

Considerations for Foreign Particulates in a Quality by Design Environment

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Outline

- **Background and Introduction**
 - What is a Foreign Particulate?
 - What can we Measure?
- **Foreign particulates and QbD or "what to do and when to do it?"**
 - Safety and quality considerations
 - When to measure what?
 - External Component, Excipient and API manufacturers, what can we expect?
 - Stability testing
 - Acceptance criteria
 - QbD and design space for foreign particulates
- **Summary**

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IPAC RS Working Group on Foreign Particulates

- This presentation is based on the work done within the IPAC RS Working Group on Foreign Particulates
 - Best Practices for Managing Quality and Safety of Foreign Particles in Orally Inhaled and Nasal Drug Products, and an Evaluation of Clinical Relevance accepted **Pharmaceutical Research J. Blanchard et al**
 - Foreign Particles Testing in Orally Inhaled and Nasal Drug Products **Pharmaceutical Research Vol. 21, No. 12, pages 2137-2147 (2004) J. Blanchard et al**

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What is a Foreign Particulate?

- Particulate material not intended to be inhaled by the patient
 - Sources can be FPs in the API, excipient and inhaler components or FPs generated when using the device
- From a practical analysis view point particulate materials not soluble in solvents needed to dissolve API and excipients
 - Excessively strong solvents should be avoided in order not to mask any FPs

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What can we Measure? Sampling

- Sampling is dependent on the drug product and there is no general method for all types of devices
- For drug product analysis sampling often restricts what is possible to measure
 - Pressure drop over filter for collection of FPs restricts pore size on filter
 - Background FPs level
- Sampling puts restrictions on lower size range and number detection limit as well as on speciation
- It is important to sample "blanks"

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What can we Measure? Enumeration

- Light obscuration is a readily available technique for counting numbers of FPs
 - The FPs are dispersed in a liquid media
 - Lower size range is 2 μm (e.g. 2-10; 10-25 and 25-400 μm)
- Microscopy methods
 - Limited practical utility in lower particle size ranges. For instance counting particles less than 5 μm would be very labor intensive
 - Automated imaging techniques may facilitate counting but reliability of the techniques regarding false positives and negatives may limit the usefulness of the technique

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What can we Measure? Identification

- No single technique can be used to identify all different types of particles but together they can give a good understanding of the different types of FPs
 - Raman microscopy is good for organics
 - IR microscopy is good for organics
 - Harvesting of individual particles may be needed
 - SEM EDX is good for inorganics
- In practical analysis work these identification techniques are limited to approximately 2 μm or larger particles
- For identification purposes it is good to create your own library of the spectra from the materials used in the device and for the analysis/sampling

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Foreign particulates and QbD or "what to do and when to do it?"

- Select appropriate materials with no safety concerns
- Ensure clean production environments through out the production chain
- Learn your product in the development phase by doing
 - Enumeration of FPs
 - Identification of FPs
 - Stability testing of FPs
- Minimize FPs contamination and if possible eliminate sources of FPs
- Implement agreements with your component, excipient and API manufacturers (if outside the pharmaceutical company) to ensure that you will be informed prior to implementation of changes
- Ensure that your testing have been done on relevant product (at least close to final product)
- And then you can probably limit your quality control of FPs for commercial product to acceptance criteria for enumeration at release
- After testing many batches without OOT or OOS results FPs testing may be reduced "skip lot testing"

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Safety Considerations

Material considerations *cf* extractables

- Evaluate materials early and avoid if possible materials with potential safety concerns
 - E.g. use materials safe for food use "21 CFR indirect food additives regulation"
 - Literature/database review
 - May be beneficial to perform tox evaluation of the materials regarding FPs together with that for leachables/extractables

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Safety considerations

EPA's NAAQS for PM₁₀

- The NAAQS for PM₁₀ is 50 µg/m³
 - Applying EPA breathing volume assumptions this corresponds to 1 mg/day
 - Considering a small fraction of this e.g. 5% as an upper acceptable level this gives 50 µg/day
- NAAQS was established to be protective of sensitive populations, e.g. affected by asthma or other lung diseases, over the life time of those populations

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Safety considerations 5% of NAAQS to numbers

- NAAQS is mass based
- 5% of the NAAQS PM_{10} mass is converted to numbers for spherical particles of a certain diameter and density
- The approach is pragmatic and we have e.g. not considered that a $10\ \mu\text{m}$ particle of density $8\ \text{g/cm}^3$ would not be inhalable

$\text{\O},\ \text{mm}$	Density g/cm^3	
	1	8
2	1.2×10^7	1.5×10^6
3	3.5×10^6	4.4×10^5
4	1.5×10^6	1.9×10^5
6	4.4×10^5	5.5×10^4
8	1.9×10^5	2.3×10^4
10	9.6×10^4	1.2×10^4

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Quality Considerations

- For particles larger than $10\ \mu\text{m}$ safety aspects are less important since these would not be inhalable
- Apart from safety aspects quality considerations may also motivate control of numbers in different size ranges e.g. 2-10, 10-25 and $>25\ \mu\text{m}$

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When to measure what?

Development vs Routine QC

- Learn your product in the development phase
 - Identification of FPs
 - Enumeration of FPs
 - Stability testing of FPs
- Routine QC
 - Could be limited to enumeration of FPs at release
 - If an OOT or OOS result is evident, identification or other characterization may be done to identify the source
 - Annual maintenance stability testing should not be needed if no stability trend is found in your development stability studies
 - Skip lot testing may be an alternative after long stable production without OOT or OOS results

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When to measure what?

Drug product vs inhaler components/APIs/excipients

- From a patient perspective it is the aerosol inhaled by the patient that is important
 - FPs may be created when using (loading/actuating) the device
 - Development stability testing would be done on the product
- Device components/APIs/excipients may be important to test to understand the sources of FPs

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Minimize or eliminate sources

- A zero FPs level is not achievable
 - random in nature
 - no *ab initio* expectations of levels
- Use your measurements to identify the sources
- At higher levels of FPs, either safety or quality perspective, sources should be minimized or eliminated

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External Component, Excipient and API manufacturers

What can we expect?

- Agreements in place to ensure information prior to implementation of changes
 - A DMF is probably not enough to ensure this
- Clean production environments
- FPs testing requires a clean room or a LAF cabinet and may better be done at the pharmaceutical company than at e.g. the component manufacturer

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Stability testing

Development vs annual maintenance

- Stability testing should be done in the development and may not be needed as annual maintenance QC testing
 - No stability trends
 - Done on the final product

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Acceptance criteria

- A combination of safety (NAAQS and other evaluations when necessary) and quality aspects and would be product specific
- Statistical approaches may be used in deriving the acceptance criteria

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OOT or OOS results

- OOT or OOS results trigger an investigation to find the source
 - Characterization could include identification of FPs
 - Minimize or eliminate source if possible
 - Evaluate any safety concerns

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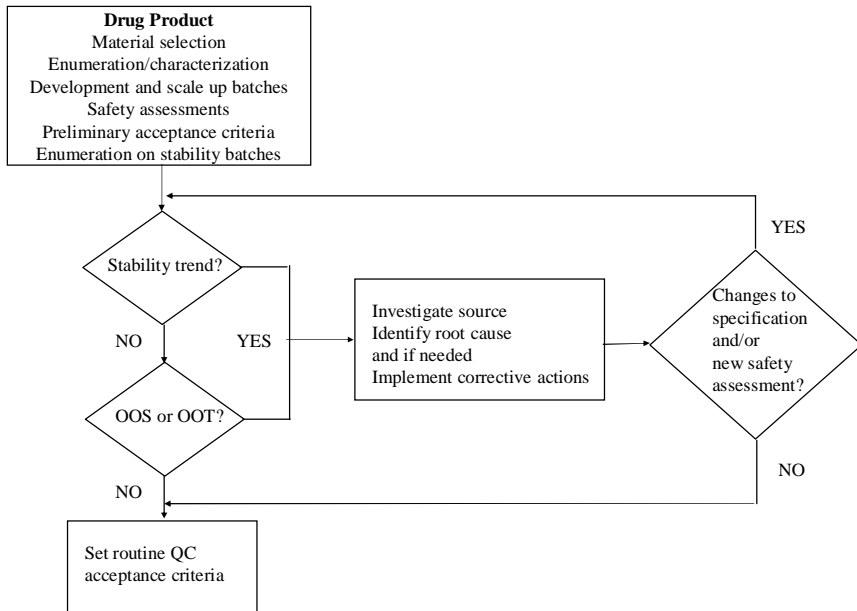
QbD and Design Space for Foreign Particulates

- Is a difficult concept for FPs in inhaled products, given the complicated nature of OINDPs
- QbD principles are beneficial
- Defining the design space for FPs is complicated
- Dan Norwood will elaborate more on this for L&E in the next presentation

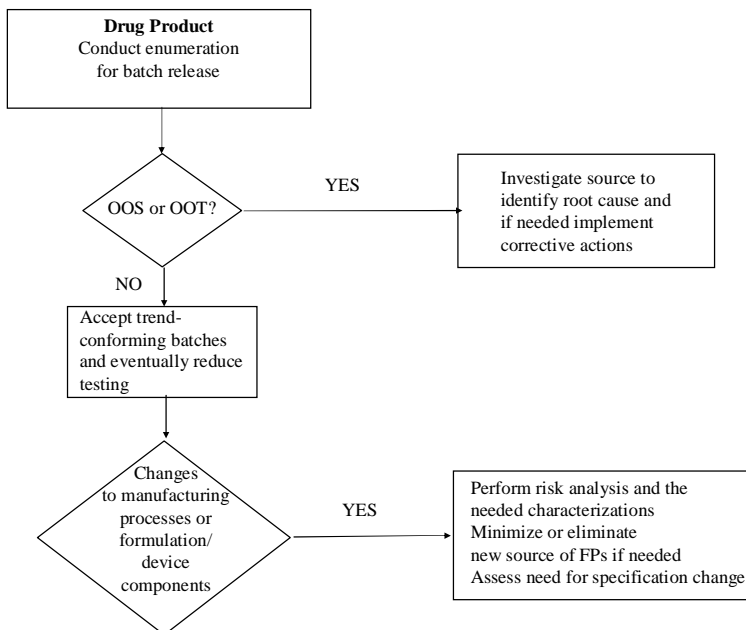
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Summary development



Summary routine QC



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**Thank you for
your attention**

