

Practical Aspects for Assessing and Controlling Exposures to "Near-Nano Sized," Highly Potent Molecules

Donna S. Heidel, CIH

*Worldwide Director, Industrial Hygiene
and Occupational Toxicology*



- **Project overview**
- **Back to basics**
 - OEL determination
 - Sampling and analytical methods
 - Exposure assessments
 - Engineering controls
 - PPE
- **Work to be done**

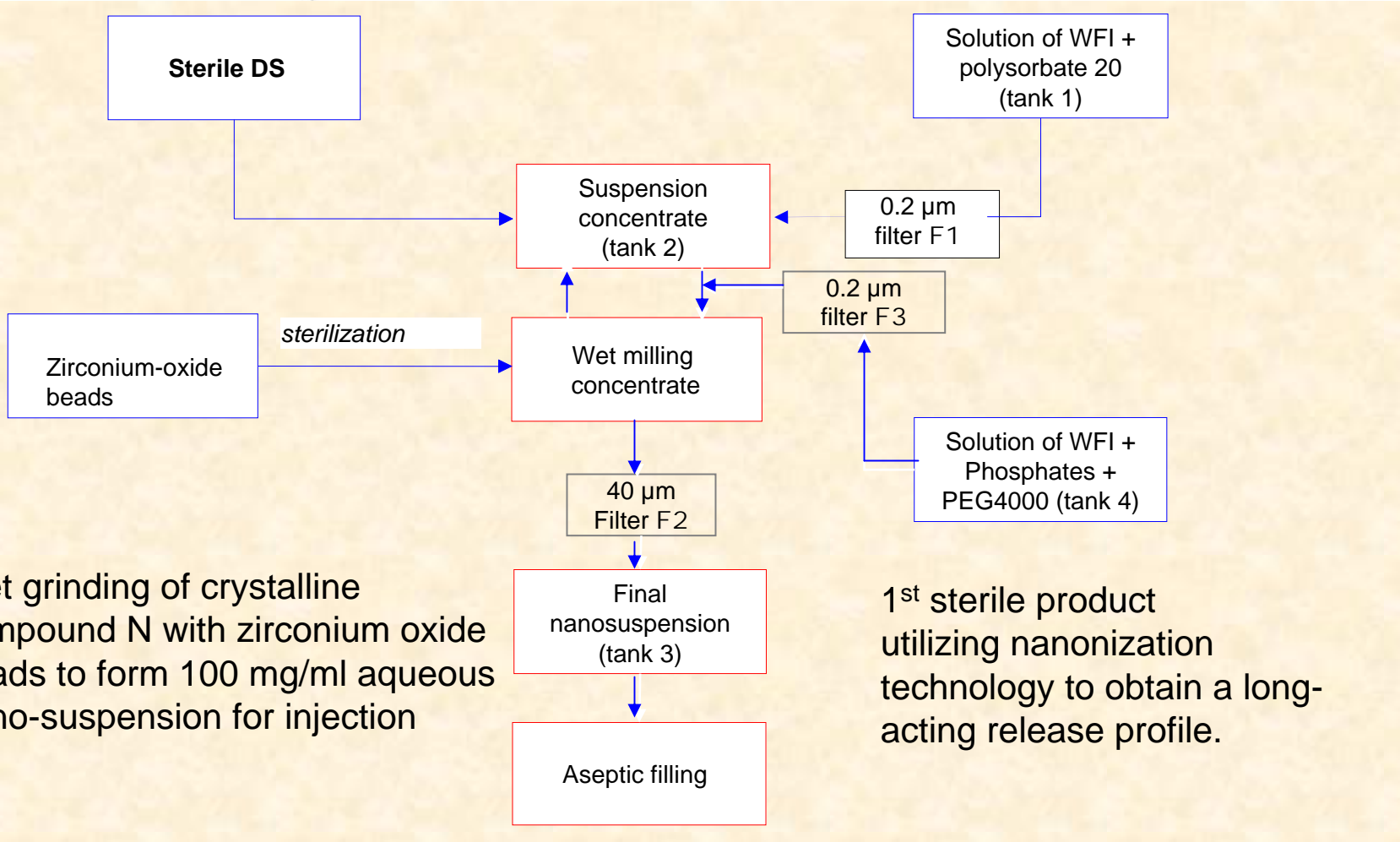
- **Develop long-acting injectable drug product containing a “near-nano-sized” aqueous suspension of a highly potent drug active (compound “n”)**

- Aerosol particle size distribution*

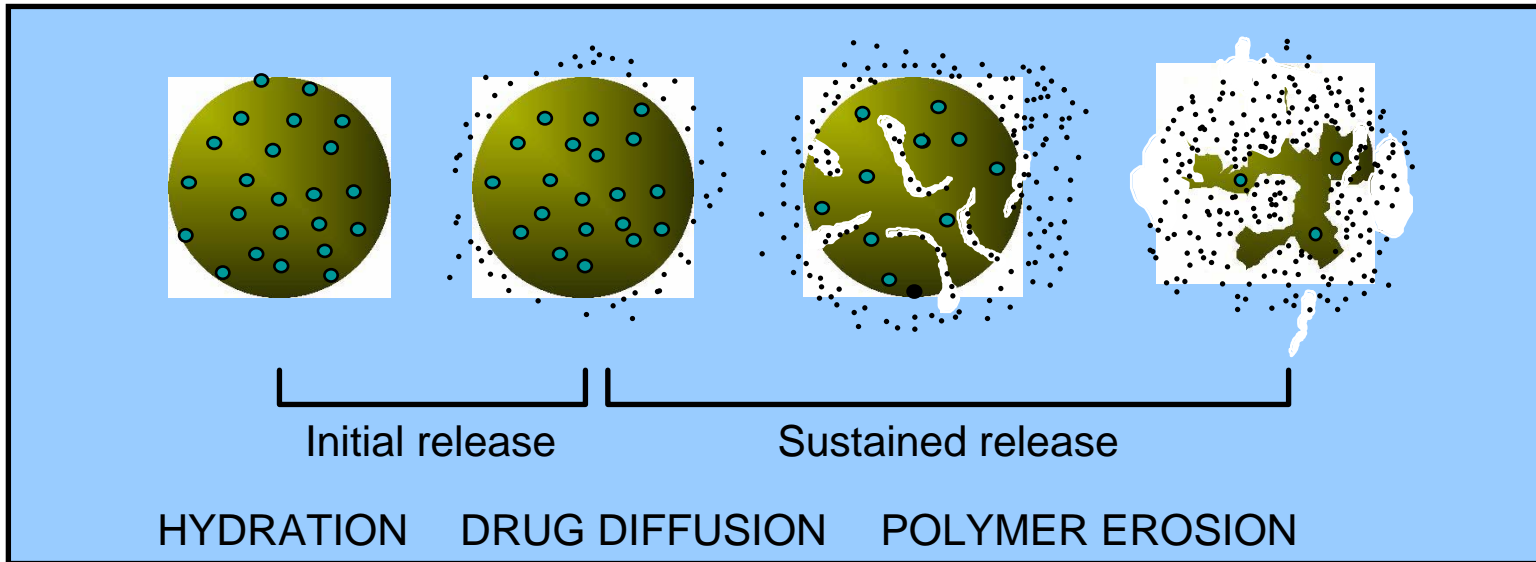
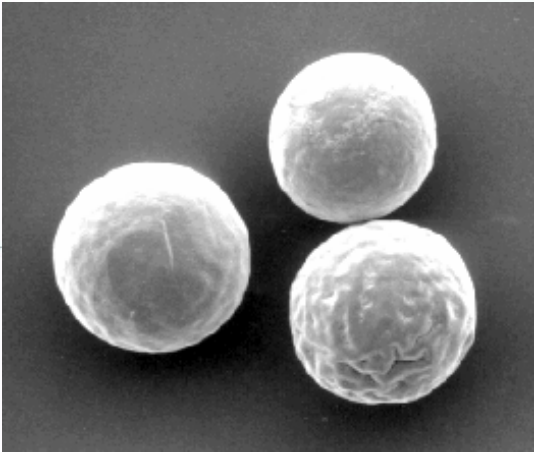
<u>Fraction</u>	<u>Diameter</u> (μm)
< 10	0.233
< 25	0.331
< 50	0.516
< 90	1.714
< 99	2.412

- OEL $0.75 \mu\text{g}/\text{m}^3$ (8-hr TWA), based on pre-milled drug with particle size distribution $d_{10} = 16 \mu\text{m}$

* Particle size distribution was not influenced by recirculation for 1 hour



Mechanism of Release



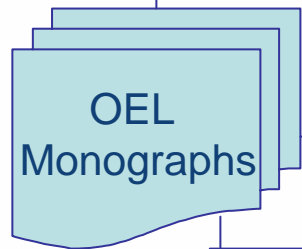
- Drug particle
- Polymer matrix

- **Protect workers from exposure to drug aerosol above the OEL**
- **Prevent skin contact**
- **Verify engineering controls used for normal sized compounds are appropriate for this “near nano” compound**

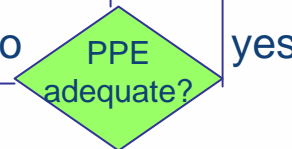
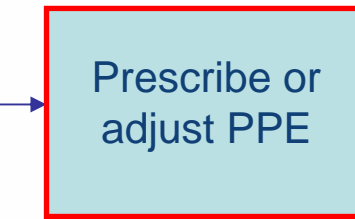
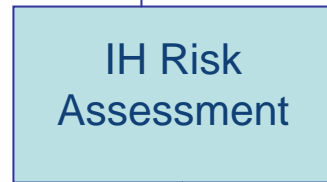
Industrial Hygiene Process

Goal: Prevent Occupational Illness
Process Outcome: Control Exposure Risks

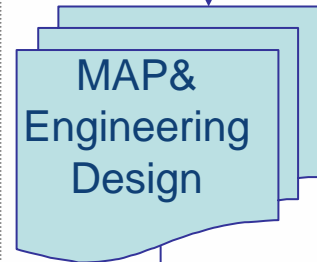
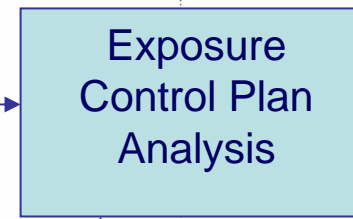
Occupational Toxicology



Industrial Hygiene



Engineering



- Active pharmaceutical ingredients (APIs) differ from typical solvents or other industrial chemicals
 - ✓ APIs are designed to target the body (receptors, enzymes) in small quantities for therapeutic benefit
 - ✓ Toxicity
- Goal of OEL process
 - ✓ Identify chemical health hazards – humans or animals (surrogates)
 - ✓ Prevent inadvertent therapy, adverse or toxic effects in employees
 - ✓ Identify the workplace exposure level which minimizes risk to the employees

- **Can the OEL of $0.75 \mu\text{g}/\text{m}^3$ for “normal-sized” compound N be applied for the “near-nano” sized compound n?**

$$\text{OEL-TWA} = \frac{\text{NOEL (mg/day)}}{V (\text{m}^3/\text{day}) \times S (\text{days}) \times \text{UF} \times \alpha} \quad \text{UF} = 100; \alpha = 100\%$$

Are the pharmacokinetic patterns altered?

Is the toxicity profile the same?

Is the current risk assessment methodology appropriate?

Goals

- 1. Characterize the pharmacokinetic (PK) patterns of nano-sized soluble drug actives**
 - How long a drug/chemical stays in the body and how the body changes the drug
- 2. Determine the toxicity profile of nano-sized soluble drug actives as compared to typical particles**
- 3. Determine if the risk assessment methodology currently used in calculating occupational exposure limits needs to be modified for nano-sized drug actives**

- **All inspirable particles of concern**
- **Method for “normal-sized” compound N**
 - 25 mm, 5 mm pore size, PTFE filter in IOM sampler analyzed with HPLC DAD with LLD of 0.02 $\mu\text{g}/\text{filter}$
 - Initial surveys results all < LLD
- **Method for “near-nano” sized compound n**
 - 25 mm, 0.45 mm pore size, hydrophilic polypropylene filter analyzed by LC/MS/MS with LLD of 0.002 $\mu\text{g}/\text{filter}$
 - Validation and stability spikes met validation criteria for recovery
 - Increased filter resistance requires personal sampling pumps capable of 2 lpm flow rates

- **Skin absorption not expected with compound N**
- **Acceptable surface limit for compound n established at $7.5 \mu\text{g}/100 \text{ cm}^2$ to address uncertainty of dermal absorption**
 - $(\text{ADI} = \text{OEL} \times 10 \text{ m}^3 \quad \text{ASL} = \text{ADI}/100 \text{ cm}^2)$
 - Issues:
 - Repeated contact with material (face, neck, nasal mucosa, etc.), re-suspension in air
- **Surface sampling method developed and validated**
 - Surface sampling used to to prescribe skin protection

- **Aseptic processing isolators**
 - Overpressure
 - Rapid transfer ports
 - Mouse hole for filling isolator
 - Filling 1500 mm from mouse hole
 - Filter efficiency > 99.999 % for 0.3 μm particles (H14)
 - Isolator integrity testing and personal exposure monitoring conducted using acetaminophen as surrogate, compound N and suspensions of compound **n**

- **Dispensing isolator testing results**
 - Surrogate test results (acetaminophen)
 - Minor detectable airborne concentrations between gloves (area survey for 4 hours; $0.03 \mu\text{g}/\text{m}^3$) and at the rapid transfer port (area survey for 2 hours; $0.04 \mu\text{g}/\text{m}^3$)
 - Personal exposures below LLD during operation and $0.1 \times \text{OEL}$ during isolator final rinsing (isolator opened)
 - Surface sampling below LLD except for minor concentrations (all below ASL) at RTPs between transfer container and isolator and between isolator and processor

- **Dispensing isolator testing results**
 - Compound N
 - Personal exposures < LLD – 1.4 $\mu\text{g}/\text{m}^3$ (2 hours) during operation and 0.8 $\mu\text{g}/\text{m}^3$ (1 hour) during final rinsing
 - 3 separate sampling campaigns
 - Conclusion
 - Results acceptable for compound N and consistent with surrogate results

- **Four operations**
 - Wet milling (closed vessel)
 - Filling (closed isolator)
 - Replacing needles and parts (open isolator)
 - Cleaning (open isolator)
- **Personal and Area sampling**

- **Wet milling of compound **n** in closed system**
 - Tanks cleaned and sterilized in place
 - Area sampling all below LLD
- **Filling of compound **n** suspensions**
 - Personal exposures range from $< \text{LLD} - 0.02 \mu\text{g}/\text{m}^3$ (2.5 hours) and $0.01 \mu\text{g}/\text{m}^3$ (5 hours)
 - All area samples, obtained at each glove box penetration (glove ports, mouse hole, filters) below LLD
- **Replacing Needles**
 - Personal exposures up to $0.17 \mu\text{g}/\text{m}^3$ (1 hour)
 - Area sampling $< \text{LLD}$
- **Cleaning**
 - Personal exposure up to $60 \mu\text{g}/\text{m}^3$ (30 minute survey)
- **Area sampling $< \text{LLD}$**

- **Area and personal results consistent with “normal sized” compounds and aerosols**
- **Gaskets, valves and connections used for normal size high potency products appear to be effective**
- **Isolator design specifications appear to be effective for aseptic filling of suspensions with compound n physical characteristics**
- **No evidence of penetration through filters**
- **Exposures during cleaning still to be resolved; additional sampling required**

- **Glove permeation studies conducted**
 - Draft ASTM method used
 - 2 chamber permeation cell, with challenge and collection solution chambers separated by a section of the glove material
 - Three gloves challenged
 - 2 nitrile and 1 latex
 - Each glove tested three times
 - Two challenge solutions
 - 100 mg/mL compound **n** suspension
 - 9:1 suspension:isopropyl alcohol
 - Results
 - No permeation was detected in any glove for both solutions during the four hour exposure experiments

- **Full-face respirators with P3 filters**
- **Tested gloves**
- **Full TYVEK jump suits**
 - Protective clothing not tested for penetrability of nanomaterials

- **Adopt standard IH process but challenge accepted assumptions**
 - OEL
 - Sampling and analytical methods
- **Additional studies required to reliably establish OELs for nano-sized compounds and to evaluate skin absorption**
- **Standard glove box isolators and high integrity gaskets and flanges for high potency compounds appear to be effective**