

# Acceptable Risk Assessment Strategies...

## Sources of EI Data

### Limited and Varied Supplier Information

## A Minerals Excipient Maker's Perspective

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**Vanderbilt Chemicals, LLC**

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# Today's topics

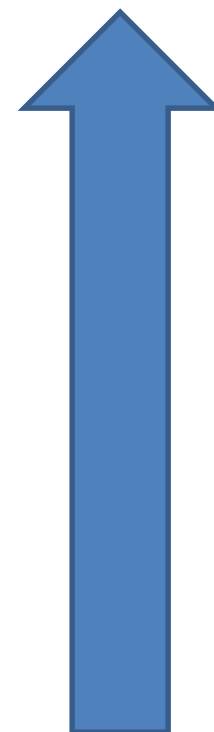
- Review *Minerals*...the *highest risk* for EIs?
- Experience with Vanderbilt Minerals.
- Hazards, Exposures, and Risks.
- Applying Bioavailability to Risk Assessments.
- Customer requests/expectations?
- Limited and varying supplier data.
- Our role to advance the science for the customers & patients.



# Minerals are the highest risk with Els...perhaps

We have seen the increased risk table:

Mined (e.g. talc)
Synthesized with metal catalyst (e.g. mannitol)
Plant origin ((e.g. cellulose derivative)
Animal Origin (e.g. lactose and gelatin)
Synthesized without metal Catalyst (e.g. colloidal SiO <sub>2</sub> )



# Minerals Are the Highest Risk For Elemental Impurities...perhaps

- High levels.
- Variations and excursions...can these be predicted?
- Some minerals are simply milled.
- Some minerals have refining steps.
- Many metal impurities are naturally present (e.g. lead) in mined excipients.
- Processing the ores may not remove Els.

# Variations and excursions...a study of Mineral Excipient Raw Materials

- Understand minerals geology, ie:
  - Volcanic ash
  - Sea shell deposits
  - Salt deposits
  - 1,000 to 1,000,000 of years
  - Ocean factors
  - Weather
  - Earthquakes/faulting activities



# Study minerals **processing**

- Some minerals are simply dug up, milled, and packaged. “What goes in,...” stays in”!  
ie... Els.



# Study minerals **processing** cont'd...

- Other minerals receive extra processing steps, ie washing, screening, and... *other classification steps*...These steps **CAN and DO REDUCE EIs** in certain applications...





# Vanderbilt Minerals Experience

- Started mining smectite clays ~ 1950.
- Minerals are sourced from AZ, CA, and NEV.
- Geology examined.
- **To Mitigate:** Drill core tests are used to confirm mining locations.
- Stockpiles are sampled, tested, and Approved by Quality before use.
- Finished excipient is tested.
- Trends evaluated for adjustments.





# Vanderbilt Minerals Experience

- Very little variations and excursions with dozens of stockpiles.
- We often see ppm **lead reduced** from the ores to the final product, due to ore processing (ie. washing and classifications).
- Test each lot, begin-middle- and end.
- No OOS results with As and Pb.
- Variations and excursions are minimized with drill core tests and downstream processing.

# Hazards, Exposures, and Risks

From *The Coalition*...we have these terms connected:

- **Hazard** is defined as the potential of a substance to cause damage;
- **Toxicity** is the assessment of its ability to poison;
- **Risk** is a measure of the probability that harm may result from exposure to a chemical.
- Thus, if there is no exposure, there is no risk regardless of the magnitude of the hazard.  
(Duffus, Worth, 2006)

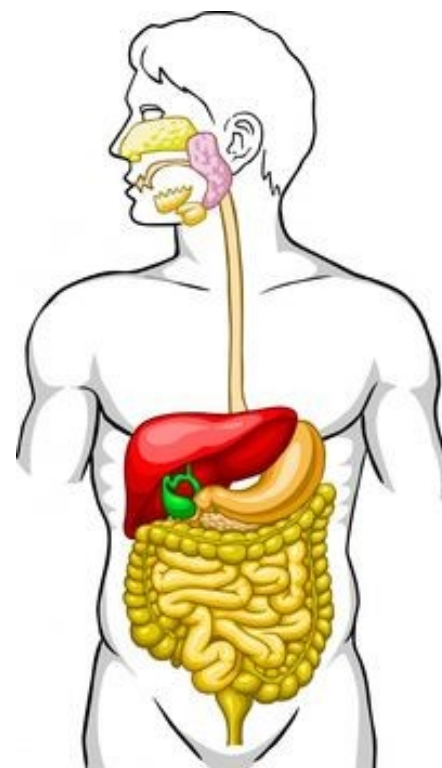
# Hazards, Exposures, and Risks... cont'd



- What is the hazard at the south pole? It's SUPER COLD!
- If we stay in the snow cat, we are not exposed to the cold.
- What is the Risk? We have no Exposure and therefore No Risk to Freezing!

# Bioavailability and Risk Assessments

- Minerals such as smectite are "*difficult to digest 100%*" for USP <232,233>.
- USP NF testing has safely used acid leach digestion methods to measure ppm As and Pb.
- What data is available from Vanderbilt for smectite clay?



# Vanderbilt Contributes Bioavailability Data

Current Biorelevant Acid leach Compendial Methods:

	AS	Pb
FCC Monograph Bentonite	1:25 HCL (0.5N);Boil 15 minutes	1:25 HCL (0.5N);Boil 15 minutes
<b>NF Monographs Magnesium Aluminum Silicate</b>	1:25 HCL (0.5N);Boil 15 minutes	1:25 HCL (0.5N);Boil 15 minutes
USP Monographs Activated Attapulgate	1 N HNO <sub>3</sub> ;Boil 30 minutes	1 N HNO <sub>3</sub> ;Boil 30 minutes

# Vanderbilt Contributes Bioavailability Data

- Clay structure captures As and Pb.
- Acid leach and total digestion.

From Team 2 Coalition Paper we have:

## Total vs. Leached Elemental Impurities in Natural Mineral Absorbants (ppm)

	Acid Activated Clay		Bentonite		Diatomaceous Earth		Perlite	
	<u>Total</u>	<u>Leached</u>	<u>Total</u>	<u>Leached</u>	<u>Total</u>	<u>Leached</u>	<u>Total</u>	<u>Leached</u>
As	0.9	0.6	1.6	1.2	12.7	2.1	0.4	ND
Pb	14.3	8.70	21.6	9.95	8.0	0.03	14.5	0.28
Cd	0.04	0.01	0.10	0.02	0.08	ND	0.07	ND
Co	0.6	0.1	1.9	1.0	4.8	ND	0.4	ND
Mo	1.0	ND	1.7	1.2	7.7	4.6	1.3	0.1
V	5.2	0.5	9.4	ND	1.0	20.6	ND	ND

# Vanderbilt Contributes Bioavailability Data

Patent Application 20080008763

- Clays used to absorb toxins from moldy grains.
- 3 grams per day dosage in humans.
- no elevated heavy metals during 3 month study in Africa.

TABLE 9

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Analysis of non-nutritional minerals in serum samples of study subjects: Baseline levels vs. High Dose of NS at the end of the trial

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Minerals	Before Trial	After Trial
Ag (Silver) ( $\mu\text{g/L}$ )	$0.23 \pm 0.03$	$0.26 \pm 0.27$
Al (Aluminum) ( $\mu\text{g/L}$ )	$132.08 \pm 71.92$	$130.17 \pm 73.56$
As (Arsenic) ( $\mu\text{g/L}$ )	$8.83 \pm 1.45$	$8.63 \pm 1.63$



# Vanderbilt Contributes Bioavailability Data cont'd...

Patent Application 20080008763

TABLE 9-continued

Analysis of non-nutritional minerals in serum samples of study  
subjects: Baseline levels vs. High Dose of NS at the end of the trial

Minerals	Before Trial	After Trial
Ba (Barium) ( $\mu\text{g/L}$ )	$80.07 \pm 15.23$	$115.92 \pm 32.89^*$
Be (Beryllium) ( $\mu\text{g/L}$ )	$1.11 \pm 0.06$	$1.11 \pm 0.12$
Cd (Cadmium) ( $\mu\text{g/L}$ )	$0.70 \pm 0.38$	$0.71 \pm 0.39$
Hg (Mercury) ( $\mu\text{g/L}$ )	$5.57 \pm 0.30$	$5.60 \pm 0.60$
Li (Lithium) ( $\mu\text{g/L}$ )	$22.30 \pm 1.15$	$22.37 \pm 2.44$
Pb (Lead) ( $\mu\text{g/L}$ )	$16.13 \pm 8.55$	$15.03 \pm 9.25$

# Expectations from excipient mineral suppliers

Explain the excipient **raw materials**

- Geology...what kind of minerals deposits?
- Drill core steps as **Mitigation Steps** useful to select the mining locations.
- Stockpile data...is it too late already?
- Trends, ie variations and excursions can be studied for adjustments.



# Expectations from excipient mineral suppliers cont'd...

Explain excipient **processing**

- Simple milling vs purification
- EI testing and frequency
- EI trend analysis for levels and variations
- Quality Agreements
- Bioavailability Data
- Packaging information which can contribute EIs

# Expectations from excipient suppliers... in general

- Can and will we supply EI data to assist drug makers with their risk assessments?
- We are not responsible for performing the drug maker's risk assessment!!
- Will we maintain their heavy metal(s) tests and limits in the (respective) monographs?
- **Failure to do EI tests can impact the drug maker's risk assessments! Is your Risk Assessment at risk?**



# Excipients supplier Reality Checks

- Some excipient makers have small volumes for pharma industries.
- The volumes sold to pharma may not justify continued support for the drug makers.
- ***After all these efforts.....***we hear  
“This is great, how can you reduce the lead?”



# Summary

- Minerals *may have* elevated Els.
- Minerals *may have* variations with Els.
- Mitigating steps may be applicable.
- **Processing** can affect Els.
- PDEs are related to **Exposure**.
- Bioavailability factors can affect Risk Assessments.
- Vanderbilt/IPEC-Americas/The Coalition are ready to assist the drug makers.
- **Reach out** to the excipient suppliers.



Thank you for your attention!



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