2006; published online January 25, 2007

INTRODUCTION

In a previous paper, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) outlined the progression of regulatory recommendations for foreign particles in orally inhaled and nasal drug products (OINDP), techniques for evaluating foreign particles, and proposed approaches for developing safety thresholds for such particles (1). In this paper we expand on some of the key ideas proposed in that first article. We present here best practices for managing quality and safety of OINDP with respect to foreign particles, based on quality by design concepts, we provide an update on current assessment techniques, and finally we examine the clinical relevance of some representative OINDP foreign particles.

QUALITY BY DESIGN

Industry is specifically interested in effective and efficient ways to manage the quality and safety of OINDP with respect to foreign particles. One way to achieve this is through a "quality by design" approach proposing that controls on the drug product, device and formulation components, manufacturing processes for drug products, and safety assessments of foreign particles should encourage incorporation of quality into the drug product through rational design of drug product development and manufacturing processes. In taking this approach the manufacturer can identify and ameliorate specific areas that pose the highest risk of contributing foreign particle mass to the drug product delivered dose, which is the key patient exposure factor. Such an approach allows the manufacturer to design quality into the product rather than testing quality into the product. The FDA is encouraging pharmaceutical manufacturers to adopt this quality by design approach to pharmaceutical development (for instance, see Pharmaceutical GMPs for the 21st Century—A Risk Based Approach, Final Report, FDA, 2004).

Publicly available guidelines (for example, ICH Q8, Pharmaceutical Development, http://www.ich.org/LOB/media/MEDIA1707.pdf) and recent public presentations by FDA have provided general descriptions of the quality by design concept. For example, FDA presentations have noted that quality by design should include developing a scientific understanding of critical process and product attributes, designing controls and testing based on the limits of scientific understanding during development, and utilizing knowledge gained over the product's lifecycle to operate in an environment of continuous improvement (J. Woodcock, AAPS Workshop on Pharmaceutical Quality in the 21st Century, October 2005, http://www.aapspharmaceutica.com/workshops/PharmaceuticalQuality100505/woodcock.pdf).

These general quality by design concepts can be translated into specific practices for management of foreign particles, such as provision of clean environments throughout the production chain, careful enumeration and characterization of foreign particles during development studies, and control and understanding of production processes and materials manufactured in-house and/or from suppliers. In some cases, application of these practices could lead to less frequent testing of foreign particles in routine production. We provide, in the following sections, a more detailed description of these practices.

CONCEPTS FOR MANAGING QUALITY OF FOREIGN PARTICLES

Control of foreign particles in OINDP can be accomplished through a comprehensive program that involves enumerating and characterizing the foreign particles, con-

The members of IPAC-RS are Aradigm, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kos, Nektar Therapeutics, Novartis, Novo Nordisk, Pfizer, sanofi aventis, Schering-Plough, and Teva Specialty Pharmaceuticals.

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ducting safety evaluation of foreign particles, identifying the potential sources of foreign particles, eliminating or minimizing the sources of foreign particles, and establishing appropriate specifications for routine control (the ICH definition of specification is used here: "A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use." http://www.ich.org/MediaServer.jser?@_ID=430&@_MODE=GLB). The flowchart in Fig. 1 provides a high level description of this approach in the pharmaceutical development process for OINDP.

The process described in Fig. 1 is divided into two main sections: evaluation and control of foreign particles during development studies and evaluation and control of foreign particles through routine quality control. We describe the key elements of the flowchart in more detail in the following sections.

Development

Information on foreign particles in OINDP is best obtained during development studies. This information can then be used to ensure appropriate control over production of drug product. In development studies, primary attention should be given to enumeration of the foreign particles within certain size ranges, characterization of the foreign particles (which may include identification and determination of size and shape, and batch to batch consistency), determination of the source of the characterized foreign particle, minimization or elimination of the source(s) of the foreign particle, and development of action limits (or acceptance criteria) for the foreign particle burden.

In development, it is important for the drug product manufacturer to determine the identity of foreign particles, i.e., speciation, and number of foreign particles within certain size ranges. Identification should be performed to the extent that allows the source of the particles to be determined. Identity and enumeration are also performed so that manufacturers may consider safety assessments and specifications during the development process. Timely evaluation of foreign particles is critical in a risk-based approach as it allows the manufacturer to anticipate potential sources of foreign particles contamination, determine the potential effects of the contamination, take steps to mitigate the cause, and create an overall development and manufacturing process that will decrease the risk of a high foreign particles burden in the final commercial drug product.

Foreign particles can be derived from a number of sources including the drug product, the active pharmaceutical ingredient (API), excipient, the container/closure system components, delivery devices, elements of the drug product manufacturing process, and processing environment.

In many cases, the drug product is the primary source of foreign particles, as the use of the drug product may actually produce these particles. In these cases, specifications on foreign particles are necessary for drug product only, and would not normally be required for API and/or excipient. Specifications should include methods and action limits or acceptance criteria that control the number of foreign particles within defined size ranges. Preliminary (or interim) action limits or acceptance criteria may be established during early stages of development, based on development process, scale-up and stability batches.

In the following sections we describe the key steps in development—characterization, enumeration, sourcing, minimization of source, and specification setting—with respect to the sources of foreign particles, as outlined in the flowchart. We also summarize typical methods used in foreign particles evaluation.

Drug Product

Initial investigations on foreign particles should focus on drug product since the drug product may contain foreign particles from all potential sources at the time of manufacture (see "Sources of Foreign Particles and Changes in Foreign Particle Profile" below for discussion of foreign particle sources). The emitted dose should be evaluated for foreign particles since this is the entity to which the patient would be exposed (although alternative sampling approaches can be adopted when they can be justified). Samples should be carefully prepared to avoid environmental contamination, and testing should be performed with suitable controls. Evaluation may be performed on process development batches, scale-up batches, and development stability batches. Process development and scale-up batches should be subject to enumeration and characterization of foreign particles within selected size ranges in order to establish a baseline of information about the number, nature, and source of the particles.

It is important to be aware of certain assumptions regarding enumeration and characterization of foreign particles. The USP General Test Chapter <788> states "Particulate matter consists of mobile, randomly sourced, extraneous substances..." It is important, therefore, to understand that unlike testing for assay, for example, there is no ab initio expectation of the number of foreign particles per dose or unit. The "expected" number of foreign particles is a value derived as the result of both intensive and extensive batch testing. This value, in turn, is then used to set the specification (see "Specifications" below).

The number of foreign particles can be linked to change in particulate identity. For example, in testing for foreign particles there is a fundamental assumption that the species observed during method development, validation, and multi-batch analyses vary within known limits per dose, per unit, per batch, etc. Were this not the case, then the only adequate approach would be 100% testing, which is not realistic. In essence, if the numbers of particles observed are constant, it is not likely that the species have changed.

After characterization, the source of the foreign particles can be determined. Those sources may include the drug product manufacturing process, or API, excipient or device and container/closure system components. Safety assessments can also be conducted at this stage. Particles of safety concern should be minimized or eliminated. Preliminary action limits (or acceptance criteria) can then be developed.

Unlike APIs and excipients, delivery system components may change with time, and, therefore it must be shown that foreign particle levels remain within known and acceptable

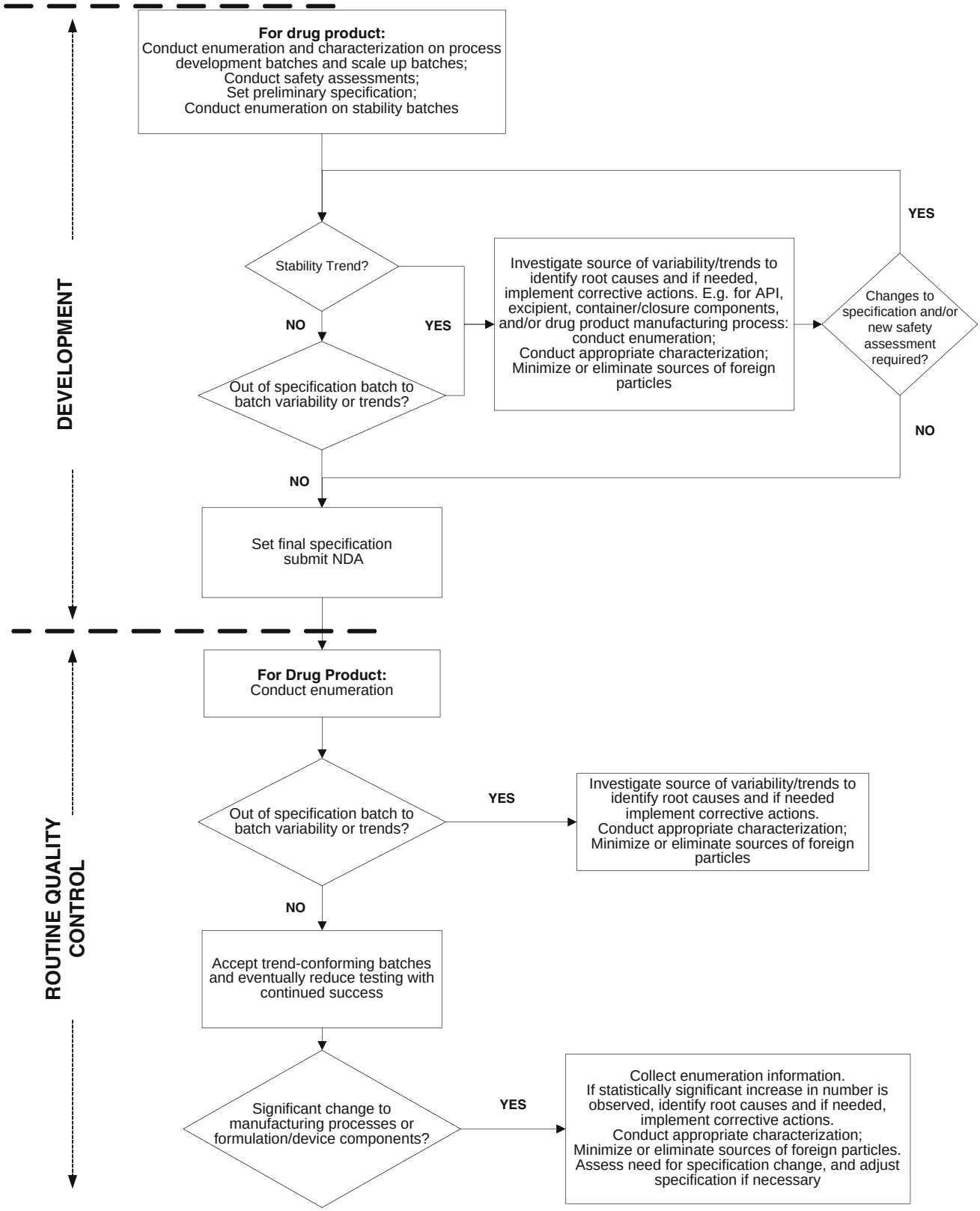

Fig. 1. Control of foreign particles in drug product development and manufacture

limits upon component aging, use or contact with drug product throughout shelf-life. To capture these different aspects of component integrity, testing should be performed on the final drug product during development stability studies, e.g., pivotal stability batches. Stability trends such as increases in foreign particles, or out of specification results for foreign particle number among batches should trigger an investigation into the root causes of the trend/variability.

Characterization of the particles may be performed in order to identify the particle sources. Once the sources of foreign particles have been identified and confirmed, the drug product manufacturer should work to eliminate, if possible, or minimize the root cause of the foreign particles. When foreign particles have been evaluated, their sources determined, and then eliminated or minimized, and safety considered, final specifications may then be developed.

Note that if all basic systems, e.g., API, excipient, components, manufacturing process, remain constant, and if the number of foreign particles found remains within known and acceptable limits in-unit, in-batch, across-batch, or through stability, then it is highly unlikely that characterization will yield significantly different results from sample to sample. Therefore, characterization should be performed only at the initial stability time point, and unless there is a statistically significant upward trend in number of particles, the drug product should be tested throughout the stability study period for particle enumeration only.

Other risk-based approaches to managing foreign particles are also appropriate. For instance, the drug product manufacturer may choose to evaluate the API, excipient, and container/closure system components for foreign particles in the development process, as soon as these entities become available to the manufacturer. Enumeration and characterization of foreign particles found from these sources may be accomplished at this stage before or in parallel to testing of the drug product. This approach is beneficial because it provides information on potential sources of foreign particles during the development process.

Sources of Foreign Particles and Changes in Foreign Particle Profile

A complete understanding of potential sources of foreign particles and how they may contribute to the foreign particle burden is important when applying a quality by design approach to foreign particles control. For example, the drug product manufacturing process should be thoroughly understood so that stages posing most risk of contributing foreign particulate matter can be easily identified and monitored. For a DPI, if the API and excipient are co-dissolved, filtered, and then spray dried, foreign particle testing (both characterization and enumeration) can be performed after the spray drying step rather than on the incoming excipients, as it is after the filtering and during the spray drying that more significant exposure to foreign particles may occur.

Conversely, for a formulation where the API is produced by jet-milling or other energetic comminution process and then is blended with a powder carrier excipient in a tumbling mixer to give the final formulation, more characterization is warranted on the API's contribution to the total particulate burden, as foreign particles may be introduced to the milled API during the API processing steps.

Likewise, the drug product manufacturer should also understand the manufacturing process for the API, excipients and container/closure system components. Major manufacturing or processing changes in the API, excipient, or components, or a change in the source of either the API or excipient could require enumeration and in some instances characterization.

Foreign particles evaluation on API may be performed on an aliquot of sample by dissolving it in a suitable, filtered solvent, and then analyzing the residual particles using appropriate methods. The results of this testing are then used to assess the overall quality of the drug substances in several ways including extrapolation to the number of foreign particles per dose, determination of the number of particles in different particle size ranges, and characterization of the particles.

Testing can be performed early in the development stage on materials that are representative of those that will be used in the manufacturing process, e.g., approved synthesis and micronization processes, approved sources for API or IPI. Since the nature and number of foreign particles associated with API and IPI do not change on stability, further testing on stability is not necessary.

If APIs and excipients are manufactured by outside vendors then such significant manufacturing changes should be reported to the drug product manufacturer and addressed appropriately as stipulated in agreements between supplier and drug product manufacturer. When the API or excipient is obtained from outside sources, every attempt should be made to include the supplier in the control process, e.g., the supplier should communicate changes in the quality system which might have an impact on foreign particle mass.

For the container/closure system components, it is important to evaluate the identity of all materials using the same techniques as would be used to identify small foreign particles. For example, analysis may be performed on all polymeric components to establish a library that serves as the basis for comparison when examining small polymeric particles in the drug product. In the end, these data would provide information about both the identity and source of foreign particles.

A similar approach can be taken in analyzing all components that are part of, or in contact with the dose stream, e.g., metal container, foil backing, etc. Testing can be performed as soon as components are identified as candidates for use in the product. The suppliers of these components provide much of the necessary information, leaving the drug product manufacturer to perform only those analyses needed to establish an analytical database. Ideally, pharmaceutical manufacturers will establish a change control agreement with suppliers to relate to the pharmaceutical company issues such as production changes to aid in assessing any potential impact of those changes to the foreign particles profile.

Foreign particles in components can be minimized by manufacture in clean environments at supplier facilities. The extent to which foreign particles are present in the individual or assembled components may be certified by the supplier using validated testing methods and documented. In lieu of such testing and/or documentation from the supplier, testing of representative samples should be performed during development by the pharmaceutical manufacturer.

Unlike APIs and IPIs, delivery system components may change with time, and, therefore must be shown to maintain their integrity throughout shelf-life. That is, the components must be shown to not degrade due to age, use or contact with drug product throughout the shelf-life. To capture these different aspects of component integrity, testing should be

performed on the final drug product during development stability studies.

Throughout development studies, the manufacturer may want to develop a detailed database containing information about sources and types of foreign particles based on supplier information and information obtained from the manufacturer's studies. This informational database will contribute significantly to establishing rigorous control of foreign particles from the beginning to end of the development process. For example, a significant advantage obtained from this inventory of sources and types of foreign particles will be evident when, and if, the number of particles should trend upwards during quality control testing. Employing infrared analysis and X-ray microanalysis, an analyst can quickly and confidently determine whether the increased number of particles is derived from drug product components or from extraneous sources, narrowing the search for sources and speeding resolution of the problem.

If a significant increase in the number of foreign particles is observed then the potential source(s) of this increase should be identified and the causes of the increase in the number of particles minimized or eliminated. As noted, the sources of foreign particles may include the drug product manufacturing process, API, excipients, or container/closure system components.

Specifications

A preliminary or interim specification can be established in development studies, based on available data and safety considerations, and would be refined toward the end of development studies. Whereas the approach for setting specifications may be slightly different from company to company, this process is generally based on a rigorous statistical analysis of both process batch history data and stability batch data.

Action limits or acceptance criteria for foreign particles should include criteria for the number of particles within particular size ranges. The limits, i.e., lower and upper bounds, of size ranges can be developed on a case-by-case basis by the manufacturer based on:

- Safety assessments of the foreign particles
- Stability data
- Batch data
- Statistical controls
- Capability of analytical methods

A lower, practical particle size limit should be established. Given current technique/method capabilities, a 2 μm lower limit may be achievable, depending on sampling constraints. Below 2 um, however, the uncertainty in detecting and identifying particles increases drastically due to much higher background levels. Additionally, the isolation of particles, i.e, collection of meaningful specimens presents a more significant technical challenge.

Examples of size ranges for foreign particles in inhalation products are 2–10, 10–25 and 25–100 μm. For nasal products, size ranges such as 2–20 μm and greater than 20 μm may be more appropriate.

Batch data can be derived from extensive testing of development stability batches, process batches and scale-up batches. Note that the number (or concentration) of foreign particles 10 μm in size or smaller, can be controlled based on safety considerations as well as quality considerations. The rationale for applying safety considerations to particles 10 μm or smaller, is based on their "inhalability" as discussed previously (1). The safety and clinical implications of commonly found foreign particles in OINDP are addressed in "Concepts for Managing Safety of Foreign Particles".

Techniques/Methods

Currently there are a number of different types of techniques that can be used to characterize and enumerate foreign particles in OINDP. Control of foreign particles will in part be dependent on the capabilities and limitations of these techniques. Application of techniques for evaluating foreign particles in OINDP may be found in the literature (1–4). Methods for characterization and enumeration of foreign particles in the APIs, excipients, components and final drug product should be validated according to ICH principles. These validated methods can then be used in routine quality control of foreign particles in the API, excipient, components and drug product.

In our previous paper, we described some commonly used techniques and their capabilities and limitations. Since that time, no new, groundbreaking analytical techniques for foreign particles testing have truly surfaced but recent technological advances and innovations brought to instrumentation might move some of these techniques from an already well-established, traditional "research and development" ground closer to the routine "quality control" testing floor. The introduction of automation or, in some cases, an increased level in automation and computer-control, increased accuracy and precision of motorized stage movement, tighter integration of complementary techniques, e.g., particle detection, imaging and image analysis, chemical identification, are among the most prominent technological advances that contributed to the development of new generations of analytical instruments. The new and improved instrumentation provided the opportunity to re-evaluate some of the analytical techniques in terms of the balance of "capabilities vs. limitations." Where previously identified limitations were substantially reduced by technological advances in instrumentation, there exists the possibility of expanding the area of applicability of some of the techniques from research and development to routine drug product release testing.

Technological advances applied to instrumentation were more evident with electron beam microanalysis and Raman microprobe than with any other analytical techniques used for foreign particles testing, e.g., light obscuration, particle counting. Perhaps one of the most notable improvements with these techniques derives from automation which, when coupled with appropriate methodology and testing procedures, may substantially reduce the duration of analysis (5). The drastic reduction of analysis time was particularly evident with the automated electron beam microanalysis when particle enumeration and size distribution were performed (5).

Even with the benefits of new instrumentation and technological advances, none of these techniques is yet

sufficiently robust and practical enough to allow complete, one-step characterization of foreign particles in OINDP, i.e., enumeration and size distribution, and chemical identification and classification of particles. Undoubtedly, one of the major limitations for chemical identification and classification of particles is the diversity of chemical species, e.g., metals, inorganics, organics and polymers, such that no analytical technique (taken alone and regardless whether manual or automated) is currently capable of providing adequate information over the whole chemical range of foreign particles that may be present in OINDP. From this perspective, chemical identification and classification of particles remain a critical component of any automated technique in terms of resolution, accuracy of detection, and duration of analysis. Due to these serious limitations, chemical identification and classification of particles, although readily available on both automated electron beam microanalysis and Raman microprobe techniques, can only be used for investigational purposes, e.g., when particle burden is out-of-trend or out-of-specification, but certainly not for routine quality control and drug product release.

Consequently, in spite of some real technological improvements, neither electron beam microanalysis nor Raman microprobe technique, taken alone or in combination, should be considered as the ultimate solution for foreign particles testing in OINDP. In the overall control strategy of foreign particles in OINDP, the selection of analytical technique(s) for routine quality control and drug product release remains a risk-based approach requiring sound knowledge of foreign particle profile, i.e., burden, chemical nature, and toxicological relevance.

Whereas detailed technical discussion of the new capabilities of analytical techniques is understandably beyond the scope of this paper, some discussion related to the choice of appropriate technique(s) is germane, since some of these improved analytical techniques are in use already. In principle, these technologies combine either electron or light microscopic imaging with particle sizing and enumeration, and they incorporate some type of technology to provide chemical characterization of individual particles. In one type of analysis, elemental composition of particles is provided by X-ray microanalysis. This approach is most useful when metallic or other inorganic materials are the major component of contaminants. The other approach, which is most useful for organic materials, utilizes Raman scattering, IR visible, or UV spectroscopy, either alone or in some combination, to provide molecular analysis of organic materials.

Both approaches use various degrees of automation to accomplish particle detection and operation of the instrument, so that they are not labor intensive. The major concern with these methods is the reliability of the imaging mode employed to detect particles and distinguish individual particles from the substrate on which they are captured, i.e., the possibility of false positive identifications, or missing particles (false negatives) that are actually present.

These newer technologies are most useful when the types of contamination are already known, and both may be employed when the contaminant particles are a mix of organic and inorganic materials. Because a large number of particles can be analyzed relatively rapidly using these methods, and as a consequence, such sources of error as operator fatigue can be minimized, the statistical confidence in the results can be high. However, the advantage of having a large number of individual analyses comes at the cost of organizing and interpreting the large number of individual analyses associated with each sample. Thus, it is most likely that these will be used during development to identify sources of contaminant particles. If used in manufacturing, they will probably be used in combination with very rapid sizing/enumeration technologies such as light obscuration to identify the causes of trends or increases in the number of particles.

Routine Quality Control

For the API, excipient and delivery system components, foreign particles testing in routine quality control would not be required unless there is a major change in a manufacturing process for any of these which, upon scientific review, are deemed likely to change the overall quality of the materials.

For commercial batches of drug product, testing during routine quality control should consist of particle enumeration only. Out of trend or out of specification results among batches would trigger an investigation to determine the origin of the change. This investigation may ultimately include characterization studies if unusual results are observed. For instance, the investigation should evaluate in a step-wise fashion, the potential sources of a trend, which might conclude that the source is due to between-analyst variability or environmental factors. If all other lab-related sources of trending are eliminated, then characterization studies may be appropriate.

As another example, a manufacturing process or component may undergo a change (for instance, the manufacturer switches to a different primary packaging component or primary container/closure component supplier). In this case, the manufacturer would collect enumeration information, and if a significant increase in foreign particle number is detected, then an investigation into the sources of the increase is conducted, which may potentially include characterization studies. If no significant increase in foreign particle number is noted, then no further investigations are necessary.

If stability data generated in development demonstrate that levels of particulate matter do not increase with time, this information can be sufficient to justify testing of foreign particles only on batch release (Guidance for Industry, Nasal Spray, Inhalation Solution, Suspension and Spray Drug Products, Chemistry Manufacturing and Controls Documentation, 2002, FDA). Thus, annual stability commitment batches need not be tested for foreign particles if there are no stability trends observed during development stability testing. If routine control data shows that testing every batch is not value-added, then less frequent testing may be appropriate, e.g., testing every tenth batch on release.

CONCEPTS FOR MANAGING SAFETY OF FOREIGN PARTICLES

Safety Limits for Foreign Particles

In our previous paper, we described how manufacturers might develop a strategy for determining size limits within

which foreign particle number could be controlled, and for determining safe levels of foreign particles within those limits (1).

In that paper we noted that safety considerations should primarily be applied to particles with aerodynamic diameter less than or equal to 10 μm. Particles having larger than 10 μm aerodynamic diameter, in general, would not reach the lungs, and therefore control of the levels of these particles can be based primarily on quality considerations. We then described how a small percentage, e.g., 1–5%, of the National Ambient Air Quality Standard (NAAQS) for particulate matter having aerodynamic diameter less than or equal to 10 μm (PM_{10}), could be used as a safety limit on the concentration of foreign particles in this size range. This small percentage was chosen so that there would be negligible increase in the overall number of particles that an individual would inhale (including particle from the ambient air).

Note that the NAAQS was established to be protective of sensitive populations, e.g., those affected by asthma or other lung diseases, over the lifetime of those populations. The NAAQS for PM_{10} is 50 μg/m^3. Applying EPA breathing volume assumptions gives 50 μg/day as 5% of the NAAQS. To relate this total daily exposure to amount of foreign particles in a drug product, an aggregate density of particles must be established, and we suggested that this can be measured or estimated using analytical techniques or assuming a worst case maximum density for all foreign particles, e.g., stainless steel at 8 g/cm^3. The number of allowed foreign particles per day using a 50 μg/day limit, for particles of various sizes, is shown in Table I.

Table I shows the number of foreign particles between 2 and 10 μm that would be allowable per day with a limit of 50 μg/day for various particle diameters and densities, assuming that all particles are of the stated diameter and density. If all the particles had a diameter of 2 μm and density of 1 g/cm^3 then up to 12,000,000 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 12,000 particles per day could be allowed.

We looked at the results of applying the limit concept to two actual products and found that the concentration of particles between sizes of 2–10 μm are more than 100 times less than the daily concentration of inhaled particulate matter allowed by the NAAQS. We used these examples to demonstrate how the limit could be used in an overall strategy for managing foreign particles in OINDP, and that the limit is a reasonable starting point for developing safety limits on concentrations of inhaled foreign particles that are adequately protective of sensitive populations using OINDP in long-term, chronic applications.

In managing the safety of foreign particles in OINDP, it is also useful to understand their potential clinical relevance and how a 5% limit can be combined with clinical assessments to provide an overall safety approach. We surveyed IPAC-RS companies to develop a list of typical foreign particulate materials found in OINDP. This list is limited primarily to the identity of foreign particles. We then looked at data and information from the current literature to examine the clinical ramifications of inhalation of these materials.

Clinical Relevance of Foreign Particles

The clinical ramifications of foreign particles in orally inhaled and nasal drug products (OINDP) will depend upon the (chemical) nature of the particle, the site of deposition, and the body's, i.e., "host," response to the foreign material. The physical properties of the aerosolized particles that affect deposition include particle size, shape and density. Particles with an aerodynamic diameter greater than 10 μm are either effectively filtered by the nasal structures, and/or oropharynx or larger airways, via inertial impaction (6). These larger particles that are trapped in the naso-oropharynx are subsequently swallowed or expectorated. On the other hand, it is the smaller particles, particularly those in the "respirable" range, i.e., <5 μm, that have the potential for eliciting lung disease if inhaled in sufficiently high concentrations. In the discussion that follows, we elaborate on the clinical manifestations and implications of exposure limits for selected materials that heretofore have been identified as having the potential to exist as foreign particles in OINDP. These materials are listed in Table II and are based on a

Table I. Number of Allowable Foreign Particles ≤ 10 μm per day with a 50 μg/day Limit

	Density, g/cm^3			
Diameter, μm	1	2	4	8
2	1.2×10^7	6×10^6	3×10^6	1.5×10^6
3	3.5×10^6	1.8×10^6	8.8×10^5	4.4×10^5
4	1.5×10^6	7.5×10^5	3.7×10^5	1.9×10^5
6	4.4×10^5	2.2×10^5	1.1×10^5	5.5×10^4
8	1.9×10^5	9.3×10^4	4.7×10^4	2.3×10^4
10	9.6×10^4	4.8×10^4	2.4×10^4	1.2×10^4

Assumes all the particles are spheres of the stated diameter and density
It is important to note that 10 μm particles with a density greater than 1 g /cm^3 may not be inhalable since the aerodynamic diameter will be larger than the commonly accepted 10 μm upper limit. However, the approach used here is a worst case scenario regarding inhalable mass, to be compared with a fraction of the NAAQS PM10 for foreign particles, and thus we have chosen not to correct for the effect of density on the diameter. When a sponsor considers it appropriate, a conversion of the Stokes diameter to aerodynamic diameter is possible, using the identity. Aerodynamic diameter is equal to the Stokes diameter multiplied by the square root of density.

Table II. Materials Potentially Found as Foreign Particles in OINDP, Based on Survey of IPAC-RS Companies

Acrylonitrile-butadiene-styrene	Aluminum
Bromobutyl rubber	Polytetrafluoroethylene
Glass	Iron
Polychlorotriflouroethylene	Paper/cardboard/cellulose
Polyamide (nylon)	Polyacetal
Polycarbonate	Polybutylene terephthalate
Polyethylene	Polyester
Polyoxymethylene	Polyimide
Polystyrene	Polypropylene
Stainless steel	Skin cells
Talc	Transparent synthetic fibers

survey of IPAC-RS companies. This discussion of this "limited list," should therefore be viewed as "points to consider" when attempting to determine acceptable safety levels of foreign particles in OINDP.

Materials that may produce foreign particles could theoretically elicit an immunologic response, e.g., nickel (as a component of stainless steel); non-immunologic response, e.g., polyolefins, talc, aluminum; or be essentially "clinically" inert. Again, the important determining factor is whether the particles are inhaled in a sufficiently high concentration. For example, polyolefins such as polypropylene and polyethylene and other synthetic fibers, e.g., nylon, when inhaled as microfibers or "flock," have been reported to induce an interstitial lung disease, termed "flock worker's lung." For example, in a study by Atis *et al.* that examined the respiratory effects of occupational polypropylene flock exposure, 20–26% of exposed workers demonstrated abnormalities in lung function compared with 4.4% of unexposed controls (7). However, total inhalable and respirable, i.e., <5 μm particle diameter, dust concentrations in the flocking department were 4.4 mg/m^3 and <0.2 mg/m^3, respectively, (mean±SD fiber diameter was 6.9±2.1 μm). Based on a daily inhaled volume of 10 m^3 for occupational exposures, these dust concentrations equate to 44 mg/day and <2 mg/day (Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Protection Agency. EPA/600/8-90/066F. National Technical Information Service, Springfield, VA. 1994). If the foreign particle exposure limit for OINDP is set to 5% of the NAAQS allowable PM_{10} mass limit (50 μg/m^3), this translates to 50 μg/day; a value well below that encountered in these occupationally exposed individuals.

Similarly, talc, which is a hydrated magnesium silicate, may lead to pulmonary disease in highly exposed workers in occupational settings and non-occupational settings, e.g., obsessive inhalation of commercial talcum powder. However, clinical and pathological evidence suggest that talc itself does not induce pulmonary fibrosis. In fact, the majority, if not all of the functionally and radiographically significant pulmonary abnormalities associated with talc are caused by other contaminating substances, e.g., asbestos and silica (8). Therefore, considering the intrinsic low likelihood of inducing impairment following any degree of inhaled talc exposure, the IPAC-RS approach to base the total daily intake upon a small percentage of the NAAQS, e.g., 5%, should further minimize any potential risk.

Workers exposed to dust containing a high concentration of iron, usually in the form of ferric oxide (Fe_2O_3), may develop a condition called *siderosis*. Pathologically, one only finds iron-laden macrophages in the peribronchovascular interstitium and alveolar air spaces. However, this condition is felt to be unassociated with pulmonary fibrosis or functional impairment (9,10). This is in contrast to the condition *silicosiderosis*, which results when the iron is admixed with substantial quantities of silica. It is this latter condition that can lead to significant pulmonary fibrosis and disability. Thus, considering the intrinsic low likelihood of inducing impairment following any degree of inhaled iron exposure, the IPAC-RS approach to base the total daily intake upon a small percentage of the NAAQS should further minimize any potential risk.

On the other hand, rare reports of pulmonary fibrosis following high exposure to aluminum dust and its oxides exist in the early medical literature. However, Gilks and Churg used electron optical analysis on lung tissue to quantify the number of particles in an aluminum pot worker who died from respiratory insufficiency; the number of fibrous and nonfibrous aluminum particles per gram of lung tissue were 1,000-fold greater than in the general population (11). Moreover, Eklund and associates measured pulmonary function and performed bronchoalveolar lavage (BAL) in 14 aluminum pot room workers (12). The workers had a mean duration of employment of 12.9±9.0 years with a mean exposure (8 h samples) of 1.77 mg/m^3 (range 0.49–4.50). The workers all had normal chest X-rays and normal vital capacity, total lung capacity and diffusing capacity. Similarly, there was no evidence of an alveolitis on bronchoalveolar lavage. Thus, the IPAC-RS approach to base the total daily intake upon a small percentage of the NAAQS should further minimize any potential risk should aluminum foreign particles exist in OINDP.

In contrast, disease has been recognized with nickel and nickel salts. These substances are used in stainless steel and other metal alloys. Workers employed in refining nickel ore were found to have an increased risk of malignancy involving both the lungs and nasal mucosa. However, this risk appeared to be confined to exposure to nickel sulfate and the combination of nickel sulfides and oxides to which these workers were exposed in the refining process (13). By contrast, workers involved in the manufacture of nickel alloys did not seem to be at an excess risk for pulmonary carcinoma (13). These data suggest that individuals exposed to stainless steel in OINDP would not be at an increased risk for respiratory tract malignancy, especially if total daily intake, based upon NAAQS is used.

Nickel allergy, i.e., to nickel sulfate, is one of the most common forms of allergic contact dermatitis, with prevalence rates of 10–15%. However, when the Danish regulatory agency limited the nickel release threshold to the skin to 0.5 μg/cm^2 per week from nickel-containing alloys and coatings, the incidence of nickel allergy in school-aged girls with pierced ears decreased (17–3.9% [before versus after the regulatory change]) compared to girls without pierced ears (5.3–5.9%) (14).

Despite its frequent involvement as a dermal sensitizer, nickel has rarely been associated with the development of bronchial asthma (10,15). It is interesting to note that the asthmatic manifestations of nickel exposure has been reported to be IgE mediated (16), whereas, the contact dermatitis is a delayed hypersensitivity reaction. Also, exposure to fumes or dusts containing nickel carbonyl may result in an acute chemical pneumonitis and/or tracheobronchitis (10,17).

As noted above, a significant fraction of the dose from OINDP is swallowed. This swallowed fraction therefore, raises the possibility of an endogenous nickel reaction. However, nickel is found in many foods, and the average human daily intake of nickel is 200 μg. Oral challenge trials to elicit nickel dermatitis have utilized doses ranging from 0.5 to 5.6 mg (18). In contrast, the amount of nickel contributed from stainless steel cooking utensils is negligible, i.e., 0–8 μg (19). Thus, it is plausible to conclude that similar total daily intake allowances from foreign particles in OINDP based upon a small percentage of the NAAQS will provide an adequate safety margin against allergic manifestations.

For foreign particles where threshold data for clinical disease is unknown, manufactures may need to use different criteria to minimize any potential risks. Additionally, it should be recognized that there may be extremely sensitive individuals who may react at very low exposure levels to certain particles.

In summary, to understand the clinical ramifications of foreign particulates in OINDP, a full characterization of the particles is essential to grasp the potential for injury. The US Environmental Protection Agency's NAAQS for particulate matter ≤10 μm is a relevant particle standard; a total daily intake of 5% of this limit should be appropriate for many, albeit not all foreign particles.

CONCLUSION

Best practices for managing the safety and quality of OINDP with respect to foreign particles can be accomplished through application of quality by design concepts. In practical terms, this means that relevant information such as amount, characterization, and safety of foreign particles in OINDP is best obtained during development studies, and where possible and appropriate from formulation and contain/closure system component suppliers. Such information can then be used to inform development of specifications and controls for production of the drug product. Knowledge gained from this information could lead to reduced testing of product during routine control.

Clinical safety limits for foreign particle exposures can be developed and are most relevant in application to particles less than 10 μm. These limits can be in the range of 5% of the NAAQS. A review of available clinical studies of representative particles suggests that a 5% limit is protective of most particles.

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