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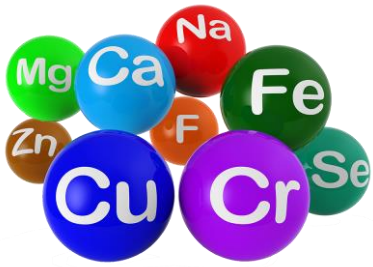

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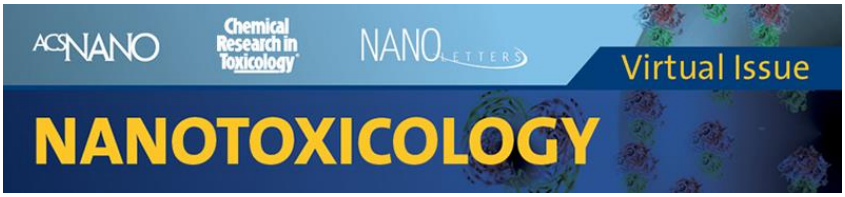

Hoping to inspires collaborations between researchers designing the next-generation of engineered nanomaterial-based technologies and those with the experimental and computational tools to probe the critical molecular interactions at the nano/bio interface.

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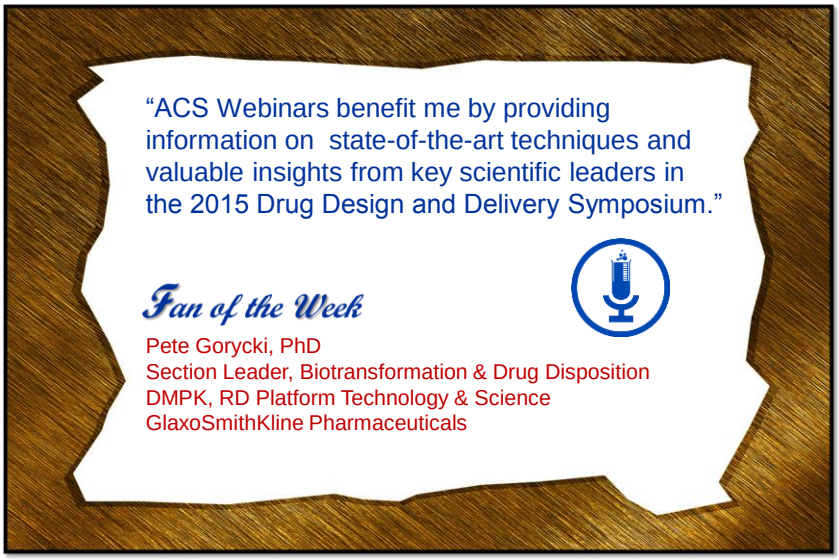

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Thursday, October 1, 2015

"**Predicting Nobel:** The Who and Why of the Next Chemistry Nobel Prize Winner"

Philip Ball, Science Writer, *Chemistry World*
Paul Bracher, Professor, St. Louis University and Blogger, *ChemBark*
Jillian Buriak, Professor, University of Alberta and Editor-in-Chief, *Chemistry of Materials*
Lauren Wolf, Asst. Managing Editor, *Chemical & Engineering News*
Matt Davenport, Associate Editor, *Chemical & Engineering News*
Co-produced with Chemical and Engineering News

Thursday, October 15, 2015

"**The Material World of Color:** Chemical Characterization of Pigments in Art"

Barbara Berrie, Head of Scientific Research, National Gallery of Art

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10

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Lecture 1: Preformulation and Biopharmaceutical Considerations in Drug Product Design and Development

Lecture 2: Drug Substance Physical Form Selection

Lecture 3: Drug Substance Physical Form Characterization

Lecture 4: Solubility: General Principles and Practical Considerations

Lecture 5: Dissolution and its Role in Solid Oral Dosage Form Development

Lecture 6: Biopharmaceutic Considerations

Lecture 7: Chemical Stability Assessment in Preformulation

Lecture 8: Excipient Compatibility Studies

Lecture 9: Impact of Material Properties on Formulation Development

Lecture 10: Prototype Formulations Screening and Characterization

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2015 Drug Design & Delivery Symposium

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Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

13

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14

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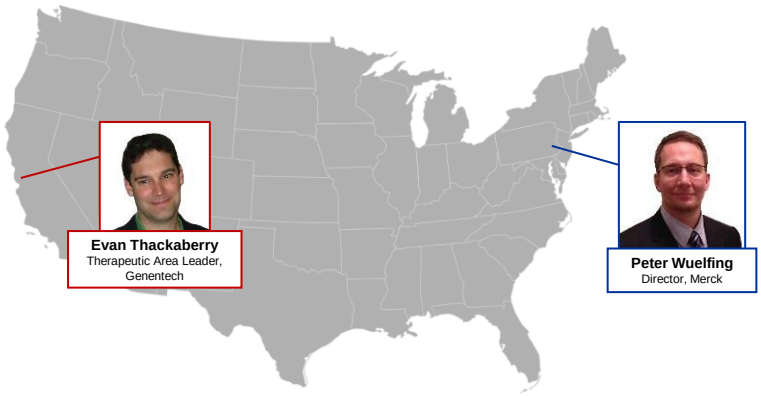
"2015 Drug Design and Delivery Symposium:
Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies"



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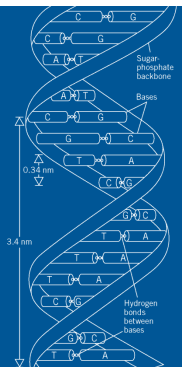
This session of the 2015 DDDS is being sponsored by Chemical Research in Toxicology



Delivery Options to Support Dose Escalation in Nonclinical Toxicology and Pharmacodynamic Activity Studies

Evan A. Thackaberry, Ph.D., D.A.B.T.
Safety Assessment
Genentech
South San Francisco, CA
thackabe@gene.com

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Outline

- **The Critical attributes of a nonclinical formulation**
  - What are we dosing and why?
  - What do we need from our nonclinical formulations?
  - Typical industry use

- **How the requirements for nonclinical formulations change over the lifespan of a drug development program.**
  - Phase-appropriate formulation selection
  - Case studies of formulation-related effects
- **The key differences between preclinical and clinical formulations.**
  - How are they different?
  - Can we use nonclinical studies to “qualify” new formulations?

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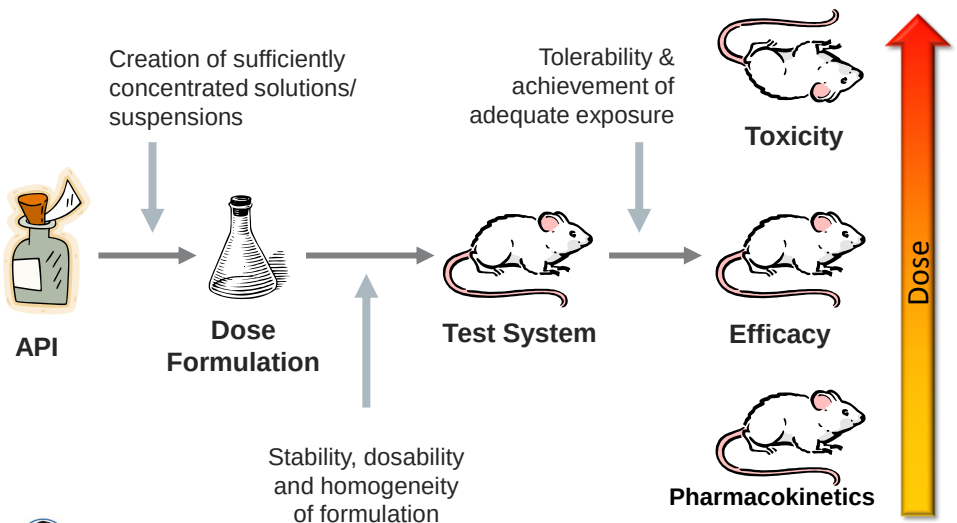
Formulation Support is Critical for *in vivo* Studies



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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Why are the dose levels so high in nonclinical toxicology studies?

- To identify and characterize target organ toxicity
- To establish safety factors for the clinic
- To define the maximum tolerated dose (MTD)
- In order to meet health authority expectations
- All of the above

19

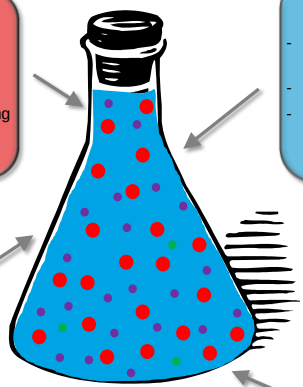
What Are We Dosing?

1) Active Pharmaceutical Ingredient (API)

- Target of Efficacy/Safety/PK Assessment
- Generally, the only analyte for PK/TK analysis
- Generally, the only ingredient providing a benefit for the patient

3) Vehicles

- Critical for producing a dosable solution/suspension
- Presumed to be inactive for purposes of efficacy/safety assessment
- Systemic exposure not assessed
- Provides no benefit to the patient – often not present in clinical formulations



2) Counter Ions

- Critical for enhancing API solubility, stability, etc.
- Presumed to be inactive for purposes of efficacy/safety assessment
- Systemic exposure not assessed
- Provides no benefit to the patient

4) Impurities

- Unwanted residuals or degradation products
- Hopefully, very low levels, no exposure analysis, risk assessments based on assumed 100% bioavailability
- Provides no benefit to the patient

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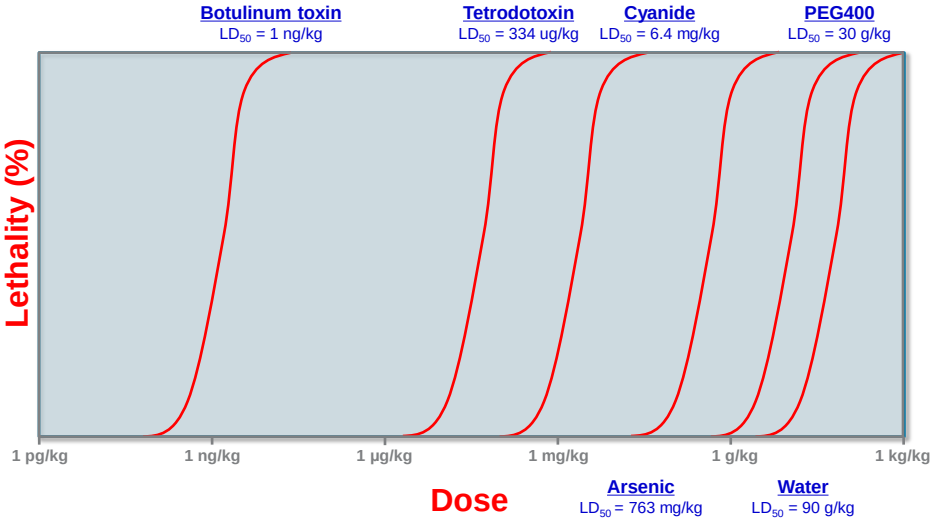
The Dose Makes the Poison



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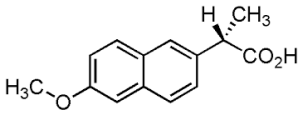
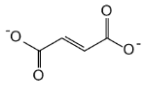
All Components of a Formulation may have Biologic Effects

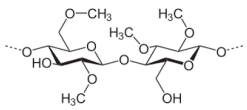
- **API**
  - PK, efficacy, and toxicity



- **Counter Ions**
  - Effects PK (therefore efficacy & toxicity), may cause toxicity in rare circumstances



- **Vehicles**
  - Effects PK (therefore efficacy and toxicity), may cause toxicity on their own



- **Impurities**
  - Rarely impact PK or efficacy, but can cause toxicity if levels are high enough

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Basic Nonclinical Formulation Requirements

- ☑ Produces adequate exposure to the API
- ☑ Allows for technically feasible dose administration
- ☑ Allows for sufficient homogeneity and stability
- ☑ Tolerated by the nonclinical species under the conditions of the study
- ☑ Does not interfere with the ability to interpret the key endpoints of the study

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Do We Really Have to Dose **THAT** High?

- **In order to provide a useful human risk assessment in support of clinical trials, the toxicity profile of a drug must be characterized**
  - This is the toxicologist's job!
- **Regulatory guidances (ICH M3) define the acceptable maximal dose levels**
  - Maximum tolerated dose (MTD) – animals cannot tolerate higher doses
  - Maximal feasible dose (MFD) – can't physically dose any higher
  - Plateau in exposure – absorption-limited compounds
  - >50X the efficacious clinical exposure - can change based on clinical data
  - 1000 mg/kg – or 2000 mg/kg for clinical doses above 1 g

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Route of Administration for Toxicology Studies

- **Most routes - Intravenous, subcutaneous, dermal, intravitreal, etc…**
  - Use the clinical formulation in all toxicity testing
  - Bridging studies may be required to support formulation changes
- **Oral drugs**
  - No need to use the clinical formulation
  - Oral gavage is generally used, but capsule dosing and dietary administration may be used as well
  - Key is to achieve high exposures in order to define the safety profile of the drug

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

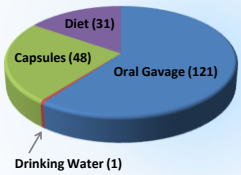
What types of formulations are most commonly used for nonclinical safety studies with novel oral drugs?

- Aqueous solutions
- Simple suspensions
- Lipid-based formulations
- Solvent formulations
- Solid dispersions

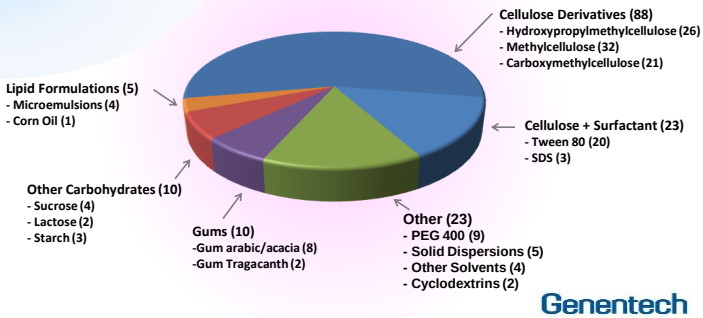
What Vehicles are Most Commonly Used in Oral GLP Studies Across the Industry?

Review of Oral Nonclinical Formulation Components; 2000-2011*

A) Method of Oral Administration



B) Vehicle Use in Oral Gavage Formulations



12

* Total = NCE 132 NDAs. Source: Thackaberry, 2013

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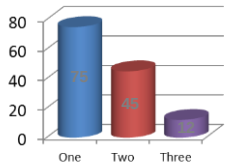
Conclusions from Survey of Successful Preclinical Formulations

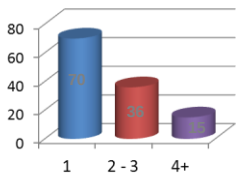
- **Method of Oral Administration**
  - Oral Gavage is used in vast majority of oral safety studies
  - Many programs used multiple dose administration paradigms
  - Capsule dosing generally limited to dog studies
  - Dietary studies limited to chronic rodent (generally, rat) studies

Methods of Oral Administration



- **Oral Gavage formulations**
  - Suspension agent (methylcellulose/gums) +/- surfactant (tween/SDS) used on >70% of all NDAs
  - Many programs used multiple oral gavage formulations
  - Formulations with potential for intolerability or biomarker effects used less frequently (lipid-based, HPBCD), or in subchronic (<1 mo) studies only

Oral Gavage Formulations



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* Total = NCE 118 NDAs. Source: Thackaberry, 2013

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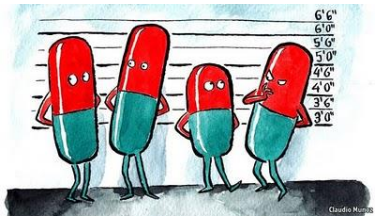
Critical Attributes & Industry Use: Key Messages

- There are no “inactive” or “nontoxic” vehicles or formulations. All vehicles have biologic effects at high doses.
- Vehicle concentration, dose volume, study duration, route of administration, species, and study endpoints will determine the acceptability of the formulation.
- In some cases, biological effects may be tolerated, as long as these effects don’t interfere with the study endpoints.
- Most sponsors use simple suspension formulations, with or without surfactants for nonclinical oral gavage studies.



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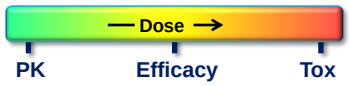
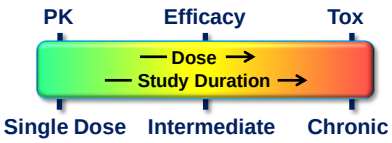
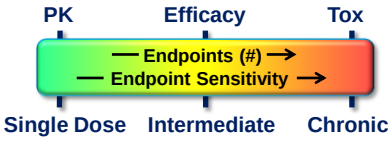
Formulation Requirements Depend on Study Design/Goals

1. Produces adequate exposure to the API
2. Allows for technically feasible dose administration
3. Allows for sufficient homogeneity and stability
4. Tolerated by the nonclinical species under the conditions of the study
5. Does not interfere with the ability to interpret the key endpoints of the study







Phase-Appropriate Formulation Strategy

Formulation strategy should take into account the current stage of a program

- Maximize flexibility for early stage lead optimization
  - Solvent-based platform formulation for pk screening
  - Grossly tolerated formulations that maximize exposure for efficacy studies
- Transition to GLP-friendly formulations with lead molecules
  - Aqueous solutions, suspensions or nanosuspensions, enabling formulations if needed
  - Avoid bridging pk work or timeline delays due to formulation switches
- If needed, switch to acceptable formulations for chronic tox/carcinogenicity
  - Suspensions, solid dispersions, nanosuspensions
  - May not be required for 1st line immediately life-threatening oncology indications

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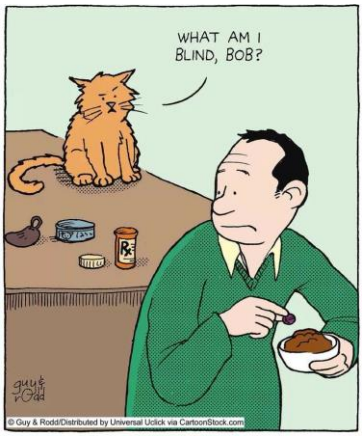
What Adverse Effects Might My Vehicle Produce in Non-Clinical Toxicology Studies?

- Acute Toxicity
- Poor Tolerability
- Repeat Dose Toxicity
- Repeat Dose Tolerability Issues
- Biochemical/Metabolic Alterations
- Interference with MS Bioanalysis



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Examples – Acute Toxicity/Tolerability Issues

- **Overt Toxicity**
  - Most often seen with i.v. vehicles
  - Intoxication (solvents such as propylene glycol, DMSO, ethanol, glycerol, etc…)
  - Generally don't see significant end-organ toxicity

- **Tolerability**
  - Emesis - Often seen with lipids, particularly medium chain triglycerides in large animals only
  - Diarrhea - Lipids, anti-foaming agents, surfactants
  - Anaphylaxis - Non-ionic surfactants (iv administration on dogs)

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Case Study: Toxicity/Tolerability of IV Solvents in Mice

Solvent	Published LD_{50}	MTD	NOEL	% of a 5 mL/kg dose volume at MTD
Diethylacetamide	2.3-3.2 g/kg	1.4 g/kg	468 mg/kg	30%
Dimethylsulfoxide	3.8-7.6 g/kg	2.2 g/kg	1.6 g/kg	40%
Ethanol	1.6-4.3 g/kg	986 mg/kg	197 mg/kg	25%
N-Methylpyrrolidine	54-3600 mg/kg!	1.3 g/kg	257 mg/kg	25%
Propylene glycol	5.0-8.6 g/kg	1.5 g/kg	1 g/kg	30%
PEG 400	8.6-9.7 g/kg	4.5 g/kg	1.7 g/kg	80%

Conclusions:
- LD_{50}'s aren't very helpful in setting a tolerated vehicle dose
- NOELs (required for studies with tox endpoints) are often much lower than MTDs (possible doses for PK studies).
- Avoiding vehicle-related tolerability issues with new formulations can be a problem in early research, particularly in PK screens – could this be mistaken for a compound-related effect?

Sources: TOXNET & Thackaberry et al (2014)

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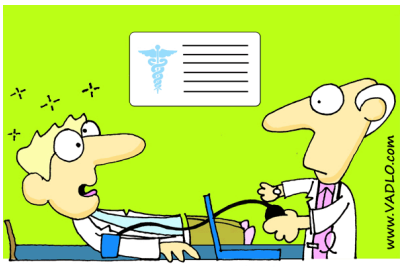
Examples – Repeat Dose Toxicity Issues

- **Repeat dose Toxicity**
  - Hepatotoxicity – Hydroxyopropyl-beta-cyclodextrin (HPBCD), Captisol, Ethanol
  - Renal Toxicity – PEG400, HPBCD, Captisol, Poloxamer 188
  - GI Toxicity – Sodium dodecyl sulfate (SDS)
  - Ocular Toxicity – Dimethylsulfoxide (DMSO)
- **Repeat Dose Tolerability**
  - Repeated exposure to some lipid formulations with "bad taste" leads to animal struggling and misdosing/aspiration
  - Cyclodextrins are not tolerated by rabbits (interfere with normal GI function?)



"Can you check my liver?
I just returned from a Gordon Conference'"

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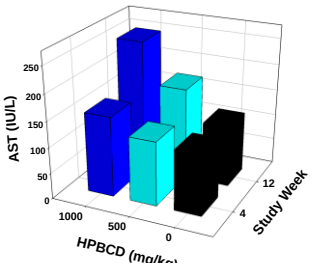
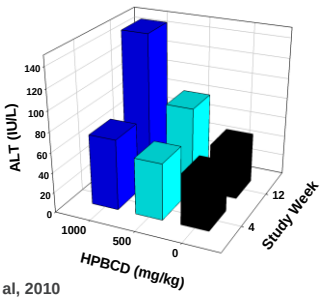
Case Study: HPBCD Impact on Critical Biomarkers of Toxicity

- **Study Design in Rats**
  - 3 mo of daily dosing at 500 & 1000 mg/kg (10 & 20%)
  - Clinical Pathology evaluated on study weeks 4 & 12
- **Results**
  - Dose- and Duration-dependent elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
  - AST and ALT are common biomarkers of hepatic damage
  - No other evidence of liver toxicity (clinical pathology & histopathology)
- **Conclusion**
  - Apparent hepatic toxicity
  - Effects appear to be minimal
  - **Impact on critical markers of hepatic damage will limit usefulness as a nonclinical formulations**





Source: Thackaberry et al, 2010

Examples – Metabolic/Biochemical Issues

- **Dramatic Shifts in Normal Metabolic Function**
  - •Chronic administration of lipids alters normal lipid metabolism, tumor incidence, & survival
  - •High dose phosphate buffers alters normal phosphate metabolism, can lead to bone/renal toxicity
- **Potential Interaction with drug metabolism, distribution, or excretion**
  - •Propylene glycol & PEG400 are excreted entirely by the kidneys – excretion may be altered by (or alter) renal effects of NCE
  - •Non-ionic surfactants inhibit CYP3A4 & Pgp in vitro (in vivo significance unknown)
  - •Anti Oxidants (Vitamin E TPGS) inhibit normal mechanisms of toxicity
- **•Vehicles which interfere with Mass Spec Performance**
  - •All PEGs (including PEG 400)
  - •High Dose Tween 80
  - •Cremophor EL
  - •Solutol HS 15
  - •Labrosol

22

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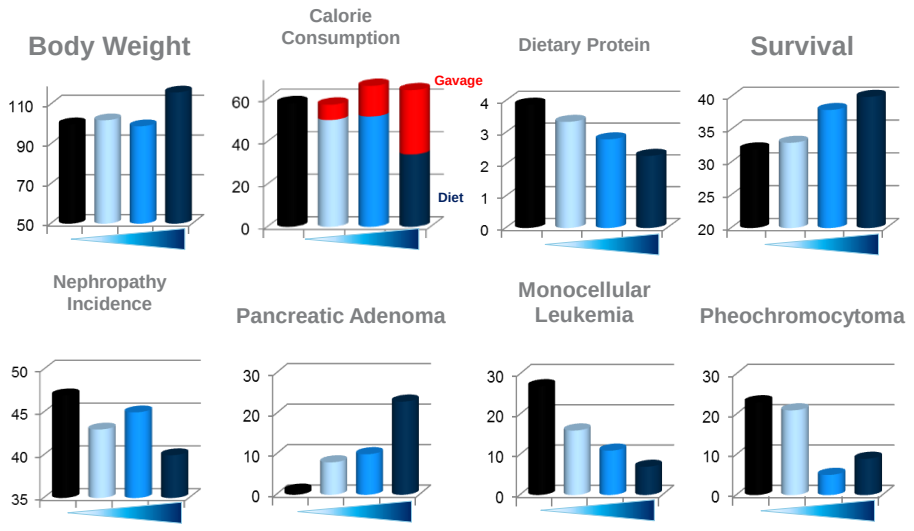
Case Study: Effects of Chronic Administration of Corn Oil* on Metabolism & Tumor Incidence in Rats



23

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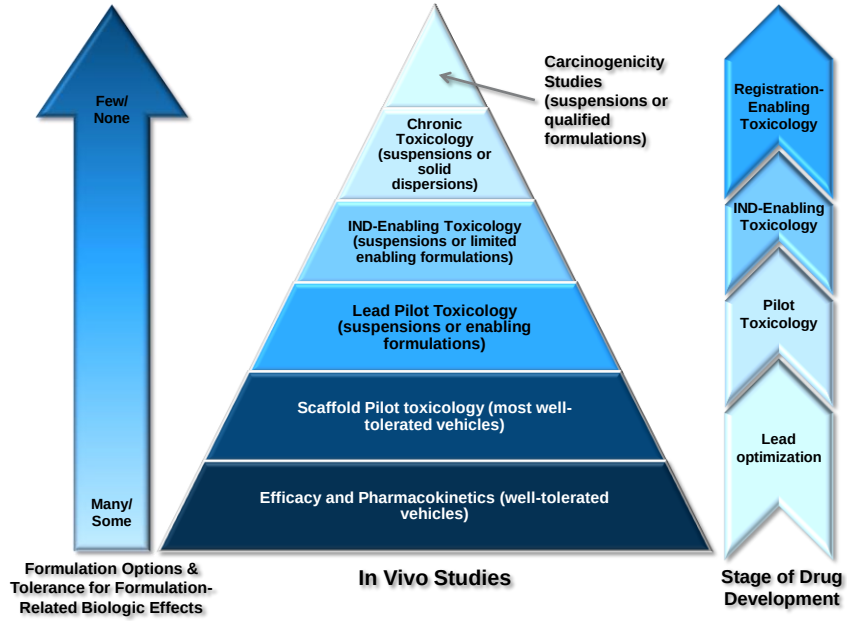
*** 2.5, 5.0, & 10.0 mL/kg of Corn oil/animal/day. Source: NTP, 1994**

Phase-Appropriate Formulation Strategy



The Toxicologist's Perspective on Formulation Selection

- **Study Requirements**
  - – Well tolerated
  - – Achieve adequate exposure
  - – **No vehicle-related toxicities or effects which can not be segregated from NCE effects, or which might inhibit our ability to interpret the study data**

"Take a few capsules each morning before you weigh yourself. They're filled with helium."

- **Molecule/Program Requirements**
  - – Use across all possible study durations (including chronic) and species. If not, develop a distinct formulation for chronic tox
  - – Limit complexity due to formulation changes or unproven vehicles

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

If we dosed patients/volunteers at the same <u>volume</u> as a typical oral nonclinical safety study, what approximate volume would they be asked to drink?

- 1 mL
- 5 mL
- 35 mL
- 350 mL
- 3 L

41

Nonclinical vs. Clinical Formulations for Oral Drugs

- For oral drugs, nonclinical and clinical formulations are typically distinct
- While the FDA regulates clinical excipients, there are no guidances dictating nonclinical formulation selection
  - Allows for more flexibility
  - Can lead to formulation-related issues on nonclinical studies
  - Makes qualifying novel excipients for the clinic more difficult

"Your prescription is cheaper if you buy it in bulk."

27

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Oral Dose Volume and Vehicle Dose are Much Higher in Nonclinical Studies

- **Standard nonclinical dose volumes are much greater than the volume used in the clinic**
  - Allows for higher doses of drug
  - Produces higher vehicle doses
  - Clinical excipient concentration (%) is not useful in assessing nonclinical tolerability
- **Doses used in non-clinical toxicology studies are generally much higher than those used in the clinic**
  - For non-oncology indications, generally 25-100X
  - Vehicle doses are much higher as well

Dose Volume

Species	Dose Volume
Rat	3.5 mL
Dog	50 mL
Human	350 mL

*Assumes a 5 mL/kg dose volume in a normal adult animal

Vehicle Dose

Vehicle %	Vehicle Dose
1%	~50 mg/kg/day
10%	~500 mg/kg/day
50%	~2.5 g/kg/day

*Assumes a 5 mL/kg dose volume

28

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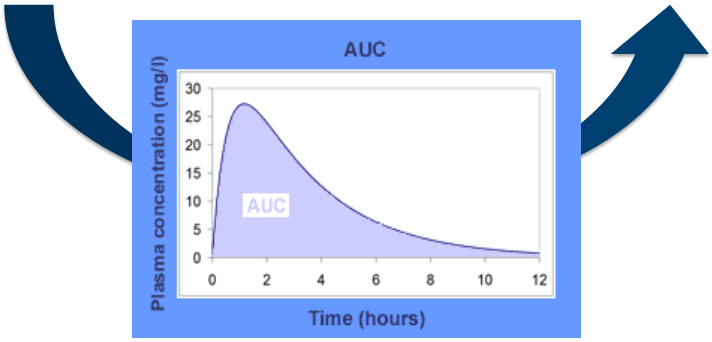
Exposure is used to Bridge Nonclinical and Clinical Safety Data

Establish plasma exposure (AUC and C_{max}) to API in nonclinical safety studies.

Compare to predicted clinical exposure (safety factors or exposure multiples) or efficacious dose (therapeutic index)



* Key assumption is that %F & Cl are likely to be different between nonclinical species and human, regardless of formulation

29

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Qualification of Novel Excipients

- The FDA requires a similar battery of studies to qualify a new clinical excipient as would be required for a new non-oncology drug (FDA, 2005)
- However the distinct composition of the nonclinical formulation for oral drugs means these new excipients are not always tested along side the drug
- There is no mechanism for gaining approval for a new excipient other than as part of a NDA/BLA
- If a novel excipient is required for your drug, it is best to identify the issue early and include it in your nonclinical tox studies, even with oral drugs

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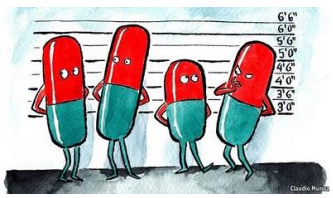
Formulation Strategy: Key Messages

- Phase-appropriate formulation strategy allows for maximum flexibility in early in vivo studies while anticipating the need for “clean” formulations in GLP toxicology studies.
- Many common vehicles may have unwanted effects that could impact the interpretation of a toxicology study, particularly in chronic studies.
- The nonclinical and clinical formulations are distinct. Exposure is used to bridge the safety data.
- Novel excipients require a similar nonclinical testing paradigm to novel drugs.



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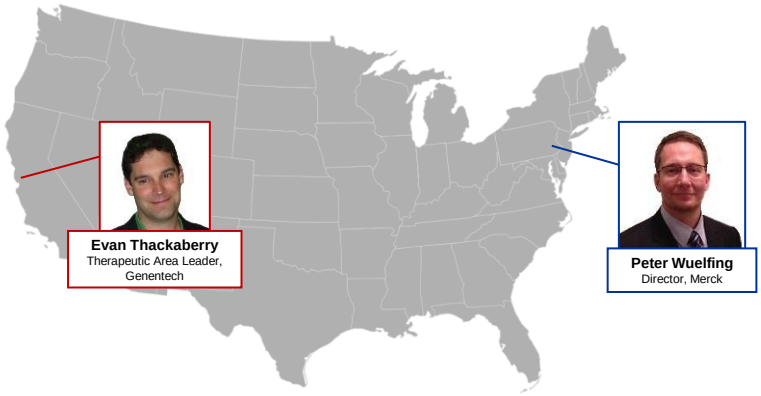

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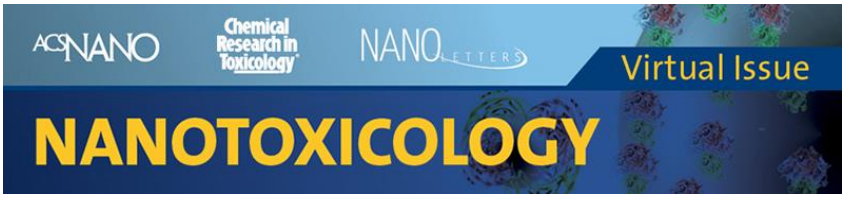

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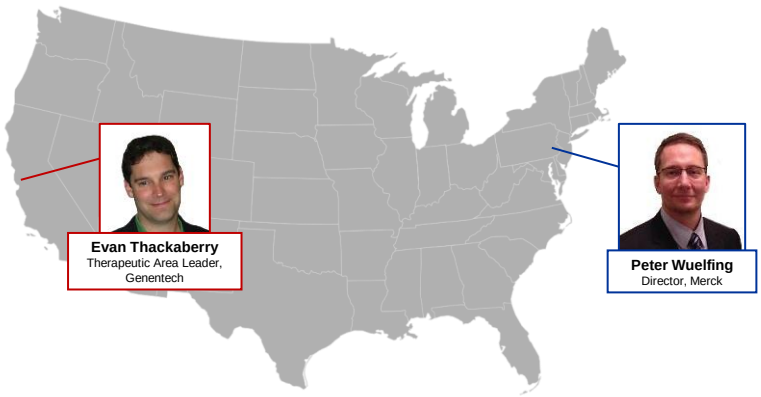

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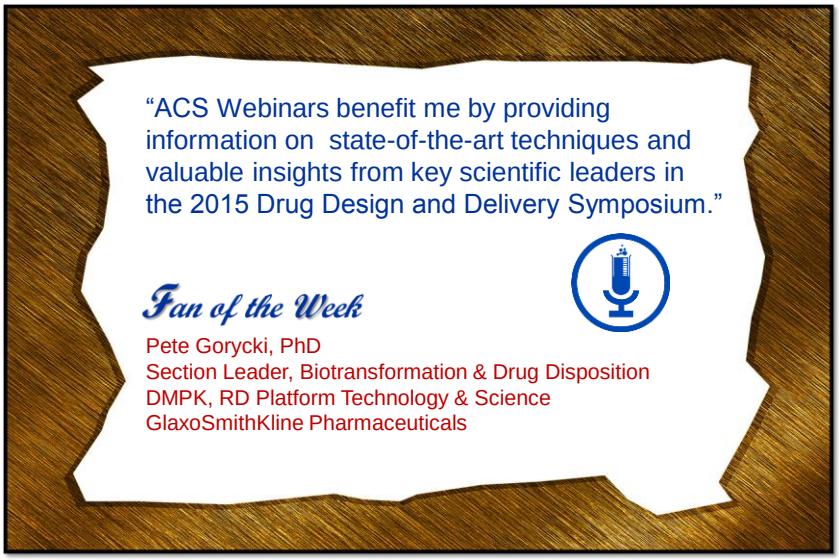

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59