

Linking Safety and Quality:  
Examples from L & E and Foreign Particulates  
in OINDP

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## Objectives

### Discuss

- General approaches for safety qualification of
  - Leachables and extractables
  - Foreign particulate
- Qualification examples
- Process improvements

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## Extractables & Leachables

- Not typically encountered with oral dosage forms
- Can be a significant issue for
  - Inhalation formulations
  - Parenteral formulations
  - Ophthalmic formulations
- No formal guidance currently available
- Issues can affect approval of drug product

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## General qualification approach

- Identify the compound
- Review the available toxicology/safety data
- Conduct SAR assessment
- Conduct toxicology studies as deemed necessary (i.e. 14-90 day toxicology, genetic toxicology)
- Conduct safety assessment based upon maximum expected daily human exposure
  - Consider patient population and duration of use

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## Inhalation drug formulations

- The device (MDIs, others) can contribute leachables from components continuously in contact with the drug
  - Canister coating
  - Rubber valve/gasket components

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## IH products - General process

- First, generate an extractable/leachable profile
  - Typically 40+ compounds, in contrast to a generally small number of drug-related impurities
- Then, conduct a risk assessment
  - Acceptable maximum exposure to the extractable?
  - If no, consider leachable level.
- Risk assessment starts with available data from toxicology databases.

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## IH products - General process

- Risk assessment has 3 components
  - Systemic toxicity
  - Route-specific toxicity (IH irritancy, local respiratory toxicity)
  - Mutagenic/carcinogenic potential
- As part of the risk assessment, determine if the analytical sensitivity (LOD) is sufficient to identify levels associated with risk

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## Systemic Toxicity

- Safety qualification threshold of  $\leq 5 \mu\text{g/day}$  (100 ng/kg/day)
  - No further systemic toxicity data needed when maximum expected daily exposure is below TH
  - Approach assumes no known potential or structural alerts for genotoxicity or local irritant effects

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## Systemic Toxicity (2)

- TH based on EPA databases for chemicals with inhalation data
- RfC's from database  $\geq 100 \text{ ng/kg}$
- 3 exceptions with "safe" doses of 80 ng/kg
- Large safety factors (1,000 – 10,000) incorporated

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## Systemic Toxicity (3)

- For exposures > 100 ng/kg, qualify based on
  - Published toxicity data
  - Relevant accepted regulatory exposure limits
  - Structural similarity to chemicals with known toxicity profiles, or
  - Toxicology studies (at least 90 days duration for chronic indications)

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## Systemic Toxicity (4)

- When toxicology data used to support proposed specifications:
  - Most relevant data should be considered
  - Safety margins calculated based upon NOAEL dose
    - Generally 10-fold SM incorporated for cross-species extrapolation
    - 100-fold SM used for data from alternate routes of administration
      - Apply 1000-fold SM if using oral animal data to support human IH use

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## Local Toxicity

- Determine if any chemical structures are associated with irritancy
- Especially important considering indicated population
- Primary examples
  - Isocyanates
  - Aldehydes
  - Organic acids
  - Strained heterocyclics

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## Local Toxicity (2)

- If no, qualification threshold exposure = 100 ng/kg/day
  - EPA databases for 20 chemicals with inhalation data show RfC's  $\geq$  100 ng/kg, except for 4, all of which had a structure associated with irritancy
- Exposure  $>$  100 ng/kg, qualify as described for systemic toxicity

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## Carcinogenic Potential

- Chemicals with negative genotoxicity and carcinogenicity data: qualified
- Chemicals that have no genotoxicity or carcinogenicity data: qualified if they lack structural alerts
- Chemicals w/ structural alerts: qualified if conducted genotoxicity studies are negative
- For known carcinogens, carcinogenicity risk (inhalation) should be  $< 10^{-6}$

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## Product Quality Research Institute (PQRI)

- L & E Working Group proposing thresholds for qualification for orally inhaled and nasal drug products
  - Qualification Threshold: 5  $\mu\text{g}/\text{day}$
  - Safety Concern Threshold: 0.15  $\mu\text{g}/\text{day}$
- Representatives from Division of Pulmonary and Allergy Products are active participants
- L & E Working Group proposals are taken into consideration during review cycle
- Concepts could eventually be applied to other types of products

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## Foreign Particulates

- Attempt to identify the nature of the particulate material
  - If possible, safety qualification should be conducted using compound-specific safety data
- If identification of the material is not possible, evaluate safety based on US EPA exposure standards (NAAQS) for inhaled particulate material
  - PM<sub>2.5</sub> – 15 µg/m<sup>3</sup>
  - PM<sub>10</sub> – 50 µg/m<sup>3</sup>

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## Foreign Particulates (2)

- EPA NAAQS standards correspond to daily human exposures of 6 and 20 µg/kg/d (assumed IH volume of 20 m<sup>3</sup> air/day)
- Particulates in the 2.5 µm range of greater safety concern due to potential for deeper lung penetration
- Anticipated human exposures to unidentified foreign particulate derived from drug product that are a fraction of the EPA standards considered acceptable

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## Qualification examples – IH

### Bis-2-ethyl-hexyl sebacate

- Proposed specification corresponding to daily human exposure of 182 ng/kg/d
- NOEL of 200 mg/kg from published chronic rat dietary study
  - Corresponds to acceptable human IH exposure of 0.2 mg/kg
- > 1,000-fold safety margin

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## Qualification examples - IH

### 4-toluenesulfonamide

- Proposed specification corresponding to daily human exposure of 1.2 µg/kg/d
- Sponsor provided no supporting rationale for proposed specification
- Only acute toxicity data available
- Sponsor was requested to lower specification to correlate with qualification TH (5 µg/day) or provide adequate toxicology data to support proposal

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## Qualification examples - IH

### Acenaphthene

- Proposed specification corresponding to daily human exposure of 1.33 ng/kg/d
- Only acute toxicity data available
- Drinking water standard: 400 µg/L
  - Corresponds to acceptable daily IH exposure of 160 ng/kg (assumed intake of 2 L/day, 50 kg BW)
- > 100-fold SM

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## Qualification examples - IH

### Nitrosamines

- Extract from rubber components
- Carcinogenic
- 6 species ID'd at various levels
- Risk assessment based on total nitrosamine exposure using slope factor for NMDA
- Carcinogenic risk estimates up to 1:100,000 have been accepted based on public health, risk:benefit and technological considerations
  - Sponsor's encouraged to reduce further or remove

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## Qualification examples - IH

### Unidentified foreign particulate

- Proposed specification for PM10 corresponded to a worst case scenario daily patient exposure of 0.07  $\mu\text{g}/\text{kg}/\text{d}$  (0.35  $\mu\text{g}/\text{d}$ )
- Sponsor contended that expected exposure was significantly below the EPA standard and was safe
- Proposed specification considered acceptable
  - ~ 285-fold lower than PM<sub>10</sub> standard
  - ~ 85-fold lower than PM<sub>2.5</sub> standard

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## Safety vs Quality

Recommendations from pharmacology/toxicology based solely on safety considerations

Recommendations forwarded to ONDQA reviewer to consider in determining acceptable product specifications

Final accepted product specifications are sometimes lower than levels supported by safety concerns based on product quality considerations

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## Agency process & timing

- Divisions alert sponsors to potential issues as early as pre-IND meetings
- Once data is submitted (usually with NDA), CMC group generates a consult to the Pharm/Tox group for safety assessment

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## Agency process & timing (2)

- Pharm/Tox group reviews safety data and coordinates with CMC to relate acceptable exposure levels to drug product specification
- Review often occurs late in review cycle; can affect drug approval

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## Process Improvements

- Select materials to limit the number and level of potential leachables.
- Use pre-extraction methods to lower potential exposures.
- Submit clear rationale to support safety of proposed product specifications.

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## Process improvements (2)

- Generate data and initiate communication with relevant division earlier in the development process
  - Data often not available until NDA submission or during review cycle

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## Process improvements (3)

- Some qualification can be incorporated into standard toxicity testing with active drug
  - Analyze drug batches for leachable levels
- For toxicity tests
  - use aged product
  - store the product in an orientation that maximizes contact with device components

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## Conclusion

- Safety qualification of extractables and leachables may be needed for various types of drug products
- Relevant toxicology/safety data should be considered to support product specifications
- Early communication and clear supporting rationale may assist in more efficient resolution of issues

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## Conclusion (2)

- Sponsors are encouraged to consult with relevant divisions to discuss anticipated issues.