American College of Toxicology

34th Annual Meeting Program

San Antonio, Texas

November 3–6, 2013

The JW Marriott San Antonio Hill Country Resort and Spa

www.actox.org

San Antonio photos are courtesy of JW Marriott Hill Country unless otherwise noted. Some photos by Barbara Kraft.

AMERICAN COLLEGE OF TOXICOLOGY

Welcome!

Dear Colleagues and Guests,

On behalf of the American College of Toxicology, welcome to ACT's 34th Annual Meeting at the JW Marriott San Antonio in the beautiful Texas Hill Country. It's my pleasure to present our meeting that's full of sessions catering to different aspects of applied and regulatory toxicology. We want you to get the most out of this meeting, so I encourage you to take a few minutes and review the schedule of scientific sessions and special events in this *Program*.

Our week kicks off on Sunday with seven half-day Continuing Education (CE) courses. It's not too late to register for a session. Stop by the ACT Registration Desk outside of the Exhibit Hall and we'll be happy to assist you. Look in the *Program* for a detailed description of each course.

Beginning on Monday, we will start each morning with a Plenary Lecture. We are pleased to announce this outstanding line-up of speakers that includes: Steven K. Galson of Amgen discussing "Science, Policy, and Risk in Public Health Regulations for the 21st Century"; Linda S. Birnbaum of the National Institute of Environmental Health Sciences speaking on "New Directions in Toxicology Testing Strategies"; and Roger A. Clemens of the University of Southern California on "Health and Policy Implications to Caffeine Exposure."

During your daily breaks, I encourage you to visit the exhibitors at their booths in the Exhibit Hall as they are a vital part of the meeting. We have introduced this year an additional incentive to visit the booths. Besides getting the latest information from the booth staff and scientists, we are offering great prizes too. You also will have the opportunity to learn of new developments from over 100 posters on display in the Exhibit Hall.

The ACT Annual Meetings are known for being collegial, with many opportunities for networking and catching up with friends and colleagues. Don't miss Monday's Awards Luncheon and evening Poster Reception, both of which are included in your registration fee. We will again feature "Jazzicology," our own home-grown band comprised of ACT members, during our Sunday reception which is a ticketed event.

I would like to extend a special thank you to Program Chair Drew A. Badger and Education Committee Chair Hanan N. Ghantous and their committees for planning an outstanding program.

We are looking forward to a fabulous week!

Robin C. Guy, MS, DABT, RQAP-GLP
2012–2013 ACT President

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Schedule of Events Overview

Saturday

3:00 PM–6:00 PM	Registration Open	Nelson W. Wolff Ballroom Foyer
5:00 PM–7:00 PM	ACT Council Meeting	Magnolia

Sunday

7:00 AM–5:00 PM	Registration Open	Nelson W. Wolff Ballroom Foyer
7:00 AM–8:00 AM	CE Continental Breakfast	Cibolo Ballroom Foyer
8:00 AM–11:30 AM	CE 1: Screening and Testing for Reproductive and Developmental Toxicity	Cibolo 3–4
	CE 2: Relevance of Animal Tumors in Assessing Human Risk of Pharmaceuticals	Cibolo 5
	CE 3: Writing for Regulatory Authorities	Cibolo 1–2
9:35 AM–10:05 AM	CE Refreshment Break	Cibolo Ballroom Foyer
12:00 Noon–1:00 PM	Lunch on Your Own	
12:00 Noon–1:00 PM	New Member Luncheon *(By Invitation Only)*	Sunday House
1:00 PM–4:30 PM	CE 4: Inclusion of Nonclinical Data in Drug Labels: Current and Upcoming Labeling Guidance, Practice, and Initiatives	Cibolo 3–4
	CE 5: Biologics 201: Advanced Topics in Nonclinical Safety Assessment of Biotechnology-Derived Drug Products	Cibolo 5
	CE 6: Inflammatory Biomarkers	Cibolo 6
	CE 7: All Eyes Focused on Ocular Toxicology and Pathology	Cibolo 1–2
1:30 PM–5:30 PM	Exhibits and Poster Set Up	Nelson W. Wolff Ballroom B&C
2:40 PM–3:15 PM	CE Refreshment Break	Cibolo Ballroom Foyer
4:00 PM–4:30 PM	Student Poster Set Up	Nelson W. Wolff Ballroom B&C
4:30 PM–6:30 PM	Student Poster Judging	Nelson W. Wolff Ballroom B&C
5:00 PM–6:00 PM	*IJT* Manuscript Submission Strategies Workshop—Recipes for Success, Formulas for Failure	Magnolia
6:30 PM–9:00 PM	Welcome Reception: Wine Tasting and Jazzicology *(Ticketed Event)*	Event Lawn 3 *In the event of rain: Nelson W. Wolff Ballroom A*

Schedule of Events Overview *(continued)*

Monday

7:00 AM–8:00 AM	Continental Breakfast *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
7:00 AM–8:00 AM	Exhibits and Posters Open *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
7:00 AM–5:00 PM	Registration Open	Nelson W. Wolff Ballroom Foyer
8:00 AM–8:55 AM	Plenary Lecture: Science, Policy, and Risk in Public Health Regulations for the 21st Century *Speaker: Steven K. Galson*	Nelson W. Wolff Ballroom A
8:45 AM–12:00 Noon	Exhibits and Posters Open *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
9:00 AM–12:00 Noon	Symposium 1: Antibody-Drug Conjugates: The Next Evolution in the Cure for Cancer	Cibolo 7
	Symposium 2: Translating Nonclinical Cardiovascular Toxicity Findings into Clinical Trial Design	Cibolo 6
	Symposium 3: Dermal Toxicology: Current Requirements, Methods, Models and Regulatory Perspectives	Cibolo 5
10:15 AM–10:45 AM	Refreshment Break *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
12:00 Noon–2:00 PM	Awards Ceremony and Luncheon *(Included with Registration Fee)* Speaker: *Albert E. Munson,* Distinguished Scientist Awardee	Nelson W. Wolff Ballroom A
2:00 PM–7:00 PM	Exhibits and Posters Open *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
2:00 PM–5:00 PM	Symposium 4: 4 M's: Mistakes, Misuse, Mismanagement, Misunderstanding…Looking at Things That Have Gone Wrong in the Past: What to Learn to Plan for the Future	Cibolo 5
	Symposium 5: Clinical, Regulatory, and Nonclinical Study Design Issues Associated with Testing and Approval of Medical Devices	Cibolo 6
	Symposium 6: Tumorigenicity Assessment in Preclinical Development of Pluripotent Stem Cell-Based Therapies	Cibolo 7
3:15 PM–4:45 PM	Refreshment Break *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
5:30 PM–7:00 PM	Poster Session and Reception *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C

Schedule of Events Overview *(continued)*

Tuesday

6:45 AM–8:00 AM	Past Presidents' Breakfast *(By Invitation Only)*	Magnolia
7:00 AM–8:00 AM	Continental Breakfast *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
7:00 AM–8:00 AM	Exhibits and Posters Open *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
7:00 AM–5:00 PM	Registration Open	Nelson W. Wolff Ballroom Foyer
8:00 AM–8:55 AM	Plenary Lecture: New Directions in Toxicology Testing Strategies *Speaker: Linda S. Birnbaum*	Nelson W. Wolff Ballroom A
8:45 AM–4:30 PM	Exhibits and Posters Open *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
9:00 AM–12:00 Noon	Symposium 7: The Art of Dose Selection: From the Bench to the Clinic	Cibolo 7
	Symposium 8: Endocrine Disruption Screening—Status of the US EPA and EU Programs: State of the Science and Slate for the Future	Cibolo 6
	Symposium 9: Secondary Pharmacology: Assay, Uses, and Evaluation	Cibolo 5
10:25 AM–10:55 AM	Refreshment Break *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
12:00 Noon–1:30 PM	*IJT* Editorial Board Meeting	Cibolo 3
12:00 Noon–1:30 PM	Resource Committee Meeting	Magnolia
12:00 Noon–1:30 PM	Lunch on Your Own	
12:00 Noon–1:30 PM	2014 Program Planning Meeting *(All ACT Members Invited, box lunch provided. Sign up at Registration Desk.)*	Cibolo 4
2:00 PM–5:00 PM	Symposium 10: The Drug Development Paradigm for a Small Molecule: Case Study of the Janus Kinase (JAK) Inhibitor Tofacitinib for the Treatment of Rheumatoid Arthritis	Cibolo 5
	Symposium 11: Impact of Combination Toxicology Studies on Pharmaceutical Development: Careful Consideration of Study Objectives, Timing, and Design	Cibolo 6
	Symposium 12: Phospholipidosis: Evaluation and Management of Its Risk	Cibolo 7
3:30 PM–3:55 PM	Refreshment Break *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
4:00 PM–12:00 Midnight	Exhibit Teardown *(Exhibit Hall)*	Nelson W. Wolff Ballroom B&C
5:00 PM–6:30 PM	ACT Members' Meeting *(All ACT Members Invited)*	Cibolo 5

Schedule of Events Overview *(continued)*

Wednesday

7:00 AM–8:00 AM	Continental Breakfast	Nelson W. Wolff Ballroom Foyer
7:00 AM–7:55 AM	Exhibitor-Hosted Program: Changes in Preclinical Safety Evaluation for Cardiotoxicity: Removal of the E14 Clinical Guidance by 2015—An Opportunity and a Challenge *Presented by: Battelle Memorial Institute*	Cibolo 4
7:30 AM–2:00 PM	Registration Open	Nelson W. Wolff Ballroom Foyer
8:00 AM–8:55 AM	Plenary Lecture: Health and Policy Implications to Caffeine Exposure *Speaker: Roger A. Clemens*	Nelson W. Wolff Ballroom A
9:00 AM–12:00 Noon	Symposium 13: Prospective Approaches to Characterize Potential Neurotoxicity	Cibolo 5
	Symposium 14: Consumer Healthcare Ingredient Issues and Potential Impact on Product Safety and Risk Communication	Cibolo 6
	Symposium 15: Managing the Regulatory Impact of Rodent Tumor Findings	Cibolo 7
10:20 AM–10:45 AM	Refreshment Break	Cibolo Ballroom Foyer
12:00 Noon–1:30 PM	ACT Council Meeting	Magnolia
12:00 Noon–12:55 PM	Exhibitor-Hosted Program: Carcinogenicity WOE and the rasH2 Mouse BioAssay *Presented by: BioReliance Corporation*	Cibolo 4
	Exhibitor-Hosted Program: Assays to Monitor T-Cell Functions: How and When to Apply to Toxicology Studies *Presented by: Charles River*	Cibolo 2
12:00 Noon–1:00 PM	Lunch On Your Own	
2:00 PM–5:00 PM	Symposium 16: Hot Topics	Cibolo 5
3:00 PM–3:20 PM	Refreshment Break	Cibolo Ballroom Foyer

American College of Toxicology

34th Annual Meeting

San Antonio
Texas Hill Country
November 3–6, 2013

2013

Program Content

The ACT *Program* is sponsored in part by the generous contribution from Huntingdon Life Sciences.

General Information

Venue

JW Marriott Hill Country Resort and Spa

23808 Resort Parkway, San Antonio, Texas 78261
Tel: 210.276.2500, Fax: 210.403.3452

ACT 34th Annual Meeting registrants will enjoy the JW Marriott San Antonio Hill Country Resort and Spa where clear streams and towering oaks and cedars meet the majesty of rugged hills and a contemporary facility well suited for meeting activities and informal interaction with your colleagues. The JW Marriott San Antonio Hill Country Resort and Spa was ranked as one of the top 500 hotels in the world in 2011 by the readers of *Travel + Leisure* Magazine and designated Marriott International's 2012 Hotel of the Year. Vibrant colors of the sunset, tooled leather, carved wood, and hewn stonework are used throughout the resort, and the meeting area is complemented by a variety of stunning indoor and outdoor spaces for conversations with your colleagues. Options during down time are numerous. The 36-hole TPC San Antonio features two championship golf courses on the PGA tour. The River Bluff Water Experience offers a complex of pools, fountains, waterfalls, and rivers for guests and an abundance of poolside lounges to soak in the Texas sun. Indulge in luxurious spa treatments, use the private fitness center, or enjoy the Texas cuisine that links the area's German legacy with spicy Southwestern flavors in over a half-dozen restaurants at the resort. Experience the natural Hill Country beauty and variety by exploring the varied terrain by foot. Only 20 minutes from downtown San Antonio, the elements of authentic roots, hacienda style, beautiful views, and healing waters at this magnificent resort will compliment the stimulating scientific exchange at the ACT meeting.

Internet Access

ACT attendees will receive complimentary Wi-Fi Internet access throughout the meeting. A pass code will be available at the Registration Desk.

Room Reservations

Meeting Rate

$229 single/double occupancy
Check-in time is 4:00 pm and check-out time is 11:00 am.

Reduced Resort Fee

A reduced resort fee of $15 per room per night (regular fee is $28.00) has been offered to ACT guests. This fee is optional for guests. The Resort Fee includes complimentary Wi-Fi Internet access in guest rooms and public space, local/domestic long distance calls from guest rooms, golf bag storage at bell stand, access to resort and Lantana Spa fitness centers, including fitness classes offered at spa, 2 complimentary signature welcome drinks in Crooked Branch lobby bar, 15% discount off meals in Replenish Spa Bistro, tennis court access with racket, and 10% discount in Range Riders Kids Club.

Parking

Complimentary self-parking is available. Valet parking is also available at $27 per day. Short-term valet parking (up to 9 hours) is also available for $10.

Hertz

Located on property at the JW Marriott, Hertz is offering special meeting rates to ACT meeting attendees. Reservations can be made online or by calling Hertz directly at 800.654.2240 or 405.749.4434. Please provide the CV #04X50002 when making the reservation. To talk to the Hertz desk at the JW Marriott, please call 210.491.5862.

Climate

November is a good month to visit the San Antonio region, with daily highs expected to be in the mid 70s, lows in the 50s, moderate humidity, and only light breezes. Daylight savings time ends on Sunday, November 3.

Attire

The meeting attire is business casual. The meeting rooms may be cool and require a lightweight layer. Additionally, comfortable shoes for walking are advisable.

Registration Information

The registration fee includes the American College of Toxicology Awards Luncheon Monday, continental breakfast Monday through Wednesday, all refreshment breaks, and a Monday evening poster session and reception. Additional registration fees are required for Continuing Education courses and for the Sunday evening Welcome Reception.

New this year: If you have registered prior to October 15, you will receive your name badge, course ticket(s), and qualifying ribbons in the mail. You will not need to stand in the registration line if you received these in advance. You may pick up the *Program* and your badge holder onsite.

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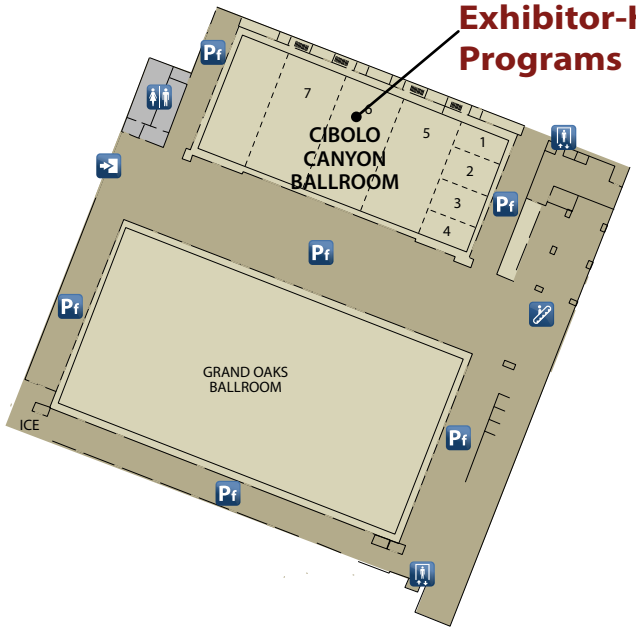
Hotel Map

LEVEL 3

LEVEL 2



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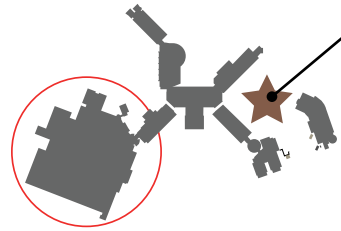

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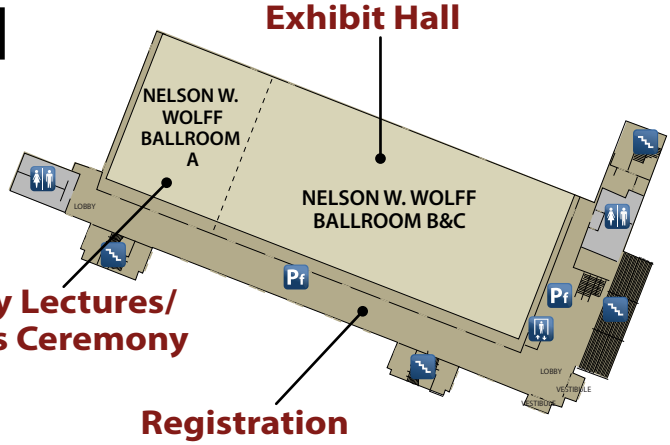


RESTROOMS
ESCALATOR
PREFUNCTION
STAIRS

JW Marriott Restaurant Listing

The JW Marriott San Antonio Hill Country Resort and Spa offers six distinct dining options plus in-room dining. Each restaurant listed below offers a unique atmosphere, from the quiet elegance of our fine dining restaurant, to the relaxing poolside environment to the thrill, and the high energy of the sports bar. Diners enjoy imaginative menus, cocktails, and beverages with a focus on fresh, local, sustainable, and organic ingredients.

Cibolo Moon

- Southwestern
  Open for breakfast, lunch, and dinner

This premier JW Marriott restaurant features Southwestern and Mexican inspired cuisine for breakfast, lunch, and dinner. Enjoy an expansive breakfast buffet, daily Blue Plate specials, traditional Mexican favorites, outstanding Texas BBQ, and more.

Crooked Branch

- Eclectic

The signature bar, located in the lobby, has beautiful views and is the perfect place to meet with friends or just to relax and unwind with a well-crafted cocktail. Order from a delicious menu of items featuring local artisan cheeses, great BBQ, Tex-Mex specialties, and more.

18 Oaks

- Steakhouse
  Open for breakfast, lunch, and dinner

Located at the TPC San Antonio Clubhouse, 18 Oaks is traditional-style fine steakhouse featuring perfectly aged steaks seared to order, fresh seafood and poultry dishes, epic sides, and an excellent variety of wine.

High Velocity

- American
  Open for lunch and dinner

This famous San Antonio sports bar puts you right in the action with a 120-foot long media display and monitors galore. Choose from a deep roster of craft beers and other beverages, plus an outstanding lineup of great food.

Rivertop Grill

- Casual

The Rivertop menu features foods built on San Antonio regional cuisine. These may include fish tacos, carne asada, carnitas, fresh barbecue pork sliders, frito pie with Texas chili and salsa fresca, grilled burgers, chicken sandwiches, and fresh grilled seafood.

Spa Bistro

- Refreshing

The distinctive Spa Bistro offers food and beverage options to assist in relaxing the body and mind. Options will range from energizing post work out smoothies to relaxing after treatment lunches.

San Antonio Restaurant Listing

Aldaco's (Stone Oak)	Mexican	6.7 miles	20079 Stone Oak Parkway San Antonio, TX	210.494.0561
Aldino's at the Vineyard	Italian	9.6 miles	1203 NW Loop 1604 San Antonio, TX	210.340.0000
BJ's Brewhouse	American	3.6 miles	22410 Highway 281N in the Village at Stone Oak San Antonio, TX	210.497.6070
Bourbon Street Seafood	Seafood	7.8 miles	2815 North Loop 1604 San Antonio, TX	210.545.0666
Chama Gaucha Brazilian Steakhouse	Steakhouse	9.1 miles	18318 Sonterra Place San Antonio, TX	210.564.9400
Coco Chocolate Lounge and Bistro	Martini Bar & Bistro	9 miles	18402 US 281 N at Loop 1604 San Antonio, TX	210.491.4480 *(Dinner only; Opens at 3:00 pm daily)*
Cover 3	American	12 miles	1806 NW at Loop 1604 San Antonio, TX	210.479.9700
Drew's American Grill	American	8.2 miles	18740 Stone Oak Parkway San Antonio, TX	210.483.7600
Kirby's	Steakhouse	8.2 miles	123 N Loop 1604 East San Antonio, TX	210.404.2221
La Hacienda de Los Barrios	Mexican	8.5 miles	18747 Redland Road San Antonio, TX	210.497.8000
Ounce Steakhouse	Steakhouse	9.7 miles	1401 N Loop 1604 W San Antonio, TX	210.493.6200
Paesano's 1604	Italian	15.9 miles	3622 Paesanos Parkway San Antonio, TX	210.493.1604
Silo Elevated Cuisine	New American	12 miles	434 N Loop 1604 West San Antonio, TX	210.483.8989
Stone Works Big Rock Grill	American	10.2 miles	1201 N Loop 1604 San Antonio, TX	210.764.0400
Sushi Zushi	Japanese	8.2 miles	18720 Stone Oak Parkway San Antonio, TX	210.545.6100
Wildfish	Seafood Grill	12.8 miles	1834 NW Loop 1604 San Antonio, TX	210.493.1600

San Antonio Map

Special Events

IJT Manuscript Submission Strategies—Recipes for Success, Formulas for Failure

Sunday, November 3
5:00 PM–6:00 PM
Magnolia
(Open Event)

International Journal of Toxicology (IJT) Editor Mary Beth Genter and Associate Editor William Brock will present this workshop. Attendees will learn strategies to improve success in publishing in the ACT journal.

Welcome Reception and Wine Tasting

Sunday, November 3
6:30 PM–9:00 PM
Event Lawn 3
(Ticketed Event)

After a stimulating day of Continuing Education, mingle with your colleagues at a special ACT-subsidized event featuring the best of Texas hospitality, food, and beverage. Gather under the Texas sky on the Event Lawn 3 of the beautiful JW Marriott San Antonio Hill Country Resort and Spa, sample wines from two premier Texas vintners, and enjoy brisket and other special dinner items. You will relax to the sounds of Jazzicology, a combo of ACT members appearing again by popular demand.

Purchase your ticket soon as there is limited seating for this fabulous event. Wine tasting is included with the ticket and cash bar will be available. In the event of rain this activity will be in the Nelson W. Wolff Ballroom A.

Awards Ceremony and Luncheon

Monday, November 4
12:00 Noon–2:00 PM
Nelson W. Wolff Ballroom A
(Open Event)

The Distinguished Scientist Award recipient, Albert E. Munson, will provide the keynote presentation at this lunch, which is included in the Annual Meeting registration. Other award recipients will be recognized and the Furst Award for the best student poster at the meeting will be announced.

Poster Session and Reception

Monday, November 4
5:30 PM–7:00 PM
Nelson W. Wolff Ballroom B&C
Sponsored by SAGE
(Open Event)

This is the opportunity to discuss the latest research findings and methodology with poster presenters and visit with exhibitors during a wine and cheese reception. Reception is included in the Annual Meeting registration fee.

ACT Members' Meeting

Tuesday, November 5
5:00 PM–6:30 PM
Cibolo 5
(All ACT Members Invited)

Come to the meeting to hear the latest ACT business and provide feedback for the future.

ACT Members' Meeting

Tuesday, November 5, 5:00 PM–6:30 PM

ACT Members Only

Join your colleagues for the annual Members' meeting.
Hear important reports from:

- President Robin C. Guy
- President-Elect Drew A. Badger
- Treasurer Norman N. Kim
- Membership Committee Chair Deborah L. Novicki
- Nominating Committee Chair David G. Serota
- Publications Committee Chair Mary Beth Genter
- And more!

Be an active member of
the American College of Toxicology and participate!

No registration required.

Apply to Become an ACT Member

Why pay full price
for another ACT Annual Meeting?
Members receive a discounted rate
on registration, plus much more!

For more information on member types,
benefits, and requirements, please visit
www.actox.org/aboutact/membership.asp

2013 Awards

These awards will be given out at the Awards Ceremony and Luncheon on Monday, November 4, at 12:00 noon–2:00 pm in the Nelson W. Wolff Ballroom A. All attendees are welcome. For a historical listing of award recipients, see page 131 or visit **www.actox.org/aboutact/pastrecipients.asp**.

ACT Distinguished Scientist Award

Recognizes an individual (not necessarily a member of ACT) who has made outstanding contributions to toxicology, its relationship to the regulation of chemicals, and the improvement of public health. The DSA winner is the Luncheon Speaker.

2013.....Albert E. Munson, PhD, National Institute for Occupational Safety and Health's Health Effects Laboratory Division, Morgantown, WV

ACT Young Professional Award

Recognizes an ACT member in good standing with no more than 10 years of full-time employment experience since completing the highest degree (not including postdoctoral training). Nominee must have demonstrated outstanding service to the College, including serving as an officer, councilor, committee member, and/or frequent participation and contribution at the Annual Meeting or any other College activity (i.e., speaker, chairperson, organizing committee, etc.).

2013.....Lisa D. Beilke, MSPH, PhD, DABT, Toxicology Solutions, Inc., San Diego, CA

ACT Service Award

Recognizes an individual for their long term dedication to the American College of Toxicology including but not limited to service to the College (e.g., councilor, officer, committee member), frequent participation and contribution to the Annual Meeting (speaker, chairperson, organizing committee), and longstanding support of the College's activities. The recipient must be a member of ACT.

2013.....John A. Thomas, PhD, DATS, FACT, Indiana University School of Medicine, Fishers, IN

ACT Carol C. Lemire Unsung Hero Award

Recognizes an ACT member or staff who has made substantive unrecognized contributions to ACT. He or she should have demonstrated on-going willingness to help in ACT activities generally behind the scenes. The person cannot have held an elected Council office within ACT in the past four years.

2013.....Winner to be announced

ACT President's Award for Best Paper Published in the *International Journal of Toxicology*

Recognizes the authors of the best paper published in *IJT* issues 5 and 6 of the previous year through and including *IJT* issue 4 (July–August) of the current year.

2013.....Winner to be announced

ACT Furst Award

The Furst Award is determined by a panel of judges during a dedicated judging session at the annual meeting for the best Student Poster presentation.

2013.....Winner to be announced

ACT Student Travel Awards

A limited number of graduate Student Travel Awards for current students will be awarded based on merit of abstracts and completed applications.

2013.....Winners to be announced

Join us for the

Welcome Reception and Wine Tasting

Sunday, November 3
6:30 PM–9:00 PM

Mingle with your colleagues at a special event featuring the best of Texas hospitality, food, and beverage.

Gather under the Texas sky on the Event Lawn 3 of the beautiful JW Marriott, sample wines from premier Texas vintners, and enjoy brisket and other special dinner items.

Relax to the sounds of
JAZZICOLOGY,
a combo of ACT members appearing again by popular demand.

Purchase your ticket today as there is limited seating for this fabulous event. Wine tasting is included with the ticket and a cash bar will be available.

Ticket $50
($100 Value. Event subsidized by ACT)

A Special Tribute to Eve Kagan

A thank you for more than 20 years of dedicated service to the American College of Toxicology.

After over 20 highly productive years with ACT, Eve will be leaving us with a legacy of success, including solid finances, friendly and truly helpful interactions while working in the main office, and being a knowledgeable liaison for exhibitors and sponsors. Eve was always the Voice of ACT. Most recently, her knowledge of our history, and scanning, compiling, and organizing photos, meeting minutes, programs, and specific Symposia and CE courses are a true tribute to her, and I will always remember the devotion that Eve put into the project. Eve and I go back about 20 years and I will miss her! Best wishes Eve!

Robin C. Guy
ACT President, 2012–2013

Eve, having served with you on Council for the better part of five years, I will fondly remember how consistently you aired a positive and sensitive vibe in the presence of a myriad of personalities, few of which are gentle… You are a great role model of patience, humility, and teamwork. All the best in your next chapter!

Drew A. Badger
ACT President Elect, 2012–2013

20 years is a lifetime for many in our industry. Thank you for all your contributions to ACT. Your detailed approach to accomplish the numerous tasks all those years is truly amazing. On behalf of ACT including all who have come before, I would like to recognize you and thank you for all you have done for us. A successful organization like ACT is where it is today because of what you made it become. Wish you all the best in your future endeavors.

Norman N. Kim
ACT Treasurer, 2011–2013

Congratulations on your well-deserved retirement! Whenever I think of you I will remember your smiling face and cheerful disposition. I hope you have fond memories of all of us at ACT. Thank you for your many years of service. Keep that sunny disposition wherever you go! All the best.

Mary Ellen Cosenza
ACT Vice President, 2012–2013

It has been my great pleasure to have worked with you over the past seven years in making ACT the great organization that it is. We both remember the 'lean' years, but through your strength of character and commitment to excellence, you have made our time together so meaningful and enjoyable. Best wishes in the future and please know that you always have a good friend in Michigan.

David G. Serota
ACT President, 2011–2012

Where to begin? Eve (with Carol) was the glue that held ACT together during my years in the presidential chain. From a tentative beginning as a "know-nothing" VP–elect to my final year as a much more experienced Past President, Eve was my "go to" person. She ALWAYS had the answers to my questions and frequently answered them before I asked! (By sending subtle reminders about what needed to be done before I knew that I needed to do it). With her quiet charm and Irish lilt, Eve guided the diverse group of personalities that was the ACT Council through the mechanics of leading the College and provided seemingly effortless support. Eve is the epitome of Grace Under Pressure, Calm in the Midst of Chaos. She was always a gracious advocate for ACT and a skilled mediator when differences of opinion needed to be resolved.

So, Eve, THANK YOU!! …..for your friendship, for your guidance, for making ACT a fun and rewarding place to be, and … for making me look good!! I will miss you.

Carol S. Auletta
ACT President, 2009–2010

My first recollection of Eve was from an ACT annual meeting (longer ago than I would like to say). I was an invited speaker, and when checking in at the registration desk, this sweet lady with a Scottish accent told me that I could stay for sessions that day, but would have to pay the registration fee to attend the entire meeting. Well, I started to cop a big-shot attitude with her, but she smiled and said "I'm sure we can work something out." I wrote her a check for registration. As we say in the South: Eve could charm the venom out of a copperhead (irony intended). She has been the welcoming face of ACT for as long as I can remember, and it has been our great fortune to have her. It is difficult to imagine ACT without her—common sense, deft touch with difficult issues, and especially dedication—and really caring—about our organization. She will be greatly missed, and I wish her all the best in the future.

Kenneth L. Hastings
ACT President, 2008–2009

A Special Tribute to Eve Kagan

A thank you for more than 20 years of dedicated service to the American College of Toxicology.

Dear Eve: Flanked by the Teratology Society and the American College of Toxicology (ACT), we have known each other for many years. I have truly enjoyed meeting your family and have treasured the stories you shared with me about growing up in Scotland. You have been a solid fixture of the ACT for many years. You have been an obvious credit to our growth and stability. The numerous tributes which are being bestowed on you are an indication of the high esteem in which you are held. I want to complement them by adding a personal expression of deep respect for you, especially for the help you provided me when I was President-Elect (2006) and President (2007). Your constant courtesy, the high commitment with which you performed many difficult tasks, (e.g., soliciting sponsorship money for ACT and dealing with exhibitors), and your many sacrifices on behalf of ACT, more than justify all the wonderful accolades which you are reading today. Thus, I say goodbye; I am thankful for our friendship. I will miss you. May you and your family continue to enjoy life at its finest!

Stephen B. Harris
ACT President, 2006–2007

I don't recall a time that Eve wasn't in the ACT office. She was most often the first voice I heard whenever I called with questions. When coming in for Council meetings, stopping to pick up registration materials at the Annual Meeting, or setting up the booth at SOT, her face was the first one I saw and she always had a smile. Her smile and happy demeanor were infectious. Her work was top notch and she made significant advances in getting new corporate members, working with the exhibitors, and getting materials ready for the Annual Meeting. As with Carol, I don't think I could have had a successful time on the Executive Council without her. Eve, you will be greatly missed by all who knew you.

Leigh Ann Burns Naas
ACT President, 2005–2006

I enjoyed working with Eve on Council and when I served as president. Not only was she able and willing to do all kinds of tasks, but she was always pleasant and smiling even in the face of difficult issues. But what I found to be the most enjoyable were the times we sat and visited after problems were solved. I especially liked meeting her family at various times through the years. I know Eve will keep on savoring life in retirement. I will miss her at all our meetings, though.

Patricia Frank
ACT President, 2004–2005

Eve, your dedication and efforts for ACT have been second to none (maybe only Carol!). It goes without saying that the College would not be where it is today without your involvement. I appreciated all your help during my time on Council. It clearly made my job a lot easier. I wish you all the best as you embark on the next chapter.

John Atkinson
ACT President, 2002-2003

Without your able assistance to Carol, I am certain that the ACT would not have accomplished all that it has. You were certainly an inspiration and great help to all of us who set up Symposia and other venues so they went off with no problems. Your smile and friendliness made it all worthwhile. The best to you always.

Robert E. Osterberg
ACT President, 2001–2002

Eve Kagan has been the "right hand" of ACT for decades and is the real person at the other end of a phone line taking care of details that are essential to making the organization work effectively and efficiently for its members. Her role in establishing how ACT approaches and successfully manages sponsor and exhibitor relations for its annual meetings has been essential to the success, financial growth, and image of ACT even in financially challenging times. When I became president, Eve had not been given complete authority to organize and manage the sponsor and exhibitor contributions to our annual meetings and the officers and members of Council were struggling with how to grow ACT sponsor support and increase the number of exhibitors (we had very few in those days and could fit them all in a hallway or small room). We decided to give Eve this authority and she spearheaded this effort into an activity with increasing success every year. Her efforts on behalf of the ACT and its members have been nothing less than spectacular. Eve, thank you for everything you've done over the years to help take the concept of ACT being a collegial, issue-focused, growing, financially healthy, and member appreciated organization from dream to reality. This could never have been accomplished without you.

David Hobson
ACT President, 1998–1999

I do not recall exactly when Eve and I first met, but it was probably through Carol Lemire about 20 or more years ago. Since that time we have had encounters pertaining to a variety of ACT events. Eve was always ready to assist and took on a variety of college-related tasks. She was a truly dedicated administrator and she toiled endlessly to promote the College. Her friendship will be missed.

My wife Barbara and I wish Eve and her family a happy, healthy, long retirement. We hope that you will enjoy your grandchildren and that you have the opportunity to travel abroad. We have cherished your friendship over the many years. Thank you Eve.

John A. Thomas
ACT President, 1996–1997

Pictured above: ACT 2011–2012 Council with Eve

Thank You Eve

PROGRAM AGENDA

Continuing Educations (CE) courses are 3.5 hours each and held either Sunday morning (AM) or Sunday afternoon (PM). Preregistration is required and seating is limited.

Morning CE Courses

CONTINUING EDUCATION COURSE—CE 1

Screening and Testing for Reproductive and Developmental Toxicity — **8:00 AM–11:30 AM** ***Cibolo 3–4***

SESSION CHAIRS: **Rochelle W. Tyl,** RTI International, Discovery and Analytical Sciences and **Jerry F. Hardisty,** Experimental Pathology Laboratories, Inc.

Supported by an educational donation provided by:
RTI International and ***Experimental Pathology Laboratories, Inc.***

Assessment of reproductive and developmental toxicity is critical for both hazard identification and risk assessment. The current test guidelines require a multigenerational (typically a two-generation) study to assess reproductive toxicity typically in rats or mice and a stand-alone developmental toxicity study typically in rats or mice and rabbits, to assess developmental toxicity. The first talk will present a new optimized study design, the Modified One-Generation (MOG) study, developed by NTP to provide F1 offspring, exposed *in utero*, for evaluation of reproductive, developmental, nervous, and/or immunologic systems, also with subchronic (13 week), or chronic study spin-offs. This assay employs the appropriate *in utero* and postnatal exposures, including the critical windows of pre- and postnatal development. Subsequent speakers will present developmental windows and vulnerabilities for the rodent and human reproductive system, immune system, and nervous system, and the toxicities associated with the development of these systems.

8:00 AM–8:10 AM	**Introduction**
8:10 AM–8:55 AM	**The NTP Modified One Generation Study (MOG): A New Approach to Test for Effects on Reproduction and Development** *Paul M. D. Foster, National Institute of Environmental Health Sciences-NTP, Research Triangle Park, NC*
8:55 AM–9:35 AM	**Toxicologically Relevant Developmental Windows in the Rodent and Human Reproductive System** *L. Earl Gray Jr., US Environmental Protection Agency, Research Triangle Park, NC*
9:35 AM–10:05 AM	*Break*
10:05 AM–10:45 AM	**What's So Special about the Developing Immune System?** *Michael P. Holsapple, Battelle, Columbus, OH*
10:45 AM–11:25 AM	**Toxicologically Relevant Developmental Windows in the Rodent and Human Nervous System** *Charles V. Vorhees, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH*

CONTINUING EDUCATION COURSE—CE 2

Relevance of Animal Tumors in Assessing Human Risk of Pharmaceuticals

8:00 AM–11:30 AM
Cibolo 5

SESSION CHAIRS: **Thomas J. Steinbach,** Experimental Pathology Laboratories, Inc.
and **James A. Popp,** Stratoxon LLC

Supported by an educational donation provided by: ***AnaPath GmbH*** and ***BSL Bioservices***

Carcinogenic hazard identification of pharmaceuticals has been based on evaluation in rodents for many decades. Initially the assessment of human risk was based on a presumption of biological similarity between laboratory animals and humans. Yet species-specific responses, such as PPARα agonist-induced liver tumors in rodents and alph2μ-globulin-induced renal toxicity leading to renal neoplasia in male rats, call into question the relevance of some animal tumors when assessing human risk. This symposium will present an overview of animal tumors that may not be relevant for human risk assessment. In addition, speakers will discuss various approaches for determining relevance of animal tumors and present specific examples where additional mechanistic data impacted the risk assessment and the approval process. The symposium will also present how regulatory agencies approach the relevance of animal tumor data to assess human risk of carcinogenicity.

8:00 AM–8:10 AM	**Introduction**
8:10 AM–8:55 AM	**Regulatory Approaches for Assessing Human Risk of Animal Tumors** *Abigail Jacobs, US Food and Drug Administration, Silver Spring, MD*
8:55 AM–9:35 AM	**Overview of Animal Tumors with Questionable Relevance to Human Risk Assessment** *Klaus Weber, AnaPath GmbH, Oberbuchsiten, Switzerland*
9:35 AM–10:05 AM	*Break*
10:05 AM–10:45 AM	**Approaches for Determining Relevance of Animal Tumors in Human Risk Assessment** *Samuel M. Cohen, University of Nebraska Medical, Omaha NE*
10:45 AM–11:25 AM	**Selected Examples of Using Mechanistic Data in Human Risk Assessment** *Barbara J. Davis, Tufts University, Harvard, MA*

CONTINUING EDUCATION COURSE—CE 3

Writing for Regulatory Authorities

8:00 AM–11:30 AM
Cibolo 1–2

SESSION CHAIRS: **Holly D. Dursema,** Boehringer Ingelheim Pharmaceuticals, Inc.
and **Melissa C. Rhodes,** GlaxoSmithKline

Supported by an educational donation provided by:
Boehringer Ingelheim Pharmaceuticals, Inc. and the ***American College of Toxicology***

This course is to provide participants with an overview of the regulatory documentation they will be required to provide as the toxicology representative in pharmaceutical industry project teams. The course will present document timing and focus. The construct of each regulatory document will be reviewed to enable the writer to compile the information necessary for regulatory agencies to conduct their evaluations. An emphasis will be on pertinent information and the interpretation, flow, and linking of data to create the intended message.

Phase I enabling package, which will review the studies required, compilation of an IND, and construction of an IB that will provide sufficient information for regulators while giving an understandable overview to clinical trial physicians. Following initiation of Phase I trials, toxicology representatives must consider toxicity studies to support Phase II, which will be of longer duration and generally include women of child bearing potential. This post-Phase I support includes incorporation of that study information into the IB, yearly regulatory updates, and construction of an end of Phase II meeting briefing document. The Pediatric Investigational Plan (PIP) is typically compiled during this time and consideration must be given to the need for, design, and timing of juvenile studies in relation to the clinical pediatric plan. The third session will focus on carcinogenicity studies, which are preceded by submission of a Special Protocol Assessment (SPA) to the US FDA. The assembly of toxicology information to support carcinogenicity dose level selection and a typical draft protocol will be reviewed. The final session will review the documentation required for NDA submission, including the integration of the toxicity study results, the nonclinical overview, and the presentation of compound toxicity for efficient regulatory evaluation. Time will remain at the end of the course for a Q&A session.

8:00 AM–8:10 AM	**Introduction**
8:10 AM–8:55 AM	**Phase I Enabling Safety Assessment Regulatory Documents** *Melissa C. Rhodes, GlaxoSmithKline, Research Triangle Park, NC*
8:55 AM–9:35 AM	**Post-Phase I Support** *Lorrene A. Buckley, Eli Lilly & Co., Indianapolis, IN*
9:35 AM–10:05 AM	*Break*
10:05 AM–10:45 AM	**Carcinogenicity Study Planning** *Douglas J. Ball, Pfizer, Inc., Groton, CT*
10:45 AM–11:25 AM	**NDA/Common Technical Document** *Holly D. Dursema, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT*

12:00 Noon–1:00 PM	***New Member Luncheon*** *(By Invitation Only)*	***Sunday House***

Afternoon CE Courses

CONTINUING EDUCATION COURSE—CE 4

Inclusion of Nonclinical Data in Drug Labels: Current and Upcoming Labeling Guidance, Practice, and Initiatives

1:00 PM–4:30 PM
Cibolo 3–4

SESSION CHAIRS: **Mary Ellen Cosenza,** Amgen Inc. and
Lynnda Reid, US Food and Drug Administration, CDER

Supported by an educational donation provided by:
Aclairo Pharmaceutical Development Group, Inc. and the ***American College of Toxicology***

Pharmaceutical labeling serves many purposes and is used for communicating efficacy and risks associated with approved indications. In February 2013, a guidance proposed by US Food and Drug Administration (US FDA) was released that changes the requirements for the content and format of labeling for human prescription drug and biological products, called the Physician Labeling Rule (PLR). This class will introduce the portions of the label covered by the new PLR, and will include speakers with real-world experience and a hands-on label writing session. The product label is used by a variety of audiences, but is written primarily for medical practitioners and patients. Animal and *in vitro* data should be conveyed in a clinically meaningful way to ensure its relevance to the patient population is clearly communicated. This session will describe what, where, and how nonclinical information should be included in pharmaceutical product labeling. The talks will focus on presentation of data in clear language with an emphasis on relevance to the prescribing healthcare professional and patient. Sections to be covered will include labeling highlights, pharmaceutical class and mechanism of action (Section 12.1), communication risk to special populations (Section 8), and presentation of carcinogenicity, genotoxicity, fertility, and animal toxicology (Section 13) results. New pregnancy labeling initiatives at US FDA in preparation for the removal of pregnancy categories will also be discussed.

1:00 PM–1:05 PM	**Introduction**
1:05 PM–1:30 PM	**Overview of Current Labeling under the Physician's Labeling Rule** *Mary Ellen Cosenza, Amgen Inc., Thousand Oaks, CA*
1:30 PM–1:55 PM	**Communicating Reproductive and Developmental Risk** *Lynnda Reid, US Food and Drug Administration, Silver Spring, MD*
1:55 PM–2:20 PM	**Communicating Risk for Drug Use in Pediatric Populations and Lactating Women** *LaRonda Morford, Covance Laboratories, Inc., Greenfield, IN*
2:20 PM–2:45 PM	**Presenting Carcinogenicity, Genotoxicity, and Animal Toxicology Data in a Clinically Meaningful Way** *Christopher Ellis, US Food and Drug Administration, Silver Spring, MD*
2:45 PM–3:15 PM	*Break*
3:15 PM–4:30 PM	**Hands-On Label Writing Session** *Janice Lansita, US Food and Drug Administration, Silver Spring, MD; Melanie Hartsough, Biologics Consulting Group, Inc., Alexandria, VA; and Lorene A. Buckley, Eli Lilly and Company, Inc*

CONTINUING EDUCATION COURSE—CE 5

Biologics 201: Advanced Topics in Nonclinical Safety Assessment of Biotechnology-Derived Drug Products

1:00 PM–4:30 PM
Cibolo 5

SESSION CHAIRS: **Patricia C. Ryan,** MedImmune and **T. Scott Manetz,** MedImmune

Supported by an educational donation provided by:
MedImmune, LLC and the ***American College of Toxicology***

This course will provide insight into the unique considerations important for designing, executing and interpreting nonclinical safety programs for biotechnology-derived drug products (also known as biologics). Approaches used for interpreting nonclinical safety results relevant to human safety to support regulatory filings and clinical development of biologics will be described using a combination of general principles, regulatory guidelines, best practices, and case examples. Given that many of the biologics products on the market and in development are monoclonal antibodies, the majority of the topics will relate to this class of biologics. This course is intended for those interested in expanding their understanding of nonclinical safety aspects of biologics drug development.

1:00 PM–1:10 PM	**Introduction**
1:10 PM–1:55 PM	**Unique Concepts in Nonclinical Safety of Biologics** *T. Scott Manetz, MedImmune, Gaithersburg, MD*
1:55 PM–2:40 PM	**Distinguishing Exaggerated Pharmacology from Adverse Effects: Determining NOAEL, Safety Margins** *Mary Jane Hinrichs, MedImmune, Gaithersburg, MD*
2:40 PM–3:00 PM	*Break*
3:00 PM–3:45 PM	**Immunogenicity in Nonclinical Studies: Impact for Human Risk Assessment** *Katie Sprugel, Amgen Inc., Seattle, WA*
3:45 PM–4:30 PM	**Safety of Immunomodulatory Biologics: Early Risk Mitigation Strategies** *M. Stacey Ricci, US Food and Drug Administration/CDER, Silver Spring, MD*

CONTINUING EDUCATION COURSE—CE 6

Inflammatory Biomarkers | **1:00 PM–4:30 PM** | ***Cibolo 6***

SESSION CHAIRS: **Lila Ramaiah,** Huntingdon Life Sciences and **William Reagan,** Pfizer Drug Safety R&D

Supported by an educational donation provided by: The ***Society of Toxicologic Pathology***

Drug-induced toxicity to the immune and inflammatory systems encompasses a wide variety of adverse effects, ranging from exaggerated pharmacology (intended immunomodulation), to immunotoxicity (unintended immunosuppression or immune stimulation), drug-induced hypersensitivity and autoimmunity. Inflammatory biomarkers are valuable tools for the identification, characterization, and monitoring of effects. Inflammatory biomarkers, often themselves mediators of inflammatory and immune responses, include cytokines, acute phase proteins, complement, and hemostatic proteins. This session explores the current use of inflammatory biomarkers in preclinical safety assessment. Topics encompass the evaluation of acute phase proteins, cytokines, and complement in rodent and large animal models of inflammation. Emphasis is on relevance, utility, application, and use of inflammatory biomarkers, as well as on their translatability and predictivity from *in vitro* to *in vivo* models and from nonclinical to clinical settings. Factors that influence study design and biomarker selection, including preanalytical and analytical considerations, technologies and platforms, and species differences will be discussed. The session also includes short case studies with opportunity for open discussion with audience members.

1:00 PM–1:10 PM	**Introduction**
1:10 PM–1:55 PM	**The Challenges for Preclinical to Clinical Translation of the Systemic Inflammatory Response Syndrome** *Calvert Louden, Johnson & Johnson Pharmaceuticals, Raritan, NJ*
1:55 PM–2:10 PM	**Case Studies—Acute Phase Proteins** *Niraj K. Tripathi, Covance Laboratories, Inc., Madison, WI*
2:10 PM–2:55 PM	**Considerations for the Use of Cytokines As *In Vivo* Safety Biomarkers** *Jacqueline Tarrant, Genentech, South San Francisco, CA*
2:55 PM–3:15 PM	*Break*
3:15 PM–3:30 PM	**Detection of Circulating Cytokines in *Cynomolgus Macaques* with Multiplex Array (Luminex) Technology: A Case Study Using SEB and LPS** *Madeline M. Fort, Amgen Inc., Seattle, WA*
3:30 PM–4:15 PM	**Analysis and Interpretation of Complement Activation from *In Vivo* Data** *Patricia Giclas, Advanced Diagnostic Laboratories, Denver, CO*
4:15 PM–4:30 PM	**Case Study: Increased Complement Fractions in Cynomolgus Monkeys Administered a Monoclonal Antibody** *Padma Narayan, Amgen Inc., Seattle, WA*

CONTINUING EDUCATION COURSE—CE 7

All Eyes Focused on Ocular Toxicology and Pathology

1:00 PM–4:30 PM
Cibolo 1–2

SESSION CHAIRS: **Brian J. Christian,** Covance Laboratories, Inc. and
Margarita M. Gruebbel, Experimental Pathology Laboratories, Inc.

Supported by an educational donation provided by:
Covance, Inc. and ***Experimental Pathology Laboratories, Inc.***

The eye is often a target organ in toxicology studies. In order to evaluate the toxicological significance of effects on the eye, it is necessary to understand the basic structure and function of ocular tissues. Differences in the ocular anatomy and physiology among laboratory animal species are important factors to consider when designing protocols for ocular toxicology studies as they can influence the ability to collect and interpret data. Likewise, it is important to understand the value and limitations of current methods used for evaluation of ocular structures and their function. This session will provide detailed reviews of the anterior and posterior ocular segments of common laboratory animal species with regard to comparative anatomy and physiology, common methods used to determine treatment-related effects in ocular structures, as well as a description of spontaneous and induced changes observed in each segment of the eye.

1:00 PM–1:10 PM	**Introduction**
1:10 PM–1:55 PM	**Comparative Anatomy and Histology of the Eye of Laboratory Animals** *Margarita M. Gruebbel, Experimental Pathology Laboratories, Inc., Research Triangle Park, NC*
1:55 PM–2:40 PM	***In Vivo* Evaluation of the Cornea and Lens** *Robert J. Munger, Animal Ophthalmology Clinic, Ltd, Dallas, TX*
2:40 PM–3:00 PM	*Break*
3:00 PM–3:45 PM	**Evaluation Anterior and Posterior Chambers and Iridocorneal Angle** *Leandro Teixeira, OSOD, LLC, Madison, WI*
3:45 PM–4:30 PM	**Examination and Evaluation of the Posterior Segment—Retina** *Steven D. Sorden, Covance Laboratories, Inc., Madison, WI*

5:00 PM–6:00 PM	***IJT Manuscript Submission Strategies—Recipes for Success, Formulas for Failure*** *See page 12 for more information.*	***Magnolia***
6:30 PM–9:00 PM	***Welcome Reception: Wine Tasting and Jazzicology*** *See page 12 for more information.*	***Event Lawn 3*** *(Ticketed Event; In case of rain: Nelson W. Wolff Ballroom A)*

PLENARY LECTURE 1

Science, Policy, and Risk in Public Health Regulations for the 21st Century

8:00 AM–8:55 AM
Nelson W. Wolff Ballroom A

Steven K. Galson, MD, MPH
Vice President, Global Regulatory Affairs at Amgen

Supported by an educational donation provided by:
Calvert Laboratories and the ***American College of Toxicology***

Steven K. Galson, MD, MPH joined Amgen as vice president of Global Regulatory Affairs in October 2010. Dr. Galson was senior vice president for Civilian Health Operations and chief health scientist at Science Applications International Corporation, October 2009 through October 2010. In October 2009, he completed 23 years of government service, most recently—for two years—as acting surgeon general of the United States. Previously, he served as director of the US FDA's Center for Drug Evaluation and Research (CDER) from July 2005, where he provided leadership for the Center's broad national and international programs in pharmaceutical regulation. Dr. Galson began his Public Health Service (PHS) career as an epidemiological investigator at CDC after completing a residency in internal medicine at the hospitals of the Medical College of Pennsylvania. He has held senior-level positions at the US Environmental Protection Agency (US EPA); the Department of Energy, where he was chief medical officer; and the US Department of Health and Human Services. Prior to his arrival at US FDA, he was director of the US EPA's Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, at the US EPA. Dr. Galson joined the US FDA in April 2001 as CDER deputy director. He is the recipient of numerous awards, including the Surgeon General's Medallion and three Secretary of Energy Gold Awards. Dr. Galson has been a board member of the National Board of Medical Examiners and a peer reviewer for medical journals. He holds a BS from Stony Brook University, an MD from Mt. Sinai School of Medicine, and an MPH from the Harvard School of Public Health. He is board certified in preventive medicine and public health and occupational medicine.

Monday Morning Sessions

SYMPOSIUM 1

Antibody-Drug Conjugates: The Next Evolution in the Cure for Cancer

9:00 AM–12:00 Noon
Cibolo 7

CHAIR: **Kenneth J. Olivier Jr.,** Merrimack Pharmaceuticals

CO-CHAIR: **Beth Hinkle**, Amgen Inc.

Supported by an educational donation provided by: ***Merrimack Pharmaceuticals***

In order to effectively cure cancer and improve the quality of life for patients, therapeutic oncology molecules must kill all cancer cells without adversely affecting normal cells. Combinations of chemotherapeutic drugs (aka small molecule cytotoxic molecules) are the best means to this end, but often have off-target dose limiting toxicities in normal cells and tissues that prevent sufficient exposure to kill all tumor cells. The advent of monoclonal antibodies in clinical oncology significantly increased the effectiveness of chemotherapies to kill more cancer cells, but more needs to be done. Antibody-drug conjugates have the advantage of specifically targeting cancer cells to deliver small molecule cytotoxic drugs. This combination has created widespread enthusiasm in the oncology drug development community and can be largely explained by the properties of these molecules in their exquisite binding specificity and their substantially decreased toxicity profile. Several approaches are being evaluated including linkage of mAbs to highly cytotoxic drugs and targeted delivery of cytotoxic drug payloads in liposomes. This presentation will discuss general considerations for how to conduct nonclinical pharmacology and toxicology studies for these novel unconventional biotherapeutic-small molecule constructs with special focus on the impact of nonclinical findings on clinical development.

S1-1	9:00 AM–9:35 AM	**Pharmacology and Toxicology of ADCs** *Beth Hinkle, Amgen Inc., Thousand Oaks, CA*
S1-2	9:35 AM–10:04 AM	**Clinical Updates on ADCs T-DM1 and TDM4450** *Sara Hurvitz, UCLA, Thousand Oaks, CA*
S1-3	10:04 AM–10:36 AM	**Innovations in ADC Oncology Programs** *Puja Sapra, Pfizer, Pearl River, NY*
	10:36 AM–10:56 AM	*Break*
S1-4	10:56 AM–11:28 AM	**Safety Evaluation of Antibody-Drug Conjugates** *Kelly Flagella, Genentech, South San Francisco, CA*
S1-5	11:28 AM–12:00 Noon	**Regulatory Strategies for Oncology Development** *M. Stacey Ricci, US Food and Drug Administration, Silver Spring, MD*

S1-1
Antibody-drug conjugates (ADCs) represent a unique class of therapeutics consisting of both large and small molecule moieties. The regulatory landscape for the nonclinical safety assessment of ADCs continues to evolve. This talk will outline some of the basic principles to consider when designing the toxicology strategy for developing ADCs. The expression of the target antigen in normal tissues is useful for predicting target-derived toxicity, but since target-independent toxicity is expected with ADCs it is important to understand the toxicity of the small molecule cytotoxic component by itself. More elaborate toxicokinetic assays are needed than would be expected for a naked antibody, since total antibody, conjugated antibody, and free small molecule drug concentrations should be measured. *In vitro* plasma stability in human and nonclinical species is important to aid understanding the potential exposure to free warhead. Because ADCs are complex hybrid molecules, the rationale for conducting each of the nonclinical safety studies with an ADC or one of its components should be carefully considered.

S1-2
T-DM1 is the first antibody-drug conjugate clinically evaluated in breast cancer. Phase I, II, and III studies have shown that targeted delivery of cytotoxic chemotherapy with this molecule leads to significant efficacy and relatively low associated toxicity in patients with metastatic HER2+ breast cancer. This presentation will review efficacy and toxicity data from phase I, II, and III clinical trials that evaluated the use of T-DM1 for advanced, HER2+ breast cancer. An overview of ongoing and planned studies in other disease settings (including early breast cancer, and other patient populations) will also be provided.

S1-3
Antibody-drug conjugates (ADCs) represent a promising therapeutic modality for the clinical management of cancer. The ADC platform currently includes a growing repertoire of cytotoxic payloads, linker technologies and conjugation methods. Key considerations in generating an optimal ADC include target biology, antibody properties, linker chemistry, and payload characteristics. This presentation will use case studies to elaborate on the multifaceted optimization required to yield a viable clinical candidate ADC. ADCs employing different mechanism of action (MOA) payloads will be used as examples to illustrate the need to match target biology with MOA of payload. Further, an update on clinical data of CMC-544, an anti-CD22 calicheamicin conjugate will be provided. Additionally, innovations, and approaches in ADC development at Pfizer Oncology Research will be described.

S1-4
Antibody-drug conjugates (ADCs) are complex molecules usually comprised of monoclonal antibodies conjugated with potent cytotoxic chemotherapeutic drugs via chemical linkers. ADCs are designed to deliver cytotoxins to tumors via tumor-specific target antigens in effort to optimize efficacy and minimize toxicity to normal tissues. The structural complexity of ADCs presents unique challenges to their preclinical development. Despite the increasing number of ADCs in preclinical and clinical development, preclinical strategies continue to evolve and remain case-by-case. This presentation will provide an overview of strategies and points to consider in the design of the toxicology program and review case study examples and the preclinical safety profile of ADC(s) in development.

S1-5
There is great enthusiasm across industry, academia, and regulatory authorities for advancing development of antibody-drug conjugates (ADCs) to treat cancer indications. To date, the two US FDA-approved ADCs and a large number of those under investigation are monoclonal antibodies conjugated to cytotoxic small molecules. Nonclinical safety evaluation of these protein-linker-small molecule combination products present unique challenges specific to each ADC. As with many other biological therapeutics, nonclinical safety evaluations have to be considered on a case-by-case basis. As US FDA's experience reviewing ADC nonclinical pharmacology and toxicology data grows, some general approaches regarding testing strategies have emerged. This presentation will provide a regulatory perspective on the considerations and challenges associated with developing ADCs for therapeutic use.

SYMPOSIUM 2

Translating Nonclinical Cardiovascular Toxicity Findings into Clinical Trial Design

9:00 AM–12:00 Noon
Cibolo 6

CHAIR: **Janice Lansita,** US Food and Drug Administration/CDER

CO-CHAIR: **David L. Hutto,** Eisai, Inc.

Can nonclinical cardiotoxicity findings be translated into meaningful clinical trial design that adequately balances risk vs. benefit to patients? Today many drug candidates are screened out of development early due to nonclinical signals of cardiotoxicity. For drug candidates that do have potential cardiovascular signals but are deemed to have an adequate risk vs. benefit profile, an understanding of the underlying mechanism may enable the design of nonclinical toxicity studies that fully characterize potential cardiovascular risk to patients. Ideally, the nonclinical data could be translated into clinical trial design that would ultimately lead to a reasonably safe yet efficacious clinical dose regimen and appropriate monitoring measures. This session will explore these issues through presentations on the underlying mechanisms and clinical monitoring (cardiac function and/or biomarkers) of xenobiotic-induced cardiac dysfunction, the state of the art of nonclinical cardiovascular safety assessment, focusing on clinically translatable endpoints, case studies of translating nonclinical cardiotoxicity into clinical trial design (industry and US FDA), and will conclude with a regulatory perspective on the interpretation and translation of nonclinical cardiovascular toxicity.

	9:00 AM–9:10 AM	**Introduction** *Janice Lansita, US Food and Drug Administration/CDER, Silver Spring, MD*
S2-1	9:10 AM–9:40 AM	**Translational Nonclinical Cardiovascular Safety Assessment: Manifestations and Markers** *Brian R. Berridge, GlaxoSmithKline, Research Triangle Park, NC*
S2-2	9:40 AM–10:10 AM	**Cardiac Imaging As an Investigative and Translational Tool in Nonclinical Safety Assessment: Opportunities, Applications and Challenges** *Robert W. Coatney, GlaxoSmithKline, King of Prussia, PA*
	10:10 AM–10:30 AM	*Break*
S2-3	10:30 AM–11:00 AM	**Investigation of the Mechanism of BMS-986094-Related Cardiotoxicity** *Marc Davies, Bristol-Myers Squibb, Mt. Vernon, IN*
S2-4	11:00 AM–11:30 AM	**A US FDA Regulatory Perspective of Cardiac Toxicity** *Elizabeth Hausner, US Food and Drug Administration/CDER, Silver Spring, MD*
	11:30 AM–12:00 Noon	**Roundtable Discussion** *All participants*

S2-1
Cardiovascular safety liabilities are varied in their presentation in both nonclinical animal studies and human patients with significant opportunity for preexisting/co-morbid disease to complicate detection and characterization in both. Accordingly, it is important to understand the pathogenesis of potential toxic liabilities in both settings and have effective strategies for protecting patients with effective monitoring strategies. This presentation will briefly introduce the cardiovascular system as a target of toxicity and review common presentations in nonclinical testing. We will project those potential liabilities to target patient populations and consider available biomarker strategies.

S2-2
Echocardiography, Cardiac magnetic resonance imaging, and Positron Emission Tomography are being used more frequently to evaluate cardiac structure and function in nonclinical efficacy and safety assessment studies. These imaging platforms offer substantial translational potential as the same platforms are used clinically as both diagnostic and research tools. In light of these opportunities there are still challenges in using nonclinical imaging platforms in safety assessment studies and translationally to clinical studies. This presentation will provide a brief overview of these imaging platforms focused on nonclinical and translational evaluation of cardiac structure and function and provide case examples of nonclinical safety studies. Additionally the challenges of performing nonclinical CV imaging safety evaluation studies and the challenges in translating to clinical studies and outcomes will be discussed.

S2-3
An in depth investigation into the potential mechanism(s) of cardiotoxicity in monkeys related to BMS-986094-treatment was conducted. Evaluations included clinical observations, *in vitro* and *in vivo* assessments of potential mitochondrial effects and ECG and echocardiographic parameters, drug and metabolite levels in target tissues including the heart, assessment of cardiac-related clinical pathology endpoints, light and EM evaluations of the heart, metabolomics, and assessments of guanosine levels/signaling in heart tissue, and transcriptional profiling of the hearts. This talk aims to discuss the background and summarize the results of the investigation into potential mechanisms of BMS-986094-related cardiac effects and discuss some planned/potential next steps.

S2-4
Nonclinical cardiac toxicity may be associated with drugs for any indication. CDER's review divisions seek a balance between allowing the clinical exploration of potentially valuable new therapeutic agents and reasonable safety for the clinical trial volunteers. What factors will permit a drug to move forward in clinical development? How does the US FDA view nonclinical cardiac toxicity, and what shapes the agency's interpretation? The same data may be viewed very differently by the US FDA and the industry sponsor. Factors such as whether an observed effect is related to the administered drug, is a spontaneous event or an enhanced spontaneous event may be points of differing opinion. This talk aims to present the general principles that guide the US FDA's interpretation of nonclinical data and opinion of potential clinical relevance, illustrated with specific case examples.

SYMPOSIUM 3

Dermal Toxicology: Current Requirements, Methods, Models, and Regulatory Perspectives

9:00 AM–12:00 Noon
Cibolo 5

CHAIR: **Dave Hobson,** LoneStar Pharm Tox, LLC

CO-CHAIR: **William J. Brock,** Brock Scientific Consulting

Supported by an educational donation provided by: ***Sinclair Research Center***

The skin is the largest organ of the body, and for many substances the skin represents a significant and even primary route of exposure. Toxicologic studies have been conducted to evaluate adverse effects to the skin and from skin penetration involving a variety of targets and endpoints and with a variety of *in vitro* and *in vivo* models for nearly a century. This has resulted in a wealth of data justifying the routine inclusion of dermal toxicity evaluation for safety assessments involving substances that could be in contact with skin as a result of their therapeutic use or from occupational or environmental exposure. Internationally, dermal toxicity assessment is often required for the registration of chemical substances, pharmaceuticals and medical devices. Knowing when to evaluate dermal toxicity as well as the appropriate models to use for toxicologic evaluation, while conceptually simple, is often complicated by many factors that require experience and expertise. Furthermore, in evaluating the potential human health risk of substances, dermal toxicity data may not be available. Therefore, how can the toxicologist evaluate the toxicity of a substance applied topically? As the technology of drug delivery expands, how does the toxicologist evaluate these potentially new advances, and what are the regulatory implications of these innovative topical products? This symposium will clarify current requirements for present accepted and emerging models, discuss current issues and present solutions to problems often encountered with dermal toxicity evaluation and the route-to-route risk assessment of xenobiotics.

S3-1	9:00 AM–9:40 AM	**Current Methods and Animal Models in Dermal Toxicology** *William J. Brock, Brock Scientific Consulting, Montgomery Village, MD*
S3-2	9:40 AM–10:20 AM	**Perspectives on Dermal Exposure and Toxicity Assessment including PBPK Models and R–to–R Extrapolations** *Robinan Gentry, ENVIRON International Corporation, Monroe, LA*
	10:20 AM–10:40 AM	*Break*
S3-3	10:40 AM–11:20 AM	**Current Innovations in Dermal Toxicology Methods and Product Design** *David W. Hobson, LoneStar PharmTox LLC, Bergheim, TX*
S3-4	11:20 AM–12:00 Noon	**Nonclinical Regulatory Considerations for Topical Products** *Jianyong Wang, US Food and Drug Administration/CDER, Silver Spring, MD*

S3-1
In conducting of dermal toxicity studies of xenobiotics, the determination of the optimal doses is critical. However, decisions about the animal model, use of intact or abraded skin, duration of treatment and multiple other factors are essential to ensure a satisfactory outcome. Expression of the dose unit also is a critical decision particularly when judging the potential human health risks. This presentation will describe the general methodologies for assessing the dermal toxicity of xenobiotics that includes *in vitro* and *in vivo* assessment. In addition, this presentation will explore cross-species sensitivities of testing of compounds and the selection of animal models for dermal toxicity testing.

S3-2
The principles and data needed for conducting a route-to-route extrapolation to predict dermal toxicity will be presented. The application of physiologically based pharmacokinetic (PBPK) modeling offers a means to relate target tissue concentration to dose, and to extrapolate target tissue concentration across species, route, and dose. PBPK models should sufficiently represent the biology or the organism and the chemical and toxicological properties of the agent. This approach can incorporate data from *in vivo* studies, *in vitro* studies and *in silico* predictions. The fundamental data required are dose response data from one route, the availability of a PBPK model sufficient to model exposure data from both routes.

S3-3
Dermal toxicology methods involving various animal models have been established over decades of successful use but these methods often must be adapted and modified forever improving and innovative product and raw material markets. Modern product designs are increasingly incorporating new ingredients including nanomaterials and study methods and designs often must be modified to compensate for the unique characteristics of these materials. *In vitro* and *in silico* methods are increasingly being used in some consumer product and in chemical substance registration (e.g. REACH). With an aging population, methods for the safety evaluation of wound healing products, particularly for chronic, wounds require novel and innovative methods. This talk will present recent innovations in dermal toxicology methods for *in vivo*, *in vitro* and *in silico* models as well as discuss how new innovations in product design necessitate adaption and modification of established dermal toxicology methods for effective safety and risk assessment.

S3-4
Regulatory pathways for approval of topical drug/biologic products in the US and nonclinical recommendations/considerations for a successful pathway will be introduced. The unique aspects of nonclinical requirements to support application of topical drugs/biologics will be discussed. This talk will also include a brief introduction of DDDP and the interactions between DDDP and sponsors of INDs/NDAs/BLAs.

12:00 Noon–2:00 PM	***Awards Ceremony and Luncheon*** *(Included in registration fee)* *See page 12 for more information.*	***Nelson W. Wolff Ballroom A***

Monday Afternoon Sessions

SYMPOSIUM 4

4 M's: Mistakes, Misuse, Mismanagement, Misunderstanding…Looking at Things That Have Gone Wrong in the Past: What to Learn to Plan for the Future

2:00 PM–5:00 PM
Cibolo 5

CHAIR: **David Woolley,** ForthTox Ltd.

CO-CHAIR: **Glenn Myatt,** Leadscope Inc.

Supported by an educational donation provided by:
ForthTox Ltd., Leadscope, and the ***American College of Toxicology***

The history of errors in toxicology is, in many ways, the history of toxicology. Changes in legislation and practice are often led not by toxicologist themselves but by their mistakes, the results of misuse of substances by users and mismanagement by manufacturers, academia, and government. Furthermore, public misunderstanding of consumer exposure has led the nontoxicologist population, via the popular media, to create perceived risks where risks sometimes do not exist. The 4Ms (Mistakes, Misuse, Mismanagement, and Misunderstanding) is proposed as a counterpart to the 3Rs (Refinement, Replacement, and Reduction) and hopes to challenge, provoke and inform. Topics covered will include, the history of errors that have led to changes in how toxicology is regulated, the application of thresholds, the selection of toxicological tests (both *in vivo* and *in vitro*) and the future of *in silico* toxicology. This symposium's goal is to examine how we can benefit from past errors to guide change and evolution in toxicology.

S4-1	2:00 PM–2:15 PM	**A Brief History of Errors in Toxicology: An Introduction to the 4Ms** *David Woolley, ForthTox Ltd., Linlithgow, United Kingdom*
S4-2	2:15 PM–2:45 PM	**Thresholds for Toxicity and Public Perception** *James S. Bus, Exponent, Alexandria, VA*
S4-3	2:45 PM–3:15 PM	**Ensuring Safety and Efficacy in New Medicines—Humanizing the Process** *Robert Coleman, Drug Discovery Consultant, Falmouth, United Kingdom*
	3:15 PM–3:35 PM	*Break*
S4-4	3:35 PM–4:15 PM	***In Silico* Toxicology: Current Usage and Future Directions** *Glenn J. Myatt, Leadscope Inc., Columbus, OH*
S4-5	4:15 PM–4:45 PM	**Regulatory Strategies for Oncology Development** *Adam Woolley, ForthTox Ltd., Linlithgow, United Kingdom*
	4:45 PM–5:00 PM	**Panel Discussion**

S4-1
The history of errors in toxicology is, in many ways, the history of toxicology. Changes in legislation and practice are often led not by toxicologist themselves but by their mistakes, the results of misuse of substances by users and mismanagement by manufacturers, academia, and government. Furthermore, public misunderstanding of consumer exposure has led the nontoxicologist population, via the popular media and the Internet, to create perceived risks where risks sometimes do not exist. Conversely, the same information sources can lead to unnecessary exposure to potentially dangerous chemicals. This introduction to the 4Ms (mistakes, misuse, mismanagement, and misunderstanding) will give an overview of historical errors, their impacts on legislation and the potential sources of new errors.

S4-2
"Mistakes" and "misunderstandings" around the toxicology principle of "the dose makes the poison" often create the potential for overestimates of human health hazards and risks. High-dose animal testing without consideration of possible high-dose specific saturation of toxicokinetics often results in findings with limited relevance to human health, and particularly so when test doses are highly separated from measured or modeled real-world human exposures. Likewise, with the advent of high-throughput *in vitro* toxicity testing, there is growing evidence of more "high dose" mistakes, i.e., toxicity at concentrations far higher than those in whole animal treatments, and many more orders of magnitude above actual human exposures, are not relevant to human hazard or risk. Consideration of the principle of "the dose makes the poison" in future testing paradigms will reduce the likelihood of inappropriate high-dose confounding in evaluation of human health risks of environmental chemicals.

S4-3
Laboratory animal data are currently required before any new medicine can be tested in human subjects. However, the fact that all modern medicines have undergone animal testing is used as evidence that such testing is necessary in order to ensure the safety and efficacy of those medicines. This is clearly a circular argument. What's more, we know that despite such testing, over 90% of new drugs fail in the clinic. These issues, together with the negative conclusions of virtually all published reviews on the subject of the predictive value of animal data, question the pharmaceutical industry's continued reliance upon them. The key question of course is "What is the alternative?" and a focused approach to explore whether the introduction of more human-centric approaches to drug testing, either as adjunct to or replacement for animal-based methods, is urgently required. A proposal will be presented.

S4-4
Recent regulation and ICH guidance documents have emphasized the importance of *in silico* approaches as part of the overall safety assessment; however, their usage has been limited historically because of their lack of transparency and ability to explain the mechanistic basis. This presentation will focus on three case studies to illustrate how different *in silico* approaches have been developed to improve predictive performance and the interpretation of the results. The first case study will describe the process and results for improving the predictive performance of (Q)SAR models to support the ICH M7 impurities guideline. The second case study will focus on how computation models for prediction of Torsade de Pointe, based on multiple ion channels effects, can improve predictive performance dramatically. The third case study will discuss how in the future *in silico* approaches coupled with different *in vitro* technologies might be used in the assessment of repeated dose toxicity.

S4-5
This presentation will consider an evolution of the current framework for toxicity testing and risk assessment that takes account of current understanding (and prejudice). This should be useable as a base for safety evaluation of chemicals from all classes. This talk will review briefly the current toxicity testing paradigm, including carcinogenicity testing, and look at recent developments in discussion and understanding that will drive the future of toxicity testing. Much information can be gathered from an appropriately designed 90-day toxicity study, which can be combined with a carefully selected battery of *in vitro* studies to assess effects on pharmacological and toxicological targets. There should be a careful assessment of the extrapolability of results obtained *in vitro* to those obtained *in vivo*, and of both to humans. The tools currently available will be considered together with their potential utility in the new paradigm.

SYMPOSIUM 5

Clinical, Regulatory, and Nonclinical Study Design Issues Associated with Testing and Approval of Medical Devices

2:00 PM–5:00 PM
Cibolo 6

CHAIR: **Kathleen A. Funk,** Experimental Pathology Laboratories, Inc

CO-CHAIR: **Maralee McVean,** Pre-Clinical Research Services, Inc.

Supported by an educational donation provided by:
Experimental Pathology Laboratories, Inc and ***Pre-Clinical Research Services, Inc.***

Regulatory and scientific requirements for medical device testing and clinical use differ substantially from traditional drug development. This symposium will discuss how the regulatory environment has changed and new approaches needed to evaluate the safety of medical devices. The design of pilot and regulated studies has special challenges due to species used, complexity of surgical procedures and the need to assess proper in life and histopathological endpoints. Regulatory environment and needs differ in various parts of the world and the pros and cons of different areas will be discussed.

	2:00 PM–2:02 PM	**Introduction** *Kathleen A. Funk, Experimental Pathology Laboratories, Inc, Sterling, VA*
S5-4	2:02 PM–2:49 PM	**The Requirements for Strategies in Selecting a Clinical Trial Site in Different Parts of the World** *Ivan Vesely, ValveXchange Inc., Denver, CO*
S5-2	2:49 PM–3:10 PM	**Key Considerations in Medical Device Study Design and the Importance of Pilot Studies** *Jeff Castleberry, Endoshape, Boulder, CO*
	3:10 PM–3:30 PM	*Break*
S5-3	3:30 PM–4:17 PM	**Pathology Endpoints to Consider When Designing a Medical Device Preclinical (Toxicity) Study** *Serge D. Rousselle, Alizee Pathology, Thurmont, MD*
S5-1	4:17 PM–5:00 PM	**Evolution and Current Practice in the Regulation and Approaches to the Safety Evaluation and Extractable and Leachable Testing of Medical Devices** *Shayne Gad, Gad Consulting Services, Cary, NC, and Samantha Gad-McDonald, Gad Consulting Services, Cary, NC*

S5-1
The talk will provide an overview of the history of medical device regulations and how these regulations drive the safety evaluations of medical devices. Sample preparation and analysis of extracted substances will also be covered since all devices now require that extractions be performed to generate test materials (eluents) for base line biocompatibility testing and most require chemical analysis of substances extracted (leachables and extractables).

S5-2
This talk will serve as an introduction to the considerations needed when designing initial and GLP-compliant surgical studies. Case studies on the *in vivo* experiments used for FDA submission will be presented.

S5-3
An overview of the special approaches that may have to be taken to provide optimal samples of device: tissue interfaces from necropsy collection through gross trimming, processing, staining and histopathologic evaluation will be presented. A few findings will be shown to illustrate some of the unique problems encountered when evaluating devices and how these results were ultimately interpreted.

S5-4
The relatively burdensome US FDA requirements for evaluating safety and efficacy of new medical devices have driven most early clinical evaluations outside the US. Europe and South America are now the leading parts of the world where initial human implants and large-scale clinical trials are carried out. These non-US clinical sites pose a number of opportunities and challenges, such as language, culture and infrastructure. Usually, these challenges are offset by considerable advantages of cost and time. Often, costs of a trial are hidden in areas not clearly recognizable, such as delays and re-do's. Depending on where and how the trial is run, the data may or may not be usable for subsequent US FDA approval. But increasingly, the US market is being deferred in preference for the EU or other countries around the world. The presenter will review the advantages and disadvantages of conducting a trial in a given region of the world, share experiences on do's and don'ts, and discuss examples of what can happen if a clinical site is not properly vetted in advance.

SYMPOSIUM 6

Tumorigenicity Assessment in Preclinical Development of Pluripotent Stem Cell-Based Therapies

2:00 PM–5:00 PM
Cibolo 7

CHAIR: **Justine Cunningham,** Allergan

CO-CHAIR: **Joy Cavagnaro,** Access BIO

Pluripotent stem cell (PSC)-based therapies are being heralded as the medicinal breakthrough for a wide range of debilitating human diseases. However, the potential for the formation of teratomas or other neoplasms is a major safety roadblock to clinical application of PSC therapies. Preclinical assessment of the risk of tumor formation in this context poses considerable scientific and regulatory challenges, especially because animal xenograft models may not properly reflect the long-term tumorigenic potential of human cells. While regulatory agencies are requiring demonstration that a PSC-based product is free from tumorigenic potential, no standard assays exist allowing investigators to individually define how these assessments are made. The goal of this symposium is to bring together industry experts currently developing PSC-based therapies together with experts from teratoma pathology to open a cross functional discussion to assess tumorigenic potential. This symposium aims to help investigators successfully develop a nonclinical strategy for PSC-based therapies that addresses the issue of tumorigenicity.

S6-1	2:00 PM–2:35 PM	**Setting the Stage: Strategies for Tumorigenicty Testing of Cell-Based Therapies** *Joy Cavagnaro, Access BIO, Boyce, VA*
S6-2	2:35 PM–3:10 PM	**Morphologic Findings of Potential Concern for Human Stem Cell Transplants** *Thomas M. Ulbright, Indiana University School of Medicine, IU, Indianapolis, IN*
	3:10 PM–3:30 PM	*Break*
S6-3	3:30 PM–4:05 PM	**Preclinical Tumorigenicity Assessment of an Embryonic Stem Cell-Derived Therapy for Diabetes** *Eugene P. Brandon, ViaCyte, Inc., San Diego, CA*
S6-4	4:05 PM–4:40 PM	**Determining the Fate of a Cellular Therapeutic: Designing an Appropriate Biodistribution and Tumorigenicity Study** *Mark D. Johnson, MPI Research, Mattawan, MI*
	4:40 PM–5:00 PM	**Roundtable Discussion**

S6-1

Stems cells hold great promise for regenerative medicine. However the unlimited potential for renewal and their capacity to proliferate and/or differentiate into any human cell type also carries a unique burden of safety not associated with other therapeutic classes. The specific concern for tumorigenicity has been heightened as investigators have begun to evaluate the use of cells propagated for prolonged periods in cell culture. Unlike assessment of carcinogenicity risk, which is needed to support marketing of chronically administered therapeutics, assessment of tumorigenicity is needed prior to first in human (FIH) clinical trials. However, there is currently no scientific consensus regarding the selection of the most relevant animal models to evaluate tumorigenic potential or the ability of current animal models to predict clinical outcome. The goal of this presentation is to provide a general introduction of the challenges and key factors influencing the design of tumorigenicity assessments based on product attributes. Potential product specific derisking approaches will also be discussed.

S6-2

A potential undesirable complication of stem cell-based transplants is the development of germ cell-type neoplasms, including teratomas. The classification of the naturally occurring human counterparts to these neoplasms is complex but strongly correlates with their clinical behavior. Failure to recognize the biodiversity of spontaneously developing human teratomas and misapplication of concepts from testicular teratomas to human embryonic stem (hES) cell-based transplants have led to confusion. This talk will discuss the findings from naturally occurring human teratomas that are associated with a potentially malignant clinical course. The presentation will focus on the subtype of human teratoma that appears to be most analogous to a teratoma that could result from a hES cell-based transplant, namely the teratoma of "type I" germ cell tumors. The speaker is a practicing diagnostic pathologist with an extensive clinical experience with human germ cell tumors, not a stem cell biologist, but has reviewed pluripotent stem cell-derived transplant material. The point will be made that the sacrococcygeal teratoma of infants, a form of type I germ cell tumor, is the best match for hES cell-derived teratomas. Malignant behavior of these neoplasms correlates with specific anatomical features, either high grade immaturity or yolk sac tumor elements. A proposal for the grading of immaturity in hES cell-based transplants will be presented based on clinical studies of naturally occurring human teratomas with immature elements. Images of immature elements and yolk sac tumor will be shown. The attendee should gain an increased understanding regarding what is innocuous and what would be concerning if teratomatous complications of hES cell-based transplants occur.

S6-3

ViaCyte is developing the VC-01™ combination product (cell therapy in an immunoprotective macroencapsulation device) for insulin-requiring diabetes. The combination product, consists of cell therapy in an immunoprotective macroencapsulation device is currently in preclinical testing and clinical trials are expected to begin in 2014. The cell component is manufactured by directed differentiation of human embryonic stem cells (hESC) into a pancreatic progenitor cell population. This PEC-01™ cell population contains pancreatic endoderm cells that become glucose-responsive insulin secreting endocrine cells following subcutaneous implantation. When implanted within the macroencapsulation device, known as Encaptra® drug delivery system, the mature endocrine cells regulate blood glucose, and can protect animals from experimentally induced hyperglycemia/diabetes. hESC have the potential to form tissues of all three primordial germ layers, and will form multitissue largely disorganized teratomas when administered to immunocompromised animals. Thus, for cell products manufactured from hESC, such as PEC-01™ cells, prior to clinical testing the sponsor needs to demonstrate (1) the absence of residual hESC in the final cell composition, and (2) that the cell product does not form teratomas when administered to immunocompromised animals. The presentation will describe methods to assess residual hESC in a cell product and to preclinically test the tumorigenicity of an hESC-derived product *in vivo*. Further, the effects and benefits of administering the cell product in a durable removable delivery device will be discussed.

S6-4

Within the field of regenerative medicine, the development of the number of stem cell therapies has substantially increased over the past decade. To date, the scientific and regulatory requirements are not clearly defined for this type of therapy. In the development of a cellular therapeutic, several factors must be taken into account prior to initiation of clinical trials. Preclinical trials should be designed to assess biologic activity, persistence, distribution and safety. Given the potential for stem cells to migrate from the site of administration, differentiate and/or proliferate, the primary concerns are biodistribution and the potential for tumor formation. The purpose of this presentation is to provide an overview of species selection, preclinical study design, and the selection of endpoints to properly assess biodistribution and tumorigenicity.

5:30 PM–7:00 PM	***Poster Session and Reception*** Sponsored by: ***SAGE*** *See page 61 for more information.*	***Nelson W. Wolff Ballroom B&C***

Notes

6:45 AM–8:00 AM	***Past Presidents' Breakfast*** *(By Invitation Only)*	***Magnolia***

PLENARY LECTURE 2

New Directions in Toxicology Testing Strategies

8:00 AM–8:55 AM
Nelson W. Wolff Ballroom A

Linda S. Birnbaum, PhD, DABT, ATS
Director, National Institute of Environmental Health Sciences and National Toxicology Program

Linda S. Birnbaum, PhD, is director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the National Toxicology Program (NTP). As NIEHS and NTP director, Birnbaum oversees a budget of $730 million that funds biomedical research to discover how the environment influences human health and disease. The Institute also supports training, education, technology transfer, and community outreach. NIEHS currently funds more than 1,000 research grants.

A board certified toxicologist, Birnbaum has served as a federal scientist for nearly 34 years. Prior to her appointment as NIEHS and NTP director in 2009, she spent 19 years at the US Environmental Protection Agency (US EPA), where she directed the largest division focusing on environmental health research. Dr. Birnbaum started her federal career with 10 years at NIEHS, first as a senior staff fellow in the National Toxicology Program, then as a principal investigator and research microbiologist, and finally as a group leader for the Institute's Chemical Disposition Group.

Dr. Birnbaum has received many awards and recognitions. In October 2010, she was elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health. She was elected to the Collegium Ramazzini, and received an honorary Doctor of Science from the University of Rochester and a Distinguished Alumna Award from the University of Illinois. Other awards include the 2011 NIH Director's Award, Women in Toxicology Elsevier Mentoring Award, Society of Toxicology Public Communications Award, US EPA's Health Science Achievement Award and Diversity Leadership Award, National Center for Women's 2012 Health Policy Hero Award, Breast Cancer Fund Heroes Award, 2013 American Public Health Association Homer N. Calver Award, 2013 Children's Environmental Health Network Child Health Advocate Award, and 14 Scientific and Technological Achievement Awards, which reflect the recommendations of US EPA's external Science Advisory Board, for specific publications.

Dr. Birnbaum is also an active member of the scientific community. She was vice president of the International Union of Toxicology, the umbrella organization for toxicology societies in more than 50 countries; former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society for Pharmacology and Experimental Therapeutics; and former vice president of the American Aging Association.

She is the author of more than 600 peer-reviewed publications, book chapters, and reports. Dr. Birnbaum's own research focuses on the pharmacokinetic behavior of environmental chemicals, mechanisms of action of toxicants including endocrine disruption, and linking of real-world exposures to health effects. She is also an adjunct professor in the Gillings School of Global Public Health, the Curriculum in Toxicology, and the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, as well as in the Integrated Toxicology and Environmental Health Program at Duke University.

A native of New Jersey, Dr. Birnbaum received her MS and PhD in microbiology from the University of Illinois at Urbana-Champaign.

Tuesday Morning Sessions

SYMPOSIUM 7

The Art of Dose Selection: From the Bench to the Clinic

9:00 AM–12:00 Noon
Cibolo 7

CHAIR: **Hervé Lebrec,** Amgen Inc., Toxicology Sciences

CO-CHAIR: **Kenneth J. Olivier Jr.,** Merrimack Pharmaceuticals

Supported by an educational donation provided by: ***Charles River***

Different types of molecules (small molecules, biologics) and clinical indications (oncology or nononcology) require different types of approach when designing nonclinical studies to support clinical development and marketing authorization. This session will review the current regulatory landscape guiding dose selection for different types of nonclinical toxicology studies for human pharmaceuticals; it will illustrate through case studies how the right dose selection, using PK/PD modeling when applicable, enables proper safety assessment and transition from the nonclinical setting to studies in humans.

	9:00 AM–9:12 AM	**Introduction** *Hervé Lebrec, Amgen Inc., Toxicology Sciences, Irvine, CA*
S7-1	9:12 AM–9:49 AM	**Dose Selection in Toxicology Studies: Regulatory Overview and Case Study of a Small Molecule Oncology Program** *Hervé Lebrec, Amgen Inc., Toxicology Sciences, Irvine, CA*
S7-2	9:49 AM–10:26 AM	**Enabling First in Human Studies of Novel Immunomodulatory Therapies: Anti-CD28 and Beyond** *Theodora Salcedo, Bristol-Myers Squibb, New Brunswick, NJ*
	10:26 AM–10:46 AM	*Break*
S7-3	10:46 AM–11:23 AM	**Modeling and Simulation-Based Approach to Support Dose and Regimen Selection of Therapeutic Monoclonal Antibodies in the Clinic** *Hong Xiang, Genentech, Inc., South San Francisco, CA*
S7-4	11:23 AM–12:00 Noon	**Enabling First in Human Studies of Novel Oncology Therapies** *Kenneth J. Olivier Jr., Merrimack Pharmaceuticals, Cambridge, MA*

S7-1
Different types of molecules (small molecules, biologics) and clinical indications (oncology or nononcology) may require different approaches when designing nonclinical studies to support clinical development. This presentation will first briefly review the current regulatory landscape guiding dose selection for nonclinical toxicology studies for human pharmaceuticals. The case study will include the designs of rodent and nonrodent toxicology studies to support a first-in-human clinical trial with a small molecular weight oncology molecule, including species and dose selection. It will include the study of the correlation between *in vivo* toxicity dose responses and species-specific target binding. It will provide the rationale for determination of the human starting dose and examine how anticipated tolerability based on animal data translated to humans.

S7-2
Targeting CD28-CD80/86 with an anti-CD28 antagonist is a promising therapy for autoimmunity. However, generating anti-CD28 mAbs lacking stimulatory activity is challenging. Further, targeting CD28 presents factors influencing risk, as described in the EMA Committee for Medicinal Products for Human Use Guideline on strategies to identify and mitigate risks for first in human clinical trials. These include a first-in-class molecule targeting an immune system cell surface receptor that may elicit a biologic cascade or cytokine release not sufficiently controlled by a feedback mechanism. The FIH dose selection for a novel antihuman CD28 receptor antagonist domain antibody (dAb), with potent inhibition of T cell activation, will be discussed. To mitigate potential risk to humans, conventional and specialized nonclinical safety assessments supported an integrated approach to identify the FIH dose. The strategies used for this case study highlight an approach that may be applicable for human dose selection of other high-risk immunomodulatory molecules.

S7-3
The safety profile of most therapeutic monoclonal antibodies (mAbs) is generally more desirable than that of small molecule drug candidates. Furthermore, the approaches to identify first-in-human (FIH) as well as potentially efficacious doses for mAbs are distinct. Modeling and simulation based approaches can provide quantifiable information from animals to human to project dose ranges in early clinical trials. Multiple and unique properties of each mAb influence the choice of method to be used. The practical applications and considerations to scale nonclinical pharmacokinetic, safety, and efficacy data to human with modeling and simulation approaches will be discussed for multiple mAbs. These include design of studies, selection of suitable methods to analyze the data, data interpretation and integration to select appropriate doses and dose regimens in clinical studies.

S7-4
Starting dose level selection for first in human studies in oncology is informed by data from multiple sources. Phase I oncology studies exclusively recruit patients, thus there are ethical and moral obligations to be considered in accommodating specific patient populations with active disease. Computational biology and protein engineering have evolved a better understanding of cancer biology enabling more effective designs and constructs for antitumor molecules as well as more focused and accelerated clinical protocol designs in the individualized medicine arena. Network Biology, a novel discovery platform, and the regulatory and safety considerations for the selection of dose levels in ongoing Phase I oncology trials of a bispecific antibody, a monoclonal antibody mixture and an immunoliposome will be discussed as well as implications and future considerations for use of computational biology to inform clinical drug development.

SYMPOSIUM 8

Endocrine Disruption Screening—Status of the US EPA and EU Programs: State of the Science and Slate for the Future

9:00 AM–12:00 Noon
Cibolo 6

CHAIR: **Elliot Gordon,** Elliot Gordon Consulting, LLC

CO-CHAIR: **Susan Borghoff,** ToxStrategies, Inc.

Hormones play a critical role in our development, health maintenance and reproduction. Disruption of normal hormone activity results in marked abnormalities exemplified by dwarfism, gigantism and infertility. The importance of maintaining hormone homeostasis was reflected in passage of the Food Quality Protection Act of 1996 that mandated US EPA develop a program to identify estrogen-disrupting agents. This Symposium discusses the evolution of the endocrine disruptor screening program (EDSP), its accomplishments, challenges and future directions. We will highlight differences in approach between Europe and the United States. Lessons learned during the development and execution of the Tier I screening assays should drive refinements to this program.

S8-1	9:00 AM–9:35 AM	**Endocrine Screening Program: Background** *Elliot Gordon, Elliot Gordon Consulting, LLC, Princeton Junction, NJ*
S8-2	9:35 AM–10:04 AM	**The US EPA Endocrine Disruptor Screening Program (EDSP) Tier I Assays: Retrospective Performance Evaluation** *Susan Borghoff, ToxStrategies, Inc., Cary, NC*
S8-3	10:04 AM–10:36 AM	**Case Study: Integration of the EDSP Screening Assay Data with Other Available Data for a WoE approach** *Sue Marty, Dow Chemical Company, Midland, MI*
	10:36 AM–10:56 AM	*Break*
S8-4	10:56 AM–11:28 AM	**Regulatory Update on the Endocrine Disruptor Screening Program** *Mary Manibusan, US Environmental Protection Agency, Washington, DC*
S8-5	11:28 AM–12:00 Noon	**Dealing with Endocrine Active Substances: History and Present Regulatory Issues in Europe** *Christian Strupp, Makhteshim Agan Corporate Toxicologist, Cologne, Germany*

S8-1
Congress told US EPA to Develop and apply a screening and testing program for chemicals with the potential to disrupt the endocrine process. Timeframes, in retrospect, were short: develop a screening program for pesticides that may have estrogenic, androgen, or thyroid effects within two years of enactment; implement the program within three years of enactment; and report progress to Congress within four years of enactment. US EPA and Industry have worked together to advance this congressional mandate. We are now poised to continue Tier I screening on a second list of chemicals as well as initiate Tier II definitive studies designed for dose-response evaluation.

S8-2
The US EPA EDSP Tier I assays consist of five *in vitro* assays, four *in vivo* mammalian assays, and two *in vivo* nonmammalian assays. Based on results from screening conducted on the first list of chemicals with these 11 assays, experience was gained in the ease of conduct and consistency of assay performance. Challenges were identified, along with proposed solutions will be discussed along with individual assay performance. Dose selection to meet the guideline requirements to achieve a maximum tolerated dose (MTD) for the *in vivo* assays was most challenging and resulting in dose range finding studies, which needed to be conducted to insure, the high dose selected approached, but did not exceed the MTD. All the assays will be discussed with focus on the more challenging assays for conduct and data interpretation.

S8-3
The EDSP Tier 1 battery contains five *in vitro* and six *in vivo* assays designed to detect potential test material interactions with the estrogen, androgen, and thyroid pathways. Results from these studies are used in a WoE assessment to determine potential endocrine activity of a test compound and possibly provide information on the endocrine mode of action (MoA). This presentation will examine the EDSP Tier 1 battery for assay redundancy, complementarity, and concordance, three key factors in a WoE assessment. The focus will involve an integration of EDSP Tier 1 results with other available toxicity information (i.e., toxicity studies, published data, ToxCast, etc.) to look for patterns that may indicate a potential endocrine MoA. In addition, the impact of stress, systemic toxicity, and other confounding factors are considered in the evaluation of potential endocrine activity. A case study will be used to illustrate some issues related to WoE assessments; specifically, 1) that the profile of expected Tier 1 responses for a specific MoA may not occur; and 2) that it may be difficult to discern the specific MoA for endocrine effects, particularly with the reliance of the battery on apical endpoints that can be altered indirectly. The results of the Tier 1 WoE are used to determine whether further endocrine testing is needed and if so, which Tier 2 tests might be appropriate to better characterize endocrine hazards and dose-response relationships.

S8-4
US EPA has worked hand-in-hand with the scientific community through EDSTAC, FIFRA Scientific Advisory Panels and other entities to implement FQPA's mandated endocrine testing program. Challenges included structuring the program with regard to initial screens and definitive studies and identifying and validating the initial screening assays. The first list of Chemicals ("List 1") has gone through the eleven Tier 1 screening assays (or have reliable data that are equivalent to the Tier 1 screens). The agency is reviewing these results and conducting evaluations to determine if specific Tier 2 definitive tests are indicated. Our risk-based approach toward protecting the environment requires careful analysis and integration of potential endocrine disrupting activity with anticipated exposures. This is a dynamic program at US EPA; as science evolves, our approach will be refined to maximize both efficiency and scientific soundness of our conclusions.

S8-5
The United States and Europe have focused attention to potential risks of exposure to chemicals deemed to be endocrine disruptors. US EPA targeted an experimental characterization of a broad range of substances for endocrine activity but did not concurrently issue an articulated regulatory outcome, based on these data. The European Commission, in contrast, put the regulatory consequence in place first (i.e., a hazard-based ban of Endocrine Disruptors) and is now developing scientific and regulatory criteria to identify disruptors key players in Europe are the EU Commission and its subcommittees. They work together with scientific experts in developing a definition for endocrine disruptors as well as setting the threshold between substances that require regulatory action and those that do not. Their goal, also, is to investigate if a hazard-based cut-off is appropriate in all cases or if quantitative risk assessment should determine the fate of chemicals where endocrine activity is low. The final position is scheduled for December 2013; a summary of the scientific and regulatory positions developed will be presented in this talk.

SYMPOSIUM 9

Secondary Pharmacology: Assay, Uses, and Evaluation

9:00 AM–12:00 Noon
Cibolo 5

CHAIR: **Vincent Murphy,** Array BioPharma, Inc.

CO-CHAIR: **Donna M. Dambach,** Genentech

Supported by an educational donation provided by:
Eurofins Panlabs and the ***American College of Toxicology***

During the discovery and development of pharmaceuticals, compounds are evaluated for selectivity and potential side effects using *in vitro* and *in vivo* pharmacology assays. These assays include integration of ligand binding or isolated enzyme assays, cell functional assays, tissue assays and animal models. These data are reported in the "Secondary Pharmacology" section of regulatory submissions. This symposium will cover what assays are available and how to choose them; inform on structural prediction of compound effects on these assays, provide experiences from representatives of the pharmaceutical industry on use, evaluation and relevance of these assays; and provide guidance from the US FDA as to what the agency expects in the secondary pharmacology section and how the information is used in evaluation of a pharmaceutical compound.

S9-1	9:00 AM–9:35 AM	***In Vitro* Pharmacological Screening for Clinical Liabilities** *Gonzalo Castillo, Eurofins Panlabs, Bothell, WA*
S9-2	9:35 AM–10:04 AM	**Predicting Secondary Pharmacology from Molecular Target Networks** *Michael J. Keiser, SeaChange Pharmaceuticals Inc., San Francisco, CA*
S9-3	10:04 AM–10:36 AM	**Uses of Secondary Pharmacology Data in Small Molecule Candidate Identification: Strategies to Reduce Off-Target Promiscuity and "Bad Actor" Compounds** *Donna Dambach, Genentech, Inc., South San Francisco, CA*
	10:36 AM–10:56 AM	*Break*
S9-4	10:56 AM–11:28 AM	**Assessment of the Relevance of Findings in Secondary Pharmacology Screens** *Vincent Murphy, Array BioPharma Inc., Boulder, CO*
	11:28 AM–12:00 Noon	**A Regulatory Perspective on the Utility of *In Vitro* Secondary Pharmacology Data to Assess Potential Off-Target Activity of New Drugs** *Thomas Papoian, US Food and Drug Administration, Silver Spring, MD*

S9-1

Over the last decade the pharmaceutical industry has observed a dramatic increase in drug candidate attrition rates particularly in late-phase clinical trials (Phase II and III). Being able to predict clinical liabilities early can mitigate the economic impact of late stage failures. *In vitro* pharmacological profiling plays an increasingly important role in reducing drug related safety attrition as it identifies off-target activities and adverse reaction potential by testing compounds for activity in pharmacologically relevant targets like Serotonin $5H^{2B}$, hERG and others. *In vitro* profiling, testing compounds in select panels of assays, allows for the early risk assessment of compounds in a drug development pipeline. Early assessment of a lead compounds adverse reaction potential can improve the success rate in later stages of clinical development by providing the right information sooner to kill a drug early and with confidence. There are several advantages of *in vitro* profiling, it allows optimizing compounds for specificity and selectivity, enables cost effective testing of multiple compounds in parallel, uses species relevant targets and provides fast turnaround times. *In vitro* screening, when coupled with pharmaco-informatics tools can provide valuable information related to potential adverse events, therapeutic applications, repurposing and *in vivo* efficacy.

S9-2

Many drugs modulate more than one protein target at standard dosages. This multitarget engagement can underlie a drug's therapeutic action or account for its undesired side effects. Drawing on systems pharmacology techniques, we computationally predict a drug's side effects from its disruption of molecular target networks. Methods such as the Similarity Ensemble Approach (SEA) have revealed hundreds of new and therapeutically relevant links between drugs and the targets comprising these networks; the next challenge is to mechanistically associate specific target combinations with their disease and toxicological phenotypes. To do so, we have turned to chemical-genetic epistasis experiments on model organisms, wherein we cross a genetic (knock-down) with a chemical (drug) perturbation to identify the protein target underlying an induced phenotype. In proof of concept work with *C. elegans*, we uncovered four novel yet conserved pathways modulating worm feeding rate in the presence of different drugs. When applied at scale in cell lines that model disease and toxicity outcomes, this approach may be an automated way to determine the mechanistic targets underlying drug effects.

S9-3

Off-target toxicity is an identified significant contributor to small molecule drug attrition and minimizing the potential for off-target effects is an important component of a drug candidate identification strategy. Such a strategy begins with screening and investigational activity to identify potential liabilities, determine their functional significance, and influence chemical design of molecules to minimize identified liabilities during the discovery phase concurrent with optimization for ADME, efficacy and pharmaceutics characteristics. The goal of this type of secondary pharmacology lead identification strategy is to identify the best candidates with regard to minimal promiscuity and high selectivity, as well as to characterize off-target liabilities that have been identified for a lead candidate. The desired outcome is to minimize unexpected toxicity and to more fully characterize the identified liability during the IND-enabling studies to inform the clinical monitoring plan.

S9-4

Prior to running secondary pharmacology screens, one must understand and decide how these screens will be used. For example, different modes of measurement may provide a large difference in potency, both being appropriate, but one used to prioritize compounds (high assay potency) and the other to compare to *in vivo* plasma levels to predict possible adverse effects (potency relevant to *in vivo* effects). Once a "hit" is identified during secondary pharmacology screening, the relevance of that finding needs to be addressed. Questions to be asked are: Is the finding reproducible, can it be confirmed in another assay, is the finding due to a nonspecific effect, is the concentration that produces the finding in the screen similar to concentrations in animals and humans, do effects seen in animals resemble those excepted with the finding. Spurious findings can result from aggregate formation in enzyme assays, quenching in radio-ligand binding assays and compound effects on the cells or measurement method in cell functional assays. Lack of secondary pharmacology assay findings correlating to animal or clinical effects in addition to nonspecific effects in the assay could be species specificity, protein binding, pharmacokinetics and active metabolites. Case studies will be presented to demonstrate some of the means to address these questions and to show some examples of assessing relevance.

12:00 Noon–1:30 PM	**IJT *Editorial Board Meeting***	*Cibolo 3*
12:00 Noon–1:30 PM	***2014 Program Planning Meeting*** *(All ACT members invited. Sign up at the Registration Desk. Box lunch provided.)*	*Cibolo 4*

Tuesday Afternoon Sessions

SYMPOSIUM 10

The Drug Development Paradigm for a Small Molecule: Case Study of the Janus Kinase (JAK) Inhibitor Tofacitinib for the Treatment of Rheumatoid Arthritis

2:00 PM–5:00 PM
Cibolo 5

CHAIR: **Douglas J. Ball,** Pfizer Inc.

CO-CHAIR: **W. Mark Vogel,** Pfizer Inc.

The nonclinical components that are required during the lifecycle of the development of a small molecule extend beyond what are expected based on regulatory guidelines. Each small molecule has unique issues that arise that will require additional investigations to better understand underlying mechanisms for observed effects in *in vitro* and *in vivo* studies. In addition, unanticipated adverse effects may be observed in human clinical trials that may require specialized nonclinical studies to characterize the risks associated with the findings.

The new chemical entity, tofacitinib citrate (Xeljanz®) will be used as a case study to follow nonclinical development from basic biology of the pathway, to selection of a molecule for development, toxicology studies conducted to support human clinical trials, clinical development, investigative studies to derisk findings, and a regulatory perspective on the review of the nonclinical overview (NCO) for a small molecule.

S10-1	2:00 PM–2:45 PM	**From Target to Molecule: Efficacy Models, Compound Selection, Early Risks, and PK/PD Modeling** *James D. Clark, Pfizer Inc., Cambridge, MA*
S10-2	2:45 PM–3:17 PM	**From Molecule to Human: Nonclinical Development Program from First in Human to End of Clinical Development** *Douglas J. Ball, Pfizer, Inc, Groton CT*
S10-3	3:17 PM–3:49 PM	**Translation of Risk: Building the Bridge from Nonclinical to Clinical Development** *John Bradley, Pfizer Inc., Groton, CT*
	3:49 PM–4:09 PM	*Break*
S10-4	4:09 PM–4:41 PM	**Regulatory Considerations from the Nonclinical Perspective for the Development of Tofacitinib from IND to NDA** *Timothy W. Robison, US Food and Drug Administration, Silver Spring, MD*
	4:41 PM–5:00 PM	**Q&A**

S10-1
Discuss the rationale for targeting constituents of the JAK/STAT pathway; the physiologic role of these elements and the potential consequences, positive and negative of pathway inhibitor Discuss highlights of identification of tofacitinib: selectivity across the kinome and within the JAK family: relative potency in inhibiting JAK/STAT dependent cytokines and in vivo characterization of activity.

S10-2
The nonclinical toxicology program that was conducted to support first in human to the completion of the Phase III development program will be discussed with particular emphasis on study design and outcomes relative to tofacitinib pharmacology.

S10-3
As tofacitinib (Xeljanz®) moved from the nonclinical arena to patients, the initial safety assessments were based on the observed effects from the nonclinical studies and effects predicted by the known mechanism of action. This presentation will describe the identification, assessment and mitigation strategy for the safety concerns observed in the tofacitinib (Xeljanz®) rheumatoid arthritis Phase 2 and Phase 3 studies, and the role of the nonclinical and toxicology studies to help better understand and manage these safety issues in the clinical program.

S10-4
The presentation will focus on the process for regulatory review of nonclinical data when first received in an IND submission through to the New Drug Application using tofacitinib as the case study example. Emphasis will be placed on the significance of nonclinical findings to human clinical trials during IND development with particular focus on considerations for initial clinical trials and Phase 3 clinical trials, review of the NDA, and nonclinical content in the US package insert. Discussion will include target organs of toxicity identified in toxicology studies with rodents and nonrodents and monitorability of findings in clinical trials and adequacy of the investigator brochure and informed consent for describing potential reproductive toxicity and carcinogenicity findings.

SYMPOSIUM 11

Impact of Combination Toxicology Studies on Pharmaceutical Development: Careful Consideration of Study Objectives, Timing, and Design

2:00 PM–5:00 PM
Cibolo 6

CHAIR: **Christopher Ellis,** US Food and Drug Administration/CDER

CO-CHAIR: **Leigh Ann Burns Naas,** Gilead Sciences, Inc.

Supported by an educational donation provided by: ***Cubist Pharmaceuticals Inc.***

Combinations of small molecule and/or biologic pharmaceuticals are often critical for the successful treatment of disease. Therapeutic indications commonly utilizing pharmaceuticals in combination include diverse areas in oncology, rheumatology and cardiovascular, infectious and metabolic disease. The necessity of combination toxicology studies to support pharmaceuticals to be used in combination (fixed-dose formulation, co-administered products…) depends not only on the extent of available nonclinical and clinical safety data for each individual pharmaceutical, but also on unique indication specific considerations (e.g., seriousness/severity of disease, benefit of existing therapies, intended patient population etc.) for tolerating clinical risk. Despite the importance of these combinations, nonclinical safety assessment strategies of pharmaceuticals to be used in combination can be quite challenging to devise. This Symposium will present a detailed discussion of the value of combination toxicology study data to support the overall development of pharmaceuticals to be used in combination from both an industry and regulatory perspective, beginning with an overview of current regulatory guidance regarding combination toxicology studies, followed by specific study design considerations, numerous examples and case studies, and conclude with an open roundtable discussion.

	2:00 PM–2:05 PM	**Introduction** *Christopher Ellis, US Food and Drug Administration/CDER, Silver Spring, MD*
S11-1	2:05 PM–2:35 PM	**A Regulatory Perspective on Combination Toxicology Studies** *Janice Lansita, US Food and Drug Administration/CDER, Silver Spring, MD*
S11-2	2:35 PM–3:05 PM	**Designing Nonclinical Combination Toxicity Studies for Pharmaceutical Agents: Challenges and Points to Consider** *Sushmita M. Chanda, Alios BioPharma, South San Francisco, CA*
S11-3	3:05 PM–3:35 PM	**Case Studies: Combination Evaluation for Antivirals and Cardiovascular Programs** *Roy Bannister, Gilead Sciences, Inc., Foster City, CA*
	3:35 PM–3:55 PM	*Break*
S11-4	3:55 PM–4:25 PM	**Impact of Pharmaceutical Candidate Characteristics and Regulatory Requirements on Combination Toxicity Testing Strategy** *William E. Achanzar, Bristol-Myers Squibb, New Brunswick, MH, Canada*
	4:25 PM–5:00 PM	**Roundtable Discussion** *All presenters*

S11-1
The US FDA regulatory requirement for combination toxicology studies takes into consideration a number of factors that include: the potential for adverse consequences of combined pharmacological effects, the anticipated toxicity of the combination, the indication/severity of disease, the patient population, and existing safety information. Based on these factors, the requirement for combination toxicology data may be considered on a case-by-case basis. This presentation will summarize key points from existing guidances on combination toxicology studies, provide examples of how regulatory guidance has been applied and interpreted in the conduct of these studies, and conclude with a regulatory perspective on their utility.

S11-2
The primary goal of the nonclinical combination toxicity study is to identify whether there is a change in the toxicity profile when two or more pharmaceutical agents are combined. The presentation will outline points to consider in designing these studies including timing, species and dose selection, duration and endpoints. Case studies that highlight challenges of designing and conducting these studies will also be discussed.

S11-3
International regulatory recommendations for combination toxicity testing have been refined over the preceding 10 years. This presentation will summarize Gilead's experience developing fixed dose combinations (FDC) for HIV, including Truvada® (2 drugs; US approval in 2004) and the single tablet regimen (STR) Stribild® (4 drugs; US approval in 2012). Case studies will also be provided from Hepatitis C (HCV) and cardiovascular disease programs.

S11-4
The nature of combination toxicity assessments are usually dependant on pharmaceutical candidate characteristics, stage of development, and input from global health authorities. To highlight the role these factors play, two combination toxicity case studies will be presented. The first case study involves a fixed dose combination of a late-stage small molecule with a marketed small-molecule compound where combination testing consisted of repeat-dose toxicity and embryo-fetal development studies in rodents. The second case study describes combination toxicity testing in nonhuman primates to support combined use of an early-stage biologic on top of the current small-molecule standard of care in clinical studies. For each case study, the scientific and regulatory rationale for combination toxicity testing, the design and timing of the studies, the role of pharmacologic activity in species selection, and the impact of the results on both the safety assessment of the compounds and overall development trajectory will be presented.

SYMPOSIUM 12

Phospholipidosis: Evaluation and Management of Its Risk

2:00 PM–5:00 PM
Cibolo 7

CHAIR: **Kok Wah Hew,** Takeda Pharmaceutical Company Limited

CO-CHAIR: **Kenneth L. Hastings,** Sanofi US

Supported by an educational donation provided by: ***Takeda Pharmaceutical Company Limited***

Drug-induced phospholipidosis (PLD) is characterized by an abnormal intracellular accumulation of phospholipid in various tissues and organs. Phospholipidosis is generally associated with exposure to drugs containing a cationic amphiphilic structure. However, with a few notable exceptions, its translatability and significance to human safety remains unknown. This symposium will discuss the pathology of PLD, biomarkers for PLD, management of PLD by pharmaceutical industry, and regulatory agency's view of PLD. The first talk will summarize the biology and pathology of PLD and discuss the toxicological significance of PLD in the clinics. The second talk will discuss the utility of potential biomarkers for PLD in nonclinical and clinical studies. The third talk will present industry's experience in managing and monitoring PLD in clinical trials and steps taken to mitigate potential risks in humans. The final talk will discuss regulatory agency's current thinking on PLD plus an update on the activities of PLD Working Group in the FDA. The symposium will end with a panel discussion where speakers will address questions or comments from attendees.

2:00 PM–2:05 PM	**Introduction** *Kok Wah Hew, Takeda Pharmaceutical Company Limited, Deerfield, IL*
2:05 PM–2:35 PM	**Biology and Pathology of Phospholipidosis** *Kenneth L. Hastings, Sanofi US, Bethesda, MD*
2:35 PM–3:05 PM	**Biomarkers for Phospholipidosis** *Frank Hsieh, Nextcea, Inc., Woburn, MA*
3:05 PM–3:40 PM	**Industry Perspective on How to Manage Phospholipidosis in Drug Development** *Kenneth L. Hastings, Sanofi US, Bethesda, MD*
3:40 PM–4:00 PM	*Break*
4:00 PM–4:30 PM	**Phospholipidosis: Drug-Induced Lysosomal Storage Disorder, A Regulatory Perspective** *James Willard, US Food and Drug Administration, Silver Spring, MD*
4:30 PM–5:00 PM	**Panel Discussion**

5:00 PM–6:30 PM	***ACT Members' Meeting*** *(All ACT Members Invited)*	***Cibolo 5***

EXHIBITOR-HOSTED PROGRAM

7:00 AM–7:55 AM

See page 121 for more information.

PLENARY LECTURE 3

Health and Policy Implications to Caffeine Exposure

8:00 AM–8:55 AM
Nelson W. Wolff Ballroom A

Roger A. Clemens, DrPH, CNS, FACN, FIFT
Chief Scientific Officer of Horn and Adjunct Professor of Pharmacology and Pharmaceutical Sciences at University of Southern California, School of Pharmacy

Dr. Roger A. Clemens is chief scientific officer of Horn and part-time faculty within the USC Regulatory Science program where he also enjoys an adjunct appointment as professor of pharmacology and pharmaceutical sciences within the USC School of Pharmacy. He served as scientific advisor for Nestlé USA for more than 21 years.

Dr. Clemens has published more than 50 original manuscripts in nutrition and food science, participated in more than 300 invited domestic and international lectures, and served as an expert panel member for the food industry, scientific organizations, trade associations and regulatory agencies in the United States, Canada, and Europe.

Dr. Clemens is the immediate past president (2012–2013) of the Institute of Food Technologists (IFT) and member of the IFT Board of Directors. He served on numerous IFT expert panels, including Functional Foods, and Making Decisions about the Risks of Chemicals in Foods with Limited Scientific Information. He co-founded, established and contributes to a Food, Medicine and Health column published monthly in Food Technology. As a spokesperson for IFT, Dr. Clemens has been cited and interviewed by more than 500 domestic and international health journalists, and has appeared on numerous televised (e.g., Good Morning America, CNN, CBS 48 Hours) discussions on contemporary health, nutrition and food safety issues.

Dr. Clemens was a spokesperson for the American Society for Nutrition (ASN) while serving on the society's quick response team for breaking news on food, nutrition and health issues. He chaired the Public Information Committee, and serves as a member of ASN's Finance Committee, ASN's Medical Nutrition Council, and ASN's Membership Committee.

Dr. Clemens was a member of the USDA 2010 Dietary Guidelines Advisory Committee, and is a second-term member of the US Pharmacopeia Food Ingredient Expert Committee. He was a member of the Commission on Dietetic Registration for the Academy of Nutrition and Dietetics.

Dr. Clemens, a certified food scientist, is a professional member of and Fellow in IFT. Dr. Clemens received many awards for his leadership in IFT, the Academy of Nutrition and Dietetics, and in local universities. He is a fellow in the American College of Nutrition, a Fellow in the International Academy of Food Science and Technology, and a Fellow in the Marilyn Magaram Center for Food Science, Nutrition and Dietetics. He is also an active member in the Society of Toxicology.

Dr. Clemens received an AB in bacteriology, a MPH in nutrition, and a DrPH in public health nutrition and biological chemistry from the University of California, Los Angeles.

Wednesday Morning Sessions

SYMPOSIUM 13

Prospective Approaches to Characterize Potential Neurotoxicity — **9:00 AM–12:00 Noon** — ***Cibolo 5***

CHAIR: **Robert Sills,** National Institute of Environmental Health Sciences

CO-CHAIR: **Susan J. Borghoff,** ToxStrategies, Inc.

Supported by an educational donation provided by:
WIL Research Laboratories, LLC and the ***American College of Toxicology***

Speaker travel support provided in part by:
Experimental Pathology Laboratories, Inc. and ***Integrated Laboratory Systems (ILS), Inc.***

Direct neurotoxic effects of environmental chemicals or those that may contribute to neurodegenerative disease progression or developmental disorders remain an important concern for public health. Due to the complex nature of the nervous system, a multidisciplinary approach has been routinely demonstrated as necessary to sufficiently assess neurotoxic effects, especially during screening of chemicals and pharmaceuticals with unknown potential for neurotoxicity. While neuropathology is an unambiguous endpoint for neurotoxicity and can direct additional examination, predicting where neurotoxicity will occur remains a challenge. Moreover, neurotoxicity can occur by multiple physiological mechanisms and prior to detection by standard neuropathological assessment. This session will present and discuss our current approach and understanding of assessing chemical-induced alterations in integrated nervous system function by behavior and neuroanatomy, the identification of pathological endpoints, and the characterization of neoplasms in the brain using immunohistochemical markers. Efforts to establish *in vitro* model systems reflective of critical neurotoxic endpoints will be discussed.

S13-1	9:00 AM–9:40 AM	***In Vitro* Models for the Evaluation of Potential Neurotoxicity** *G. Jean Harry, National Institute of Environmental Health Sciences, Research Triangle Park, NC*
S13-2	9:40 AM–10:20 AM	***In Vivo* Approaches for Evaluating Potential Neurotoxicity** *Jonathan Toot, WIL Research Laboratories, LLC, Ashland, OH*
	10:20 AM–10:40 AM	*Break*
S13-3	10:40 AM–11:20 AM	**Functional Neuroanatomy and Neuropathology: Where Do We Look for Lesions?** *Deepa B. Rao, Integrated Laboratory Systems (ILS), Inc., Research Triangle Park, NC*
S13-4	11:20 AM–12:00 Noon	**Immunohistochemical Characterization of Spontaneous and Chemically Induced Brain Neoplasms (Rodent vs. Human)** *Holly Kolenda-Roberts, SNBL USA, Ltd, Everett, WA*

S13-1

The strengths and limitations of *in vitro* techniques will be discussed in light of their usefulness to identify neurotoxic hazards. Because of the complexity of the nervous system and the integrated nature of the circuitry and function the ability of *in vitro* systems to detect or predict neurotoxic effects remains in question. *In vitro* systems are well suited to the study of biological processes in a more isolated context and have been most successfully used to elucidate mechanisms of toxicity, identify target cells of neurotoxicity, and delineate cellular and molecular changes induced by neurotoxicants. Both biochemical and morphological end points can be used, but many of the end points used can be altered by pharmacological actions as well as toxicity. Therefore, criterion to allow for discrimination between pharmacological activity and neurotoxic effects can become a critical issue. Association of specific cellular mechanisms with cell morphological changes may allow for a distinction between the types of effect and provide a characterization of the neurotoxic potential. Therefore, *in vitro* tests continue to have their greatest potential in providing information on basic mechanistic processes that may offer a profile for predicting *in vivo* neurotoxicity and refine specific experimental questions to be addressed in the whole animal.

S13-2

Due to the variety of biochemical targets and toxic effects, a wide array of test strategies is available. This talk will present commonly used *in vivo* techniques for the evaluation of neurotoxicity including a staged approach aimed to identify (Tier 1) and characterize (Tiers 2–3) the neurotoxicity of a chemical. Tier 1 is usually a basic repeated dose toxicity study. The US EPA and OECD have published guidelines which outline a variety of tests that can be used to characterize potential neurobehavioral and neuropatholgical effects. The five categories of neurotoxicity endpoints, 1) structural or neuropathological, 2) neurophysiological, 3) neurochemical, 4) behavioral and neurological, and 5) developmental, detailed in the guidelines will be reviewed along with the functional observation battery (FOB) which is a standardized screening battery for assessing many aspects for behavior and neurological function in rodents.

S13-3

Neuropathology remains a cornerstone in the evaluation of neurotoxicity. Critical to the identification and interpretation of neuropathological findings is an understanding of functional neuroanatomy and neuronal circuitry. This talk is based on the concepts underlying the modified approach in neuropathology for routine screening of potential neurotoxicants as currently applied in the National Toxicology Program Studies. A review of neuroanatomical subsites and circuitry relevant to neurodegenerative diseases and those sites susceptible to toxicants will be highlighted. An emphasis on screening for toxicants with unknown neurotoxic potential and examples impacting neuronal circuitry and potential secondary target sites will be provided.

S13-4

Spontaneously occurring brain neoplasms have been documented in humans and a wide range of animals but are relatively rare. The highest rates of spontaneous tumors, and occurrences of chemical induction of tumors in the brain, appear to occur in the rat. The brain tumor incidence in several strains of rats exceeds 2–3 times the incidence of human and domestic animal brain tumors. Based on previous literature, the most common brain tumor in the rat is astrocytoma. Using a panel of Immunohistochemical stains to study both spontaneous and induced brain tumors in rats, it appears that the most common spontaneous tumor is oligodendroglioma, not astrocytoma, and the most common induced brain tumor is of microglial cell origin. As small increases in the incidence of gliomas in chronic rat bioassays have been difficult to interpret, the use of IHC to characterize the tumors is necessary. Since it appears that many induced tumors are malignant microglial tumors, this may further call into question the relevance of these tumors to human disease. The most common human brain tumors are astrocytomas (adults) and medulloblastomas (children), and the experimental induction of malignant microglial tumors in rats may represent a species-specific manifestation.

SYMPOSIUM 14

Consumer Healthcare Ingredient Issues and Potential Impact on Product Safety and Risk Communication

9:00 AM–12:00 Noon
Cibolo 6

CHAIR: **Tracey L. Spriggs,** GlaxoSmithKline Consumer Healthcare

CO-CHAIR: **William J. Brock,** Brock Scientific Consulting

Supported by an educational donation provided by:
GlaxoSmithKline Consumer Healthcare and the ***American College of Toxicology***

Consumer exposure to potentially toxic ingredients can occur through numerous types of healthcare and food products, including prescription and OTC pharmaceuticals, dietary supplements, foods and personal care products. These compounds can be active ingredients, excipients, food additives, as well as a myriad of ingredients that are used to formulate personal care products. Over about the last decade, safety concerns have been raised over ingredients including triclosan, titanium dioxide to phthalates, bisphenol A, parabens, propylene glycols, etc. Toxicologists working in industry and government are continually challenged with identifying the hazards of those ingredients to help make a risk assessment determination based on the hazard and potential consumer exposure to those ingredients. Unfortunately, risk communication by toxicologists or other scientists has not always been adequate thereby leading to negative public perception or misrepresentation of the data. In this symposium, we will focus on ingredients in consumer healthcare products for which safety issues have been raised, and explore the hazard and risk perception for these ingredients relative to existing data on animal and human exposure. In addition, the risks associated with anticipated exposures will be discussed and how risk communication has helped, or hindered, the understanding of the hazards of these ingredients by the public.

S14-1	9:00 AM–9:40 AM	**Triclosan: Scientific and Regulatory Updates for Toxicity and Bacterial Resistance** *Wafa A. Harrouk, US Food and Drug Administration/CDER, Silver Spring, MD*
S14-2	9:40 AM–10:20 AM	**Titanium Dioxide: Safety and Regulatory Considerations** *Linda Loretz, Personal Care Products Council, Washington, DC*
	10:20 AM–10:40 AM	*Break*
S14-3	10:40 AM–11:20 AM	**Phthalates as Pharmaceutical Excipients: Hazard and Risks** *Robinan Gentry, ENVIRON International Corporation, Monroe, LA*
S14-4	11:20 AM–12:00 Noon	**Risk Communications: What We Say As Scientists and What the Public Hears** *Mark W. Lafranconi, Tox Horizons, Maineville, OH*

S14-1
Tricolsan is found in a number of personal care products. Over the last decade, concerns have been raised about the safety of this compound in association with an increase in bacterial resistance, which is compromising the effectiveness of antibiotics. In addition, because of its use, environmental risk have become of concern on the part of industry and regulatory authorities. This talk will explore the various aspects of the toxicity of tricolsan, provide an overview of recently published data and discuss the resulting impact on risk assessment and the continued use of this ingredient.

S14-2
Titanium dioxide is widely used in personal care products as both a colorant and as a UV filter. An extensive toxicological database has been developed for this ingredient. Very high concentrations of titanium dioxide administered by the inhalation route have been found to induce lung tumors in rats. The tumors have been attributed to 'lung overload', in which the high-test concentrations overwhelm the normal physiological clearance systems of the lung. The use of nanosized titanium dioxide in sunscreens has raised additional questions about safety, though penetration through intact epidermis has been shown to be insignificant. Results of safety testing and exposure assessment for titanium dioxide will be discussed and put in the context of human risk.

S14-3
Phthalates have large use in consumer products, building materials and pharmaceuticals. In numerous studies with different phthalates, these compounds have been shown to represent a potential risk of reproductive toxicity and, for some compounds, a carcinogenic response in the liver has been observed in rodents. However, risk assessment paradigms have demonstrated a low risk for these effects. Regardless, these compounds continued to be scrutinized for those risks. This talk will explore the hazards for many of the phthalates and the associated risk when used in various applications including pharmaceuticals.

S14-4
Scientists and the public at large often have different perceptions regarding risks from consumer products. Scientists are more comfortable with uncertainty and accept risk as a means of defining uncertainty. Consumers, on the other hand, do not share that level of comfort with uncertainty and translate the concept of risk into concern, particularly when it relates to products they rely on for their personal use and that of their family. As a result, communications of safety and risks with consumers presents an important challenge for toxicologists and risk managers. This talk will review current thinking for effective risk communications using case histories from a range of consumer products and the lessons learned.

SYMPOSIUM 15

Managing the Regulatory Impact of Rodent Tumor Findings

9:00 AM–12:00 Noon
Cibolo 7

CHAIR: **Jeri El-Hage,** Aclairo Pharmaceutical Development Group

CO-CHAIR: **Christine Lynn Lanning,** Merck and Co., Inc.

Supported by an educational donation provided by:
Aclairo Pharmaceutical Development Group

This symposium will include five presentations related to: 1) optimizing the design and interpretation of rodent carcinogenicity studies for pharmaceutical to minimize the impact on product approval, 2) published literature on modes of action for rodent tumors that minimize clinical relevance 3), developing mode-of-action/mechanistic data for novel tumor types sufficient to allay regulatory concerns for clinical relevance, 4) presentation on ICH S1 update activities related to recommendations for carcinogenicity studies, and 5) the expected expanding role for alternative transgenic mouse models in the future of carcinogenicity testing.

Safety concerns related to rodent tumor findings and their clinical relevance continue to impact risk: benefit and approval decisions for pharmaceuticals. Rodent carcinogenicity studies are recommended for all small molecule new molecular entity and increasingly for biologics. Optimizing the design and interpretation of rodent carcinogenicity studies and elucidating the mode of action for tumor formation can mitigate regulatory concern regarding the clinical relevance of compound-related tumor findings. Literature reviews for well-established rodent specific tumor types and/or generation of mechanistic data for novel or rare tumor types can be useful in dismissing clinical relevance and mitigating regulatory consequences. This symposium will also provide a view to the proposed future of carcinogenicity testing and should be of interest to regulators and scientists developing pharmaceuticals indicated for chronic use.

S15-1	9:00 AM–9:30 AM	**Rodent Carcinogenicity Studies: Optimizing Study Designs, Interpretation of Tumor Findings, and US FDA Interactions** *Jeri El-Hage, Aclairo Pharmaceutical Development Group, Vienna, VA*
S15-2	9:30 AM–10:00 AM	**GLP-1R Agonist-Induced Thryroid C-Cell Tumors in Rodents—The Mechanism Evaluation** *Lars Madsen, Novo Nordisk AS, Research and Development, Plaisboro, NJ*
S15-3	10:00 AM–10:30 AM	**Mechanism of Renal Tubular Tumor Formation in Rats Treated with the SGLT 2 Inhibitor Canagliflozin** *Mark D. Johnson, Janssen Research and Development, Raritan, NJ*
	10:30 AM–11:00 AM	*Break*
S15-4	11:00 AM–11:30 AM	**Opportunity to Improve Carcinogenicity Testing thru Modifications to ICH** *Vijay Reddy, Merck and Co., Inc., West Point, PA*
S15-5	11:30 AM–12:00 Noon	**Alternative Mouse Models in the Future of Carcinogenicity Testing** *Nancy Bower, Eisai, Inc., Woodcliff Lake, NJ*

S15-1

The presentation will include discussions on how to optimize interactions with US FDA review divisions and the Executive Carcinogenicity Assessment Committee (ECAC) regarding: 1) designs of rodent carcinogenicity studies, 2) review of Special Protocol Assessments (dose selections and protocol amendments), and 3) scientific justifications for carcinogenicity study waivers.

US FDA/ECAC policies for interpreting carcinogenicity study results based on survival, tumor findings at doses exceeding the MTD, use of historical control data, statistical P values, and safety margins relative to clinical exposures will be presented. In addition, the use of mode of action information from the literature or sponsor generated mechanistic studies to support rodent specific tumor formation and minimize concern for clinical relevance will be presented.

S15-2

Over the past decade, GLP-1 receptor (GLP-1R) agonists have been established as new and significant treatment options in type 2 diabetes. Of these therapeutic compounds, liraglutide, was the first for which C-cell tumors seen in rats and mice were thoroughly described. A series of nonclinical mechanistic studies were initiated to support the clinical development and subsequent regulatory submission of liraglutide. Through these studies it was demonstrated that GLP-1R agonists induce C-cell proliferation in rodents by a specific, GLP-1R-dependent mechanism. Plasma calcitonin was identified as an early biomarker for the rodent C-cell activation induced by GLP-1R agonists and calcitonin monitoring was undertaken in clinical trials. The comprehensive data supported that rodents are particularly sensitive to the C-cell effects induced by GLP-1R agonists. The presentation will describe the nonclinical work and key data from this evaluation, including the observed differences in species sensitivity, which ultimately supported the world-wide regulatory approval of liraglutide.

S15-3

Canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, caused renal tubular tumors with a low incidence of hyperplasia in a 24-month rat carcinogenicity study. There were no corresponding preneoplastic lesions in the 3-month or 6-month repeated dose toxicity studies. Canagliflozin is a low potency inhibitor of SGLT1 and causes carbohydrate malabsorption via inhibition of intestinal glucose transport at high doses in rats. Carbohydrate malabsorption is a proximal step in induction of renal tumors by acarbose in rats. Utilization of a glucose-free fructose diet prevented the effect on carbohydrate malabsorption and its sequelae including hyperostosis and increased calcium absorption. In a 6-month mechanistic study, renal tubule cell proliferation was increased in rats administered canagliflozin, and immunostaining was increased for the renal injury biomarker KIM-1. These effects were inhibited in rats maintained on the glucose-free fructose diet indicating they are due to carbohydrate malabsorption and are not direct effects of canagliflozin.

S15-4

Although carcinogenicity testing of pharmaceuticals can be traced back to the 1930s, standardization of practices was not widespread until the 1970s to 1980s. Further refinement of carcinogenicity testing occurred in the 1980s through the 1990s. Today, regulatory requirements addressing the need for carcinogenicity testing are carefully outlined in ICH guidance documents, particularly ICHS1. Now there are decades of data from 2-year rodent carcinogenicity studies available that supported pharmaceutical development and registration. Review of these data suggests, in many cases, the lifetime rat carcinogenicity assay may not provide additional insight to assess risk beyond that identified by the routine toxicology data set. These data will be summarized along with the progress from the ongoing multinational initiative to improve the efficiency and effectiveness of the 2-year lifetime carcinogenicity-testing paradigm. Specifically, the proposed changes to the ICHS1 carcinogenicity testing guidelines will be reviewed and the steps forward for adoption will be explained.

S15-5

As changes to carcinogenicity assessment of pharmaceuticals are being considered through ICH S1 modification, the weight-of-evidence approach being proposed opens up much broader opportunity for alternative short term mouse models to play a more expansive role in the future of pharmaceutical carcinogenicity testing. Recent experience with alternative transgenic mouse models in pharmaceutical development will be summarized, and the heightened value of using these animals from both a scientific and business perspective moving forward, will be described. The focus will be on two models, the p53+/- and rasH2 mouse models, with which the pharmaceutical industry has the greatest experience. These models also have the highest level of acceptance by Regulatory Authorities. The p53+/- mouse model may be the preferred model for compounds with direct or equivocal evidence of genotoxicity. The rasH2 mouse model is the only model that is acceptable for compounds with positive, equivocal or negative genotoxicity findings. This model is becoming the choice of pharmaceutical companies that have adopted an alternative mouse model into their carcinogenicity risk assessment paradigm.

The proposed modification of the ICH S1 guideline will place a strong emphasis on the results of carcinogenicity testing in the mouse. Options to eliminate or replace a 2-year rat study based on a weight-of-evidence argument are being addressed to improve human risk assessment while reducing, refining, and replacing animal testing. In some scenarios, the alternative mouse models have the potential to contribute to this weight-of-evidence, and may be the only carcinogenicity study needed to adequately assess carcinogenic risk.

EXHIBITOR-HOSTED PROGRAMS

12:00 Noon–12:55 PM

See page 121 for more information.

Wednesday Afternoon Session

SYMPOSIUM 16

Hot Topics **2:00 PM–5:00 PM**

Cibolo 5

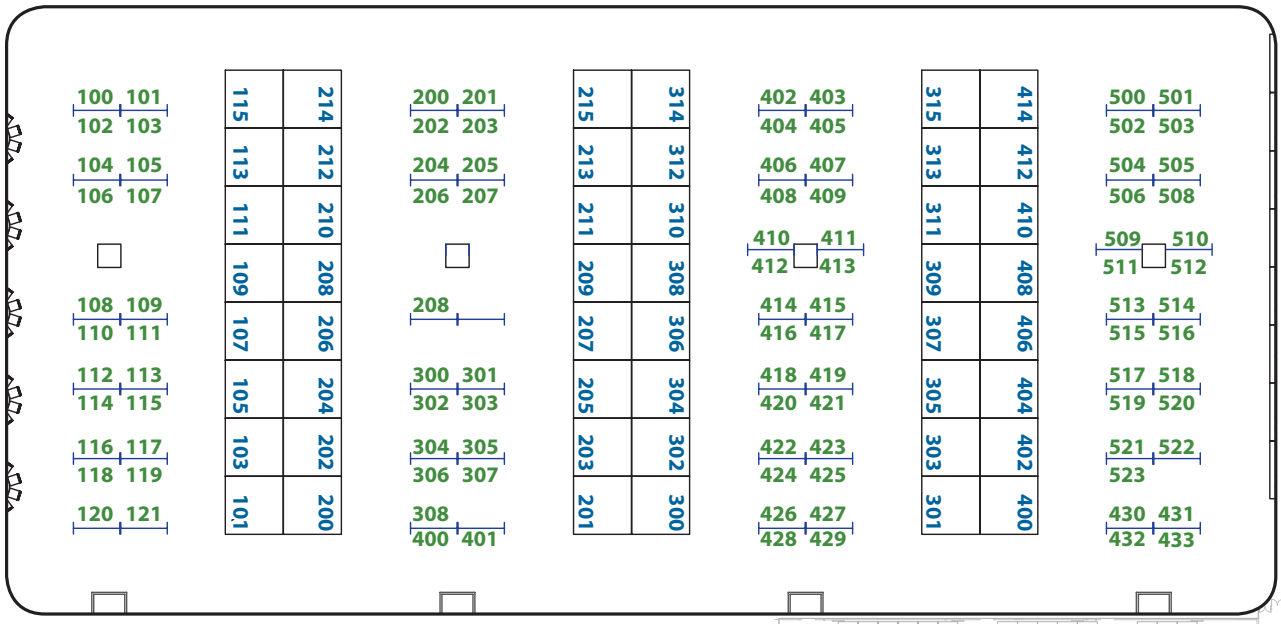
CHAIRS: **Mary Ellen Cosenza,** Amgen Inc. and **Timothy J. McGovern,** SciLucent, LLC

Supported by an educational donation provided by: ***SciLucent, LLC***

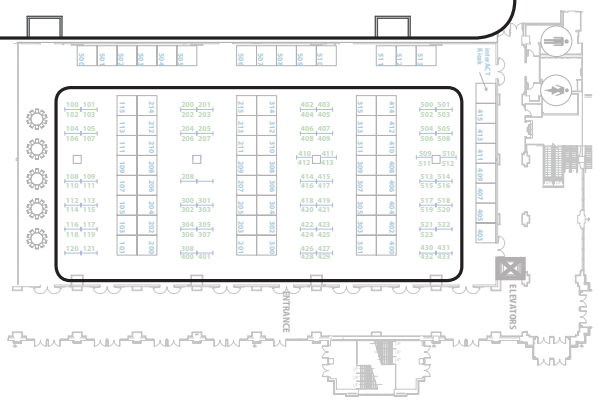
2:00 PM–2:30 PM	**European Medicine Agency (EMA) Topics That Impact Preclinical Drug Development** *David Jones, MHRA/EMA, London, United Kingdom*
2:30 PM–3:00PM	**Upcoming US FDA Guidance of Interest to the Preclinical Scientist** *Lynnda Reid, US Food and Drug Administration, Silver Spring, MD*
3:00 PM–3:20 PM	*Break*
3:20 PM–3:50 PM	**Update on the SEND Initiative** *Timothy Kropp, US Food and Drug Administration, Silver Spring, MD*
3:50 PM–4:20 PM	**Impact of US FDA Guidance on Use of ISO 10993** *Thor Rollins, US Food and Drug Administration*
4:20 PM–5:00 PM	**Global Submissions: Starting Clinical Trials in Belgium and the Netherlands with Supporting Studies Performed in China** *Sue McPherson, WuXi AppTec (Suzhou) Co., Ltd, Suzhou, China, and Ilonka van Hoof, WuXi AppTec (Suzhou) Co., Ltd, Suzhou, China*

ACT Poster Presentations

Posters may be in place as early as Sunday afternoon and will be displayed from Monday through Tuesday at 4:30 pm. Designated authors (indicated in the Poster description by an underline) will present their poster during the Poster Reception Monday, November 4, from 5:30 pm to 7:00 pm. Please join this session to engage with the authors and see some of the latest work in the field.



Posters are located in the Nelson W. Wolff Ballroom B&C.



100 Series—General Toxicology

200 Series—Regulatory

300 Series—Safety Evaluation Nonpharmaceuticals

400 Series—Toxicology Methods

500 Series—Safety Evaluation Pharmaceuticals

(ACT is not responsible for posting, removing, or storing posters.)

Poster Abstracts

100 Series—General Toxicology

P100

12 Week Bone Implantation Study in Sheep to Assess Local Tissue Reaction and Mechanical Strength. *J. Bartrom*[1], *L. Stevenson*[1]. NAMSA, Northwood, OH, USA[1].

The objective of this study was to evaluate the local tissue reaction at the bone implantation sites and mechanical bone strength following implantation in femoral defects. An experimental bone void filler was used as the test article. A marketed bone void filler was used as the comparative control article. Due to the size of the test and control articles, an animal model with bone structures of similar size to humans was needed. One metaphyseal defect was created in each femur of sixteen young adult sheep. The defect sites were implanted with either the test or control article. Immediately after implantation, one animal was euthanized to serve as a baseline for mechanical bone strength testing. Animals were observed twice daily for general health and body weights were collected throughout the study (all animals gained body weight throughout the study and were considered healthy). At 12 weeks, the animals were euthanized and the sites were harvested. The femurs of ten animals were processed and examined microscopically. Push-out testing was conducted on the femurs from the five remaining animals. The push-out data indicated that the test and control article defect sites were not statistically significantly different when comparing average maximum push-out force, average maximum shear stress, and average energy to failure. New bone formation occurred in all defect sites implanted with the test and control articles. At 12 weeks postimplantation the observed tissue response and bone formation was similar between the test and control articles.

P101

A Modified Ames Methodology for the Assessment of Mainstream Cigarette Smoke Genotoxicity Using an Aerosol-Based Exposure System. *J. Kilford*[1], *D. Thorne*[2], *M. Ballantyne*[1], *R. Payne*[1], *A. Dalrymple*[2], *J. Clements*[1], *C. Meredith*[2], *D. Dillon*[2]. Covance Laboratories Ltd, Harrogate, North Yorkshire, UK[1]; Group R&D, British American Tobacco, Southampton, Hampshire, UK[2].

Defined methods, dictated by regulatory guidelines, are followed for routine *in vitro* genotoxicity testing of compounds. To date most toxicological testing of cigarettes has been performed on the particulate phase of cigarette smoke using standard assay methods. Traditional methods are not necessarily compatible with the testing of smoke aerosols which are composed of a complex mixture made up of a particulate and vapour phase. New methods are required to facilitate the testing of whole smoke *in vitro*.

In this study we have modified the Ames assay to allow exposure to aerosol-based test articles at an air-agar interface. The methodology was evaluated using mainstream cigarette smoke generated from 3R4F reference cigarettes on a Vitrocell® VC10 smoking robot. *S. typhimurium* strains TA98, TA100, YG1024, and YG1042 and *E. coli* strain WP2(*uvrA)*pKM101 were tested at 4 concentrations of diluted cigarette smoke in the presence of S-9. Following 6 replicate experiments, dose-related increases in revertants were observed in all *S. typhimurium* strains up to mean fold increases of between 1.7 and 24.8-fold. The *E. coli* strain was unresponsive at all concentrations tested. To quantify exposure dose and enable biological response to be plotted as a function of deposited mass, Quartz Crystal Microbalances were included *in situ* of whole smoke exposure.

In conclusion, the Ames assay methodology has been successfully modified to assess the toxicological impact of mainstream cigarette smoke. This method, however, is not restricted to the testing of whole smoke but could also be applied to testing of other gases, mixtures or aerosols.

P102

Assessing the Ocular Toxicity of an Anticomplement Therapy in Nonhuman Primates When Administered by Multiple Intravitreal Injections. *M. Haskell*[1], *M. Harter*[2], *D. Patrick*[2], *J. Bartoe*[2], *D. Schrier*[1]. Alexion Pharmaceuticals, Cheshire, CT, USA[1]; MPI Research, Mattawan, MI, USA[2].

To evaluate the potential subchronic toxicity of Test Article X, an anticomplement therapy, when administered via intravitreal injection once every two weeks for two months. The reversibility, progression, or delayed appearance of toxicologic findings was evaluated following a 4-week recovery period. The doses were administered by a board-certified ophthalmologist. Topical antibiotics were applied to the eyes prior to treatment, immediately following the injection, and on the day following the injection. Mydriatic drops were applied to the eyes, followed by anesthetic drops, as deemed necessary by the ophthalmologist. The conjunctivae were flushed with topical disinfectant, and the injection was performed. After the dose administration, eyes were examined by biomicroscopy and/or indirect ophthalmoscopy to identify any abnormalities secondary to the injection procedure. Ocular toxicity was evaluated antemortem using applanation tonometry, slit-lamp biomicroscopy, ERG, and indirect ophthalmoscopy (with 20 diopter and macular lenses). Each eye was examined pretest and at 3 intervals during the study. At necropsy, samples of vitreous humor were collected for assessment of factor B levels as a pharmacodynamics marker. No evidence of toxicity was seen on tonometry, slit-lamp biomicroscopy, ERG, indirect ophthalmoscopy, or on histopathology. All microscopic observations were minimal, nondose-related, and considered to be due to the intravitreal dosing procedure. Additionally, at all dose levels, Test Article X-reduced Factor B levels to below the level of detection. These levels returned to baseline in recovery animals, showing that Test Article X successfully inhibits complement in the vitreous humor in a reversible manner without evidence of ocular toxicity.

P103

Axillary Artery Collection of Fetal Blood Enables Direct Comparison to Maternal Exposure Levels without Compromising Visceral or Skeletal Examinations. *C. Grace*[1], *L. Schroeder*[1], *J. Hardy*[1], *M. O'Hara*[1]. Covance Laboratories, Greenfield, IN, USA[1].

Classic Embryo-Fetal Development (EFD) study designs for risk assessment often include satellite groups for the assessment of toxicokinetics, increasing animal utilization and the associated labor. Additionally, if tissue analysis is performed to generate litter exposure data, this prohibits a direct comparison of drug levels in the maternal and fetal circulation. Therefore, we have investigated an alternative blood sampling method which allows for collection of fetal blood yet does not hinder either visceral or skeletal evaluations for the same fetuses. By collecting from the axillary artery and pooling by litter, sufficient blood volumes have been obtained to conduct either toxicokinetic or antibody titer analyses on the fetal blood. Clinical pathology and hematology samples of approximately 1mL were gathered across 24 litters and directly compared. Standard clinical chemistry parameters (GLU, UN, CREA, AST, ALT, etc.), hematology (RBC, etc) and coagulation (PT, APTT, etc) parameters indicate that samples collected via the axillary artery were equivalent to blood collected via cardiac puncture. However, cardiac puncture often produces structural damage to at least the thoracic cavity which would negate the possibility of further fetal evaluations. It can therefore be concluded that this bleeding procedure offers a way to meaningfully reduce satellite animal requirements without a negative impact on the visceral and skeletal evaluations required of the study design.

P104

Biodistribution and Predictive Hepatic Gene Expression of Intravenous Iron Sucrose. *R. Forster*[1], *J. Bouchard*[1], *L. Jaillet*[1], *N. Pearson*[1], *A. Rogue*[1], *C. Sabadie*[1], *P. Elford*[2]. CiToxLAB France, Evreux, France[1]; Azad Pharma AG, Toffen, Switzerland[2].

The generic Iron Sucrose Azad (ISA) or reference iron sucrose drug Venofer® were administered intravenously to (nonanemic) male rats at 15 mg/kg, a supratherapeutic dose-level. Tissue iron levels in plasma and selected tissues were determined over 28 days using an ICP-MS method. Hepatic gene expression was evaluated by microarray analysis of mRNA from samples taken 24 hours after drug administration. Iron concentration/time profiles for plasma and tissues were quantitatively similar; circulating iron levels briefly exceeded transferring binding capacity and there was a transient increase in hepatic iron. Iron levels remained elevated in the bone marrow. No increases in tissue iron were observed in the heart, stomach or lungs of treated rats and small transient increases were recorded in the kidney. Spleen iron levels increased over the 28-day period in treated and control rats. The effects of ISA and Venofer® on hepatic gene transcription were similar. There was no systematic effect of either treatment on transcriptional profiles. Only a small number of genes showed significant modulation of expression. No transcriptional pattern matches with toxicity pathways were found in the ToxFX database for either treatment. No modulation of key genes in apoptosis, inflammation or oxidative stress pathways was detected. The biodistribution of administered iron is essentially similar for Iron Sucrose Azad and Venofer® and iron sucrose partitions predominantly into the liver, spleen, and bone marrow. Hepatic gene expression studies did not provide any evidence of hepatic toxicity.

P105

Comparison of Gross and Microscopic Endpoints in a Rat Model of TNBS-Induced Colitis. *K. Long*[1], *S. Rapp*[1], *L. Branson*[1], *J. Sagartz*[1]. Seventh Wave Laboratories, LLC, Chesterfield, MO, USA[1].

TNBS-induced colitis in rats has been widely utilized as a preclinical model for inflammatory bowel disease. Pilot and validation studies were conducted to understand the relationship between the gross and microscopic pathology of this model using sulfasalazine (standard-of-care) as a positive control. Following a pilot study to determine the optimal TNBS dose, a validation study was conducted to evaluate the time course of TNBS-induced colitis. Male Wistar rats received vehicle or 100 mg/kg sulfasalazine on Days -2 through 7 via once daily oral gavage. On Day 1, animals received a single intrarectal (IR) instillation of saline, ethanol, or TNBS. Body weights, clinical observations, and fecal assessments were recorded daily. Animals were sacrificed two or six days following IR instillation (Day 3 or Day 7). The length and weight of the intact colon were measured and gross observations were recorded. Colon/rectum tissue was collected for histopathological examination. Three modified scoring methods were compared for microscopic evaluation. Intrarectal administration of ethanol induced intra-colonic inflammation and damage in most animals. This response was further exacerbated by IR TNBS instillation. The overall severity of colitis was greater at Day 3 with partial disease resolution by Day 7. Prophylactic administration of sulfasalazine resulted in partial efficacy in preventing TNBS-induced signs of disease (clinical, gross, and microscopic assessments) in some animals at Day 3, but, by Day 7, evidence of disease was similar or worsened in sulfasalazine-treated animals compared to TNBS control (diseased) animals. Microscopic correlation to colonic weights varied with the scoring system used.

P106

Comparison of Selected Parameters from Sprague-Dawley Rats Fed Diet Containing 14% or 20% Protein Levels. *B. Attalla*[1], *A. Adamou*[1], *L. Kangas*[1], *L. Huard*[1], *G. Hennig*[1]. Charles River Laboratories, Preclinical Services, Montreal, Senneville, QC, Canada[1].

In recent years, Charles River Laboratories switched to rodent diet containing 14% protein for the majority of studies. The previous diet used contained 20% protein. This change was made with the intention of improving the overall health of rats on long term toxicology and carcinogenicity studies.

A comparison of standard toxicology endpoints, including effects on body weight, food consumption and selected clinical pathology parameters (total red and white blood cell counts, platelet counts, creatinine, glucose, cholesterol, triglyceride, total protein, calcium, albumin, globulin and albumin/globulin ratio) was performed for animals fed the different diets ad libitum. Additionally, background kidney and liver lesions were compared. The selected studies were 28 days to 6 months long with rats aged between 6 and 8 weeks old at the start of the studies.

Analysis of the data from control animals showed no clear evidence that a diet lower in protein levels significantly affected any of the

toxicology parameters or pathology background lesions selected in either gender for up to 26 weeks after the start of the studies.

In conclusion, there were no significant differences on the compared parameters that could be related to the level of protein in the diet (14% vs. 20%) in studies up to 26 weeks with 6–8 week old rat at the study start. The possible effects of long term exposure to a lower protein diet in rats will be assessed by comparing background lesions and toxicology parameters from carcinogenicity studies. This data will be presented in a separate poster.

P107

Comprehensive Profiling of Inhibitory Effects on Major CNS Transporters for Drug Safety Assessment. *X. Zhang*[1], *D. Bridon*[1], *Y. Huang*[1]. Optivia Biotechnology Inc., Menlo Park, CA, USA[1].

Membrane transporters play crucial roles in brain physiology not only as gatekeepers controlling CNS entry of nutrients and drugs across the blood-brain-barrier (BBB), more importantly, they directly regulate key biological processes such as neurotransmission, energy metabolism and antioxidant defense. Pharmacological modulations of transporters including SERT, DAT, NET and GAT1 have been successful in treating CNS disorders such as depression and epilepsy; on the other hand, undesirable intervention of certain CNS transporters such as EAATs and xCT are believed to be associated with both acute and chronic CNS adverse effects including excitotoxicity and Parkinsonism. Despite of its critical implication in understanding and predicting drug CNS toxicity, information on drugs' inhibitory effects on major transporters expressed in the CNS (in contrast to on the BBB) is sparse. Against this backdrop, we have developed cell-based assays for 15 key CNS transporters and tested nearly 40 pharmaceuticals (CNS- and peripherally acting) and neuron toxins for their inhibitory effects on these transporters. It is not surprising that the prevalence of transporter inhibition by neuron toxins was found to be higher than marketed CNS-acting drugs; for example, L-Quisqualic acid, a naturally occurring excitotoxic agent, was found to be a potent inhibitor of xCT, a transporter with major role in glutathione (GSH) synthesis and homeostasis in the brain, suggesting that GSH depletion could be one mechanism of L-quisqualate's neuronal toxicity. Surprisingly, adenine synthesis inhibitor L-alanosine was found to inhibit EAATs and xCT, which raises concerns on potential CNS toxicity of this experimental anti-tumor agent.

P108

Differential Cardiovascular Physiology and Pathology in Selected Lineages of Miniature Swine and Comparison to Human. *A. Stricker-Krongrad*[1], *T.J. Madsen*[1], *B.C. Hanks*[1], *D. Brocksmith*[2], *J. Liu*[1], *L.D. Brown*[1], *G.F. Bouchard*[1]. Sinclair Research Center LLC, Auxvasse, MO, USA[1]; Sinclair BioResources LLC, Auxvasse, MO, USA[2].

The miniature swine has been increasingly recognized as a valid alternative to canine and nonhuman primates in regulatory toxicity. Cardiovascular assessments were conducted in Yucatan, Hanford, and Sinclair minipigs. Data were compared to published measurements of adult human illustrating similarities or differences. Across the three lineages, heart-to-body weights ratio ranged from 0.41 to 0.50 and were higher than human (0.42). The geometric corrections for heart rate adjustment to body size ranged from 215 to 297 and were comparable to human (241), indicating that heart volume and function were well adjusted to the reduction in body size. The miniswine hearts showed a coronary artery distribution comparable to human. The right coronary internal diameters ranged from 1.44 to 1.79 mm and were comparable to human (3.9 mm) when adjusted to body surface area (weight range: 10–30 kg). External femoral blood flows at rest averaged 93 mL/min and were slightly lower than human (260 mL/min) when adjusted to body size. Electrophysiological heart segments duration (e.g. RR ranged from 360 to 662 msec) and their ratio (QT/RR) were proportional to human and well-adjusted to body size. Macroscopic lesions were nonexistent. Histopathology findings were rare and limited to sub-level myocardial inflammation with low incidence in the Hanford lineage. In conclusion, the similarities between the cardiovascular systems make these three lineages of miniature swine suitable animals to model the human counterpart. In addition, the differences will aid investigators select a relevant lineage of miniature swine if specific cardiovascular parameters are required.

P109

Direct Intravitreal Administration of Known Phototoxins Followed by Solar-Simulated Irradiation Fails to Produce Phototoxicity in the Rabbit. *D. Learn*[1], *J. Baker*[2], *M. Brown*[3], *C. Schuetz*[4], *V. Bantseev*[4], *C. Farman*[4], *E. Thackaberry*[4]. Charles River Laboratories, Horsham, PA, USA[1]; Pathology Associates, Frederick, MD, USA[2]; The Animal Eye Center of New Jersey, Little Falls, NJ, USA[3]; Genentech, South San Francisco, CA, USA[4].

The potential for phototoxicity in the eye caused by pharmaceuticals, particularly the posterior segment and most critically in the retina, is an area of concern. To directly evaluate this possibility, this study used direct intravitreal administration (inferior temporal quadrant) of the known ultraviolet radiation-activated phototoxins 8-methoxypsoralen, lomefloxacin and doxycycline and the visible light-activated stannsoporfin, to male Dutch Belted rabbits. Triescence™ served as the negative control. Both eyes were administered the formulation, and one eye was exposed approximately 60 minutes after injection to approximately 3.75 J/cm^2 of UVA, 0.330 J/ cm^2 of UVB, and 20350 lux (57 W/cm^2) of visible light, with the other eye serving as the unexposed control. Slit lamp and indirect evaluation of the eyes were performed predose, postdose, and 1 and 3 days after UVR exposure. The eyes were then evaluated histopathologically. Despite the high vitreal concentrations produced by direct intravitreal administration, there were no adverse clinical or histopathologic effects indicative of phototoxicity induced by the phototoxins. This lack of phototoxicity is likely due to protective anatomical and biochemical characteristics of the posterior segment, including UVR filtration by the cornea and lens, and the presence of glutathione in the vitreous and retina. These results indicate that the potential for a phototoxic response in the posterior segment of the rabbit eye induced by therapeutic pharmaceuticals is very low.

P110

Evaluation of Platelet Activation by Flow Cytometry in Cynomolgus Macaques. *N. Yee[1], S. Nechev[1], P. Franklin[1], T. Beck[1], K. Fukuzaki[1], R. Nagata[1].* SNBL USA, Ltd, Everett, WA, USA[1].

Drug-induced thrombocytopenia is a relatively common adverse effect which has been mechanistically attributed to changes in platelet production, immune-mediated platelet destruction, and to alterations in platelet activation and turnover, thus warranting platelet evaluation during drug development. Several methods have been used historically to assess platelet function, including aggregometry and bleeding time. However, these techniques are limited by sample size requirements, restricted throughput and poor reproducibility, thereby discouraging routine use. We present here a flow cytometric method to detect platelet activation following stimulation with adenosine diphosphate (ADP) in *Macaca fascicularis* (cynomolgus macaque). 100 µL of whole blood was stimulated with 0.1, 1, 5, 25, or 100 µM ADP and stained for the platelet-specific glycoprotein CD61 and activation-dependent adhesion molecule CD62P (P-selectin). ADP treatment resulted in translocation of CD62P to the platelet surface after 5 minutes and dose-dependent elevations in platelet activation were observed such that 60–90% of all platelets were CD62P+ at the highest doses, demonstrating specificity of the assay. Sensitivity to ADP was variable from animal-to-animal; however, baseline (nonstimulated) platelet activation levels were uniformly under 10%, suggesting that sample collection and processing did not induce activation. Furthermore, we have demonstrated high inter- and intra-assay precision for platelet CD62P assessment among multiple analysts and have validated this assay for use in GLP studies. Together, these data demonstrate the reliability of CD61 and CD62P in identifying activated platelets in cynomolgus monkeys and highlight the benefits of a specific and reproducible flow cytometric method for assessing platelet activation.

P111

Metabolic Profiling of Hepatotoxic Compounds in Rats: Relationship of Predicted Rodent to Reported Human Phenotype. *W. Mattes[1], H. Kamp[1], V. Strauss[1], E. Fabian[1], G. Montoya[1], W. Mellert[1], N. Moeller[4], T. Walk[2], R. Looser[2], M. Herold[2], G. Krennrich[1], E. Peter[2], B. van Ravenzwaay[1].* BASF SE, Ludwigshafen, Germany[1]; Metanomics GmbH, Berlin, Germany[2]; PharmPoint Consulting, Poolesville, MD, USA[3]; Metanomics Health GmbH, Berlin, Germany[4].

Metabolomic technologies can measure treatment-related changes in the levels of hundreds of endogenous metabolite levels in biological systems, and as such offer unique analytical and predictive capabilities. The MetaMap®Tox metabolomic data base captures the metabolite profiles of rats treated for four weeks with over 500 chemicals, agrochemicals and drugs. Blood samples taken after 7, 14, and 28 days are included and have been examined for metabolite patterns that characterize distinct toxicological phenotypes or modes of action (MOAs). Previously we have shown that compounds that have caused human hepatotoxicity, yet no reported liver injury in routine animal toxicology studies, nonetheless elicit metabolic profiles in treated rats that match MoAs corresponding to various liver toxicities, including cholestasis, oxidative stress, acetaminophen-type toxicity and peroxisome proliferation. To extend this work we have increased the number of human hepatotoxic compounds to 16. Human phenotypes (e.g., cholestatic hepatitis, hepatocellular liver injury) were taken from sources such as NIDDK's LiverTox database and Hy Zimmerman's *Hepatotoxicity*). All 16 compounds elicited metabolic profiles matching MoAs for hepatotoxicity phenotypes in rats, which did not necessarily equate to the same phenotypes in humans. However, four of the hepatotoxic compounds: azathioprine, cyproterone, flutamide, and phenytoin elicited rat metabolic profiles matching the cholestasis MoA pattern; these also have been reported to cause cholestatic liver injury in humans. This results show that rat *in vivo* metabolomics can support the identification of hepatotoxic compounds. Furthermore, in some cases, rat metabolomics might assist the prediction of the human hepatotoxic phenotype.

P112

Polysomnography Using Video Electroencephalogram, Electro-Oculogram and Electromyogram Monitored Continuously by Telemetry in Cynomolgus Monkeys. *R. Kubaszky[1], M. Pouliot[1], R. Forster[1], E. Troncy[2], S. Authier[1].* CIToxLAB, Laval, QC, Canada[1]; Faculty of Veterinary Medicine, University of Montreal, St-Hyacinthe, QC, Canada[2].

Medication-induced sleep disturbances are a major concern in drug development as a multitude of prescription drugs cause abnormalities at polysomnography. Rodent sleep architecture (nocturnal) differs from larger mammals (diurnal) which present higher translational value. Polysomnography is used in clinical diagnostic but also applicable to cynomolgus monkeys when using telemetry with continuous electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) monitoring with video. Sleep stages in cynomolgus monkeys include wake, N1 (somnolence), N2 (includes Spindles and K complexes), N3 (deep sleep with slow waves) and rapid eye movements (REM) and are quantified with automated or manual scoring. Optimal cynomolgus data filters included EOG low pass <25 Hz, EEG band pass 0.7–50Hz and EMG high pass >5Hz. As observed in humans, cynomolgus present an increased duration of REM sleep the 2nd half of the night. REM sleep was characterized by muscle atonia, high frequency (mostly theta) low amplitude EEG in all animals and EOG activity in most but not all epochs. Total sleep time was 70.3±2.2% of the 12-hour dark cycle. Sleep stages N1, N2, N3, and REM were typically observed in sequence and represented 1.1±0.3%, 65.2±5.3%, 16.0±5.6% and 17.7±2.4% of total sleep time, respectively. Amphetamine (1 and 2 mg/kg, PO) significantly reduced total sleep time and all stages the night of ingestion followed by a rebound during the recovery night. Spectral analysis revealed a significant increase in higher frequency bands after amphetamine. Video- EEG, EOG and EMG by telementry is a useful nonclinical model to investigate drug induced sleep disturbances.

P113

Remote Subcutaneous and Intravenous Administration in Large Animals: Impact on Cardiovascular Safety Pharmacology Data and Sensitivity. *A. Aslam[1], A. Ascah[1], M. Pouliot[1], R. Forster[1], E. Troncy[2], S. Authier[1].* CIToxLAB, Laval, QC, Canada[1]; Faculty of Veterinary Medicine, University of Montreal, St-Hyacinthe, QC, Canada[2].

The regulatory guideline S7A supports the use of unrestrained models for safety pharmacology assays. Parenteral bolus administrations including the intravenous (IV) and subcutaneous (SC) routes are associated with CMax achieved immediately or within minutes of dosing. In this context, animal handling can constitute a major interference to data quality and can obscure pharmacodynamic responses. The current investigation compared cardiovascular changes after remote SC and IV delivery in telemetered Cynomolgus monkeys and Beagle dogs with restrained administration in the same species. Remote parenteral administrations were associated with a substantial decrease in data variance and consequently improved minimum detectable differences. Mean heart rate variations from baseline in the first 30 min after restrained IV saline dosing reached a maximum of 27% compared to 9.7% for remote administration. Recovery of cardiovascular parameters to baseline levels after animal handling was 25 to 120 minutes in both species which can constitute a major confounder during evaluation of short half-life drug candidates. Remote dosing presented optimal results when the animals remained completely undisturbed (i.e. no staff present in the animal room). Remote IV dosing is generally recognized to improve telemetry data quality but the current investigation also demonstrate beneficial effects of remote SC injections on sensitivity of cardiovascular investigations in safety pharmacology studies using telemetry in Cynomolgus monkeys and Beagle dogs.

P114

Study Design Considerations to Aid Interpretation of Inhaled ADME Studies. *C. Webber[2], S. Moore[2], B. John[2], S. Cracknell[1], J. Damiano[1].* Huntingdon Life Sciences, E. Millstone, NJ, USA[1]; Huntingdon Life Sciences, Huntingdon, UK[2].

Employing examples from recently conducted inhaled dose adsorption, distribution metabolism and excretion (ADME) studies this poster seeks to address common questions about such work. The review includes data from both rodent and dog studies in which aerosols of radiolabelled test articles have been generated from dry powders, solutions, or metered dose inhalers (MDI's). When delivering radiolabelled aerosols is important to reproduce the aerosol characteristics found during other phases of nonclinical work. Dry powders can be ambient or cryogenically milled to provide suitable material for generation as particulate or for use in suspension. Inter-animal variability is a major consideration in inhalation ADME study designs and subsequent data interpretation. Delivered radioactive dose provides insight into the likely variability encountered during toxicology studies for which delivered dose must be estimated. Dose quantification for rodent ADME studies is determined from the analysis of a small number of animals killed immediately post exposure, with the mean total radioactivity taken to represent the dose received by other exposed animals. This overall burden includes material deposited externally (primarily on the snout and ~25% of total) that would subsequently be ingested during preening activity. nonrodent dose quantification involves rigorous analysis of delivery system components used for each animal, subtracting residual radioactivity from the mass dispensed. This approach provides more precise individual dose estimate such that excretion recoveries show little variation. This poster includes specimen data and reviews design and interpretation considerations to ensure ADME study outcomes are scientifically robust.

P115

Unlike ALT and AST, microRNA-122 (miR-122) Is a Liver Injury Biomarker Not Affected by Decreased Kupffer Cells. *K.S. Rajapaksa[1], E. Doudement[1], H. Uppal[1], T. Lin[1], J. Eastham-Anderson[2], C.D. Austin[2], D.M. Danilenko[1], D.L. Misner[1], P. Katavolos[1].* Department of Safety Assessment, Genentech, Inc., South San Francisco, CA, USA[1]; Department of Research—Pathology, Genentech, Inc., South San Francisco, CA, USA[2].

Therapeutics targeting signaling pathways that promote differentiation, proliferation and migration of monocytes have been shown to significantly decrease macrophage populations in multiple organs including the liver (Kupffer cells; KC). It has been hypothesized that KCs have a role in clearing several serum enzymes, including ALT and AST, and KC reduction is associated with increased ALT and AST in the absence of hepatocellular injury. This serum enzyme increase can complicate clinical development of such therapeutics, as ALT and AST are routinely measured to monitor for liver injury in patients. Thus, this study was designed to identify alternate liver injury biomarkers not affected by KC decreases. Mice were given a monoclonal antibody (mAb) that had been shown to reduce KCs without concomitant liver damage after 12 weeks, an isotype control, acetaminophen (APAP) or vehicle control. At necropsy serum ALT, AST, SDH, GLDH, and miR-122, KC numbers and/or liver histopathology were evaluated. Increased ALT, AST, SDH, GLDH, and/or miR-122 and hepatocellular damage was observed with APAP, a liver toxicant, at several dose levels and timepoints. In mice treated with the mAb alone, a 50% decrease in KCs and mild to moderate increase in ALT, AST, and SDH were observed at all timepoints. In contrast, miR-122 and GLDH did not increase with decreased KCs. However increased GLDH has been reported previously with reduced KCs. Collectively, these data suggest miR-122 is a selective liver injury biomarker not affected by KC reduction and could be used to monitor for true liver damage with therapeutics targeting macrophages.

P116

Effect of Creatinine Clearance on Blood Level of Pralidoxime in Organophosphorus Poisoning Patients. *M. Priyadarshini[1], G. Thunga[1].* Manipal College of Pharmaceutical Sciences, Manipal, Karnataka, India[1].

Pralidoxime (PAM) has been indicated as a specific antidote for OP poisoning; however, the type of dosage regimen used in the management of OP poisoning has been in controversy among the physicians. The blood levels of pralidoxime play an important role in predicting the outcome in OP poisoning patients. Creatinine clearance mainly influences the blood level of pralidoxime irrespective of its dose. The present study aimed to identify the

appropriate relationship between the creatinine clearance and blood level of pralidoxime in OP poisoning patients. A prospective, observational study was carried out in a total of 25 OP poisoning patients reported to emergency ward of a tertiary care teaching hospital for period of one year. The patient's demographical, clinical characteristics and severity were assessed at admission. Blood levels of pralidoxime were estimated in OP poisoning patients by HPLC method and correlated with the creatinine clearance of the patients. The results showed that majority of OP poisoned patients were in the age group of 21- 30 years, and males predominated over females. Clinical Severity assessment of OP poisoning showed that majority of the patients were in the category of moderate to high severity. Blood levels of PAM were maintained uniformly at higher range (21.32±5.26 mcg/dL for 500mg/hour; 41.66±12.86 µg/mL for 1g/hour infusion). The blood level of pralidoxime negatively correlated to creatinine clearance indicating that creatinine clearance significantly affects the pralidoxime level and blood level has to be monitored in kidney failure patients.

P117

Ethanol and Age Enhances Fluoride Toxicity through Oxidative Stress and Mitochondrial Dysfunctions in Rat Intestine.

S. Singh Chauhan[1], A. Mahmood[2], S. Ojha[2]. Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India[1]; Department of Biochemistry, Panjab University, Chandigarh, India[2].

Fluoride toxicity and alcohol abuse are the two serious public health problems in many parts of the world. The current study was an attempt to investigate the effect of alcohol administration and age on fluoride toxicity in rat intestine. Six and eighteen months old female Sprague-Dawley rats were exposed to sodium fluoride (NaF, 25mg/kg), 30% ethanol (EtOH, 1ml/kg) and NaF+EtOH (25mg/kg+1ml/kg) for a period of 20, 40, and 90 days. The levels of lipid peroxidation were increased, while the content of reduced glutathione, total and protein thiol was decreased with NaF treatment. Under these conditions, animals showed an age related decline in the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase glutathione-s-transferase which were further aggravated upon NaF or/and EtOH treatment. Mitochondrial respiration rate and the activities of complex I, II and IV enzymes of electron transport chain were decreased, while the levels of nitric oxide and citrulline were increased with age and NaF or/and EtOH treatment. Histological examination revealed large reactive lymphoid follicles, excess of lymphocytes in lamina propria of villi, villous edema, focal ileitis, necrosis of villi and ulceration in NaF or/and EtOH treated animals in both the age groups. These findings suggest that fluoride mediate its toxic effects on intestine through oxidative stress and mitochondrial dysfunctions which are further augmented with alcohol consumption and advancing age.

P118

A Multibiomarker Approach to Biomonitor Exposure of Humans to Multimycotoxins via Urine.

W. Abia Abia[1], B. Warth[2], M. Sulyok[2], P. Njobeh[3], P. Turner[4], A. Tchana[1], C. Kouanfack[5], E. Mbu[6], M. Dutton[7], R. Krska[2], P. Moundipa[1]. University of Yaounde I, Yaounde, Centre, Cameroon[1]; University of Natural Resources and Life Sciences, Vienna (BOKU), Vienna, Austria[2]; University of Johannesburg, Johannesburg, Gauteng, South Africa[3]; MIAEH, School of Public Health, University of Maryland, MD, USA[4]; Central Hospital, Yaounde, Centre Region, Cameroon, Yaounde, Centre, Cameroon[5], Regional Hospital Bamenda, North West Region, Cameroon, Bamenda, NW, Cameroon[6]; Food, Environment and Health Research Group (FEHRG), Faculty of Health Sciences, University of Johannesburg, Johannesburg, Gauteng, South Africa[7].

Biomonitoring of human exposure to mycotoxin has mostly been limited to a few individually measured mycotoxin biomarkers. This study aimed to determine the frequency and level of exposure to multiple mycotoxins in human urine from Cameroonian adults. 175 urine samples (83% from HIV-positive individuals) and food frequency questionnaire responses were collected from consenting Cameroonians, and analyzed for 15 mycotoxins and relevant metabolites using LC-ESI-MS/MS. In total, eleven analytes were detected individually or in combinations in 110/175 (63%) samples, including the biomarkers: aflatoxin M_1, fumonisin B_1, ochratoxin A and total deoxynivalenol. Additionally, important mycotoxins and metabolites thereof, such as fumonisin B_2, nivalenol and zearalenone, were determined, partly for the first time in urine following natural exposures through diet. Multimycotoxin contamination was common with one HIV-positive individual exposed to five mycotoxins, a severe case of co-exposure that has never been reported before. For the first time in Africa or elsewhere, this study quantified eleven mycotoxin biomarkers and biomeasures in urine. For several mycotoxins estimates of intake indicate that the tolerable daily intake is being exceeded in this study population. Given that many mycotoxins adversely impact the immune system, future studies will examine whether combinations of mycotoxins negatively impact Cameroonian populations in general, and particularly immune-suppressed individuals.

P119

Distribution Patterns for the CB2 Receptor Vary between Human B-Cells, T-Cells, and Malignant Cell Lines.

J. Theresa Castaneda[1], A. Harui[2], S. Kiertscher[2], M. Roth[1]. Interdepartmental Program in Molecular Toxicology, School of Public Health at UCLA, Los Angeles, CA, USA[1]; The Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA[2].

Cannabinoids, the primary bioactive constituents of marijuana, activate cannabinoid receptors CB1 and CB2. The toxicity of cannabinoids due to their activation by marijuana smoke can have wide-ranging health effects. While widely distributed, the highest expression of CB2 is by cells from an immune origin. We hypothesize that CB2 may play an immunoregulatory role. The expression of CB2 at extracellular versus intracellular sites may play an important function in mediating the biologic and toxic effects of cannabinoids. A monoclonal anti-CB2 antibody and 5-color flow cytometry were used to assess CB2 protein expression by human

B-cells and T-cells with respect to their differentiation/activation state and cellular environment (tonsils, adult blood, cord blood, or malignant cell lines). Immature B-cells from human tonsils alone (CD20high/CD38high/IgM-/IgD-/CD27dim) expressed less cell surface CB2 than mature and/or activated B cells from either tonsils, adult blood, or cord blood. In contrast, malignant B-cell lines did not express any extracellular CB2. Similarly, both fresh T-cells and malignant T-cell lines did not express cell surface CB2 despite their source and/or differentiation state. However, all leukocyte subsets and cell lines demonstrated intracellular CB2 protein regardless of extracellular expression levels. Exceptionally high levels of intracellular CB2 were observed in some malignant cell lines. Extracellular and intracellular CB2 protein expression patterns are different for B-cells and T-cells and appear to vary with their state of differentiation. The role of these differences in CB2 signaling, function, and in the immunologic consequences of cannabinoids remain to be determined.

P120

Effect of Creatinine Clearance on Blood Level of Pralidoxime in Organophosphorus Poisoning Patients. *M. Priyadarshini*[1], *G. Thunga*[1]. Manipal College of Pharmaceutical Sciences, Manipal, Karnataka, India[1].

Pralidoxime (PAM) has been indicated as a specific antidote for OP poisoning; however, the type of dosage regimen used in the management of OP poisoning has been in controversy among the physicians. The blood levels of pralidoxime play an important role in predicting the outcome in OP poisoning patients. Creatinine clearance mainly influences the blood level of pralidoxime irrespective of its dose. The present study aimed to identify the appropriate relationship between the creatinine clearance and blood level of pralidoxime in OP poisoning patients. A prospective, observational study was carried out in a total of 25 OP poisoning patients reported to emergency ward of a tertiary care teaching hospital for period of one year. The patient's demographical, clinical characteristics and severity were assessed at admission. Blood levels of pralidoxime were estimated in OP poisoning patients by HPLC method and correlated with the creatinine clearance of the patients. The results showed that majority of OP poisoned patients were in the age group of 21–30 years, and males predominated over females. Clinical Severity assessment of OP poisoning showed that majority of the patients were in the category of moderate to high severity. Blood levels of PAM were maintained uniformly at higher range (21.32±5.26 mcg/dL for 500mg/hour; 41.66±12.86 µg/mL for 1g/hour infusion). The blood level of pralidoxime negatively correlated to creatinine clearance indicating that creatinine clearance significantly affects the pralidoxime level and blood level has to be monitored in kidney failure patients.

P121

Oxidative Stress Generated by Arsenite Toxicity in Rat Aorta and Trachea. *S. Kundu*[1], *L.A.Khan*[1]. Department of Biosciences, Faculty of Natural Sciences, Jamia Millia Islamia, New Delhi, India[1].

Arsenite toxicity causes hyper-contraction in wistar rat aorta and trachea. To investigate, the toxicity due to arsenic exposure in cardiovascular system and pulmonary system, *in vitro* arsenic exposure was given to the tissues in an organ bath. Three different concentrations of 10 µM, 25 µM and 50 µM arsenite caused concentration dependent increase in vasoconstriction and pulmonary contraction. This heavy metal toxicity, in tissues, aorta and trachea was due to oxidative stress induced by reactive oxygen species and calcium elevation. Tissues were incubated with 10^{-4} M apocynin, to block the Reactive oxygen species generation, which effectively improved the altered contraction in both tissues. Thus, toxic effect of arsenite results in altered contraction of the rat aorta and rat trachea is due to oxidative stress generated by the heavy metal.

200 Series—Regulatory

P200

Application of Sound Science in Safety Assessment: Sucralose As a Case Study. *V. Lee Grotz[1], A. Wallace Hayes[2], D. Huggett[3], C. Kruger[4], G. Williams[5].* McNeil Nutritionals, Fort Washington, PA, USA[1]; Harvard School of Public Health, Cambridge, MA, USA[2]; University of North Texas, Denton, TX, USA[3]; Spherix Consulting, Inc., Rockville, MD, USA[4]; New York Medical College, Valhalla, NY, USA[5].

A rich database exists on the safety of sucralose, including carcinogenicity testing. Using internationally recognized procedures, there were no positive findings in a battery of genotoxicity studies. Similarly, two OECD-compliant 104-week carcinogenicity studies in mice and rats revealed no statistical difference in tumor incidence, survival, or clinical condition. Consistent with this, the consumption of sucralose by millions of people around the world has resulted in no case studies or other medical literature that would indicate carcinogenic potential. The Ramazzini Foundation (RF) has recently reported (preliminary findings) an increased incidence of leukemia in male mice, using alternative testing methods. The testing methodology used by RF has come under regulatory scrutiny both in the US and in Europe. Moreover, the RF report is unexpected, given the physicochemical characteristics, metabolic and physiologic fate of sucralose. The results of a critical evaluation of RF methodology will be presented to help explain why RF studies can result in artefactual findings. For example, the atypical design of RF studies, including dosing until death and nonstandard laboratory processes and conditions, introduces potential confounders. It is therefore critical to apply caution in interpreting results from atypical study protocols. Carcinogenicity studies of food ingredients must establish whether the conclusions reported are the result of a methodology that is reproducible, robust, scientifically rigorous, and vetted by scientific and regulatory consensus.

P201

Approaches for the Safety Risk Assessment of Inconclusively or Tentatively Identified Compounds from Medical Device Leachable and Extractable Evaluations. *S. Gad-McDonald[1], D. Sullivan Jr.[1], Q. Pham[1], S. Gad[1].* Gad Consulting Services, Cary, NC, USA[1].

Under ISO 10993 and current US FDA regulatory guidelines, a critical function of safety assessments for medical devices with internal body (systemic) contact includes the identification and quantification of chemical compounds which may migrate out of a device and into an individual. Medical devices are often evaluated using aggressive extraction conditions in polar and nonpolar extract solutions after which the resulting extract is analyzed by a variety of analytical techniques to identify and quantify compounds that may have migrated from the product. Because exaggerated and exhaustive extraction techniques are often used, greater amounts of chemical constituents or unexpected breakdown compounds may be released as compared to leachable material levels that would be available to the patient or user from devices during routine use. In addition, many of the identified compounds are either unknown or only tentatively identified, thus adding further complexity to the characterization of the potential toxicity of devices. We will review the current techniques utilized in the collection and identification of compounds that may migrate from a device. Parameters such as extraction vehicles, conditions of the extraction, analytical methods, and use of the device are all vital in the design of such studies and the following risk assessment. Finally, we will discuss and provide case studies of how unknown or tentatively identified compounds may be evaluated for safety, including the use of QSAR techniques or representative (analog or chemical class family members) compounds.

P202

BioSafe Industry Survey: Assessing Developmental Toxicity of Biopharmaceuticals. *D.L. Blanset[1], C.J. Bowman[2], G.J. Chellman[3], N. Makori[4], P.L. Martin[5], J.S. Moffit[1], G.F. Weinbauer[6].* Boehringer Ingelheim, Ridgefield CT, USA[1]; Pfizer, Inc., Groton CT, USA[2]; Charles River Preclinical Services, Reno, NV, USA[3]; Shin Nippon Biomedical Laboratories Ltd., Everett WA, USA[4]; Janssen Research and Development, LLC, Spring House PA, USA[5]; Covance Laboratories GmbH, Muenster, Germany[6].

BioSafe conducted a survey to assess current general practices and past product-specific experiences for developmental toxicity assessment of biopharmaceuticals. Twelve (12) companies provided 60 product-specific responses (mostly monoclonal antibodies, mAbs), including 14 completed ePPND (enhanced pre- and postnatal development) studies. All 14 ePPND studies were for mAbs or mAb-like molecules, with 13 in cynomolgus monkeys, and most were conducted prior to ICH S6(R1) and M3(R2). Therapeutic categories were mainly anti-inflammatory, pulmonary, and oncology. Endpoints evaluated in infants included: serum TK/ADA, immunophenotyping, TDAR, external/visceral/skeletal evaluations, and neurobehavioral test battery. Survey results indicated that for ~50% of the studies: embryo/fetal losses required additional pregnancies to be assigned; some endpoints were not recommended for future studies due to interpretive difficulty; and/or microscopic evaluation of infant tissues was limited to selected tissues. Eleven of the studies had findings consistent with the known pharmacology of the administered drug products. Company responses for current general practices (for future studies) were aligned with ICH S6(R1) and M3(R2) guidelines. Cynomolgus monkeys (when the only relevant model) were preferred over alternative models (e.g., surrogate molecule, transgenic animals). If an ePPND study was indicated, most will conduct the study concurrent with Phase 3 (before licensing), using three dose groups (including control), 16–20 pregnant females/group, targeting 8–9 live infants/group, with a postnatal phase of 4–6 months. Immunogenicity and/or pregnancy losses limit the ability to reduce the number of pregnant females assigned per group. Reuse of control cynomolgus monkeys from previous ePPND studies is being considered/implemented by most companies consistent with 3Rs.

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Microscopic Vacuoles Reported in US FDA BLA Reviews of Pegylated Proteins Were Associated with Drug Accumulation in Repeat-Dose Studies, Greater Than Dose Proportional Plasma Concentrations, and High Clinical Multiples. *L. Kaufman*[1]. PDS, Inc, Mt. Arlington, NJ, USA[1].

US FDA BLA reviews for 9 of 11 pegylated proteins marketed in the US were analyzed to obtain a more complete understanding of microscopic vacuoles in nonclinical toxicology studies. Exposure across these programs was measured using ELISA, activity assays, or hybridization assays, which measured protein levels or activity and did not distinguish between conjugate or pegylated protein fragments. Across programs, toxicology doses were reported to result in protein or activity levels that were greater than dose proportional, whereas doses used in clinical trials were in a considerably lower and dose-proportional range. Vacuoles were reported in toxicology studies for Omontys, Cimzia, Macugen (IV route), Krystexxa, and Somavert. Both within and across studies and programs, the vacuoles were dose related and associated with the highest levels of drug accumulation (up to 2,000-fold) and clinical multiples (up to 700-fold). Vacuoles were most often reported to occur in macrophages of organs/tissues associated with the macrophage/phagocyte system and were not associated with functional changes. The remaining four programs (Neulasta, PegIntron, Pegasys, and Mircera), for which vacuoles were not reported, were associated with lower drug exposure, either due to the use of considerably lower doses or to the development of anti-drug antibodies that accelerated drug clearance. In conclusion, the dose-response relationship of microscopic vacuole occurrence across toxicology studies and programs for pegylated proteins supports using appropriate PK/PD principles as outlined in ICH S6(R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) to justify dose selection and avoid the use of excessively high doses, excessively high clinical multiples, and accumulation.

P204

Pharmacodynamic in Early Safety Studies Is Feasible, in Line with the 3Rs and Informative for the Design of Further Toxicology Studies. *C. Dumont*[1], *R. Bourgeois*[1], *P. Phosavath*[1], *J. Forget*[1], *S. Ante Lundberg*[2], *M. Christin-Piché*[1]. Charles River Laboratories, Preclinical Services Inc., Montreal, QC, Canada[1]; Alexion Pharmaceutical Inc, Cambridge, MA, USA[2].

Pharmacodymamic and pharmacokinetics(PD/PK) studies are an integral part of safety assessments to support the use of new drugs in humans. PD/PK studies can be conducted independently or added to early preclinical safety studies to select optimal dose levels in repeat and chronic toxicity studies. This allows the reduction of animal use (3Rs) by preventing the conduct of independent toxicology study or the addition of satellite groups for PD/PK. In the present study, PD characteristics of a humanized $IgG_{2/4}$ monoclonal antibody (mAb) were included in a range-finding and an expended acute toxicity study in NHP. The primary PD properties were to reduce plasma C5a concentrations (measured by ECL) and to decrease C5a-mediated-proinflammatory events such as neutrophil oxidative burst activity (measured by flow cytometry). A trend for dose- and concentration-dependent decreases was observed in plasma C5a concentrations and PMN oxidative burst activity. It was determined that a dose of 10mg/kg was sufficient to induce a decrease in both PD parameters. It was possible to characterize the primary PD effects of the mAb within the early safety studies and to establish the dose at which these effects were observed. The determination of the optimal pharmacologic dose in NHP can help in the design of subsequent toxicology studies and prevent the use of additional animals. Depending on the MOA of a compound and given the advances in the range of available methodologies, whenever feasible, the inclusion of PD assessments or the screening of potential PD parameters (primary/secondary) should be considered in early toxicology studies.

P205

Reassessing the Two-Year Rodent Carcinogenicity Bioassay: A Review of the Applicability to Human Risk and Current Perspectives. *P. Ann Marone*[1], *W. C. Hall*[2], *A. Wallace Hayes*[3]. Product Safety Labs, Dayton, NJ, USA[1]; Hall Consulting, Mt. Airy, MD, USA[2]; Harvard School of Public Health, Boston, MA, USA[3].

The two-year rodent carcinogenicity test has been the regulatory standard for the prediction of human outcomes for industrial and agro-chemicals, food additives, pharmaceuticals and environmental pollutants for over 50 years. The extensive experience and data accumulated over that time has spurred a vigorous debate and assessment, particularly over the last 10 years, of the usefulness of this test in terms of cost and time for the information obtained. With the renewed interest in the United States and globally, plus new regulations in the European Union, to reduce, refine and replace sentinel animals, this review offers the recommendation that the time has come to realize and rely on information obtained from detailed shorter-term 6 months rodent studies combined with genotoxicity and traditional chemical mode of action for effective prediction of human carcinogenicity instead of the classical two year rodent bioassay. The aim of carcinogenicity studies should not be on the length of time, and by obligation, number of animals expended so much as on the combined systemic pathophysiologic influence of a suspected chemical in determining disease. This perspective is in coordination with progressive regulatory standards and goals globally to effectively utilize resources of animal usage, time and cost for the goal of human disease predictability.

P206

Scope for Substantive Reduction of Animal Numbers on Regulatory Toxicology Studies by Using Microsampling or Sample-Sparing Techniques. *D. Mitchell*[1], *R. Lawrence*[1], *D. Coleman*[1], *I. Love*[1], *L. Ramaiah*[2]. Huntingdon Life Sciences, Huntingdon, Cambs, UK[1]; Huntingdon Life Sciences, Princeton, NJ, USA[2].

Satellite animals are commonly added to rodent toxicology studies to provide blood samples for toxicokinetic assessment (TK), often increasing the size of a typical study to double or more that required for toxicology endpoints. For biopharmaceuticals, essential pharmacodynamic and antidrug antibody markers also add significantly to the study sampling burden and lead to further increases in satellite animal numbers, especially in mouse studies. There is an industry drive to reduce numbers of

animals used on safety assessment studies where this can be done without compromising scientific integrity. Huntingdon Life Sciences has therefore embarked on a programme of work aimed at the establishment of reduced volume or microsampling techniques for blood sampling. A comparison of capillary microsampling (CMS) and conventional sampling on a 4-week rat toxicity study, in which validated bioanalytical methods were used to measure drug concentrations in CMS and conventional samples, has demonstrated mean plasma concentrations using microsampling within 1% of that from conventional sampling. Statistical analysis confirmed close agreement between results from the two methodologies. This shows that it is possible to reduce satellite numbers and obtain a full serial profile of TK samples from individual animals. A comparison of clinical pathology results generated using sample-sparing procedures against those from conventional sampling has demonstrated good correlation for some but not all parameters measured. The data generated provides a basis for further investigation of the potential for reducing clinical pathology volumes for main study animals, with the aim of routine TK sampling from these instead of satellite animals.

P207

The Replacement Ocular Battery (ROBatt): An Integrated Testing Strategy for Ocular Irritation Classification. *D. Cerven[1], D. Hall[1], M. Carathers[1], G. DeGeorge[1].* MB Research Labs, Spinnerstown, PA, USA[1].

Alternatives to the Draize Rabbit Eye Test have been available since the 1980s but none have yet been fully successful due to no appreciable regulatory adoption to date. To address this need, we have developed an integrated testing strategy (ITS) for ocular toxicity testing: the Replacement Ocular Battery (ROBatt).

ROBatt incorporates four alternative ocular irritation assays—the Chorioallantoic Membrane Vascular Assay (CAMVA), the Bovine Cornea Opacity/Permeability test (BCOP), the Porcine Cornea Opacity/Reversibility Assay (PorCORA), and the Porcine Confocal Assay (PorFocal) into a logical testing approach for ocular irritancy potential ranging from nonirritant to ocular corrosion. A decision tree was devised that integrated these assay and allows for a thorough evaluation and categorization of test materials. Fifty two chemicals were selected from the ECETOC Technical Report No. 48—Eye Irritation: Reference Chemicals Data Bank (Second Edition). The ECETOC data and classifications were supplemented by data provided by the US FDA and US EPA. These 52 chemicals were tested using the ROBatt ITS to establish criteria that would lead to regulatory classification of chemicals with respect to ocular toxicity. The results are reported here and compared with *in vivo* observations to provide the basis to evaluate the performance of ROBatt as an informative and efficient tiered testing strategy to categorize chemicals into regulatory classification without using the Draize test or employing live animals.

P208

The Use and Development an Expert Rule-Based System to Support the ICH M7 Guideline on Impurities. *D. Bower[1], K. Cross[1], G.J. Myatt[1].* Leadscope, Inc, Columbus, OH, USA[1].

The ICH M7 guideline on drug impurities states that two distinct *in silico* methodologies can be used to qualify certain drug impurities as not mutagenic. This poster outlines the development and use of a new expert rule-based system to predict the results of a bacterial mutagenesis assay. In the development of this system, an initial library of mutagenicity structural alerts was identified from the literature. This process included consolidating the same or similar alerts cited in multiple publications. Information on plausible mechanisms was collected alongside the structural definitions. Factors that deactivate the alerts were also identified from the literature and through an analysis of the corresponding data using the Leadscope data mining software. Over 150 distinct alerts were identified and these alerts were further validated against a database of over 6,000 chemicals with known bacterial mutagenesis results. Only validated alerts with a sufficiently strong association with positive expert-reviewed calls from either *Salmonella* or *E. coli* strains were included. A prediction of the bacterial mutagenesis assay can be made using these validated alerts; however, this is only possible where the compound is within the applicability domain of the alert system. In addition, a confidence score based on information collected for each alert is provided alongside the positive or negative call. This poster outlines the process of developing the expert system, including the criteria used to validate the alerts, the methodology adopted to assess the applicability domain, and the generation of a confidence score.

300 Series—Safety Evaluation Nonpharmaceuticals

P300

DHASCO-B and DHASCO: A 3-Week Dietary Bioequivalence Study in Preweaning Farm Piglets. *I. Dahms[1], B. Thorsrud[2], E. Bailey[1], N. Salem[1].* DSM Nutritional Products, Columbia, MD, USA[1]; MPI Research, Mattawan, MI, USA[2].

Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are components of human breast milk and commonly added to infant formula worldwide. The first commercially available DHA-containing oil for infant formulas was DHASCO produced from the microalgae *Crypthecodinium cohnii*. Recently, new DHA-rich oil was obtained from the microalgae *Schizochytrium sp.*, herein named DHASCO-B.

The objectives of this study were to evaluate the bioequivalence of DHASCO-B to DHASCO when administered in a blend with ARASCO and the potential effects after three weeks' administration in milk replacer formula to preweaning farm piglets. Diets 1 and 2 contained DHASCO-B while Diets 3 and 4 contained DHASCO. Diets 1 and 3 targeted 0.32% DHA and 0.64% ARA in the formula (1x of US infant formulas levels); Diets 2 and 4 targeted 0.96% DHA and 1.92% ARA in the formula (3x). The control group was fed the Land O'Lakes® ProNurse® Specialty Milk Replacer which contained no DHA and 0.21% of ARA.

The results indicated that there were no adverse test article-related effects of any diet on piglet growth and development (clinical observations, body weights, food consumption), or clinical pathology parameters (hematology, clinical chemistry, coagulation and urinalysis). Similarly, there were no adverse effects at terminal necropsy (macro- and microscopic pathology evaluations). DHA content in plasma, RBC and brain showed dose-related accumulation and confirmed no differences between DHASCO-B and DHASCO groups.

Therefore, dietary exposure to DHASCO-B and DHASCO was well tolerated by the preweaning piglets during the 3-week dosing period right after birth and DHASCO-B and DHASCO were bioequivalent.

P301

Effect of Type of Food on Body composition in Osteopenic OVX Sprague-Dawley Rats. *E. Lesage[1], A. Varela[1], S. Smith[1].* Charles River Laboratories Preclinical Services Montreal, Senneville, QC, Canada[1].

The study objectives were to determine the diet effects on body composition evaluated by DXA in rats. Six-month old female rats (18 to 20/group) were randomly assigned to 4 groups. Two groups were ovariectomized (OVX) and two other groups underwent Sham surgery (ovaries remained intact). One OVX and one Sham group were fed with PMI certified rodent chow 5002 (21% protein) for 14 months following the OVX surgery (Sx) while the second pair of OVX and Sham groups was fed with PMI certified rodent chow 5CR4 (14% protein) for 15 months following Sx. Within 2/3 weeks after Sx, OVX rats gained BW vs. Sham (+15%). With 5CR4, BW differences stabilized after 6 months to +10%, whereas with 5002, BW differences continued to increase up to +22%, 8 to 12 months after Sx. 5002-fed Sham gained 20% more BW. FC was 10% larger in 5002 vs. 5CR4 shams and 22 % in OVX. These differences were due to larger gains in fat mass in 5002-fed OVX rats (fat % was 50% higher vs. 5CR4-fed OVX rats). 5002-fed Sham BW were increased compared to Sham rats fed with 5CR4, due to larger gain in lean mass (+20%) and bone mass (+15%). These data suggested that controlling diet may be important in long term rat studies as evidenced by different DXA body composition even after 13 weeks. The influence of diet should be considered as a potential confounding factor in preclinical safety studies.

P302

Genotoxicity of Clomiphene Citrate in Bacterial and Mammalian Test Sytems. *S. Yilmaz[1], F. Ünal[2], E. Yilmaz[3], D. Yüzbasioglu[2], S. Erkal İlhan[1].* Ankara University, Faculty of Health Sciences, Ankara, Turkey[1]; Gazi University Faculty of Science, Ankara, Turkey[2]; Gazi University Vocational School of Health Services, Ankara, Turkey[3].

Clomiphene citrate is a selective estrogen receptor modulator and primarily used for enhancing follicular development in women receiving *in vitro* fertilization (IVF). Although some studies suggested large increases in ovarian cancer risk related to fertility medications, relationship has not been confirmed by some other studies. Whether there could be residual smaller risk is still an open question. As it is known, genomic instability and multiple genetic changes may be required in carcinogenesis. Genomic instability such as single base changes, chromosomal rearrangements or aneuploidy may accelerate this process. Due to these reasons, this study was planned to examine genotoxic effect of clomiphene citrate in human lymphocytes by using comet assay and AMES test by using *Salmonella typhimurium* TA98 and TA100 strains. 0.40, 0.80, 1.60, 3.20 µg/ml concentrations of clomiphene citrate significantly increased the DNA damage (tail length, $p<0.05$, except 0.80 µg/ml) in isolated lymphocytes compared to their respective controls. AMES test showed that the concentrations of CC used in this study induced neither base-pair substitutions nor frame-shift mutations in *Salmonella typhimurium* TA98 and TA100 strains.

P303

Novel Delivery of Pterostilbene and Caffeine in a Multicomponent Co-Crystal System. *D. Conze[1], C. Kruger[1], D. Kalman[2], A. Samson[2], S. Feldman[2], D. Krieger[2].* Spherix Consulting, Inc., Rockville, MD, USA[1]; Miami Research Associates, Miami, FL, USA[2].

Co-crystals have been reported to alter the aqueous solubility, dissolution rate, and bioavailability of compounds. Caffeine is an US FDA-approved food ingredient, however the US FDA recently went on record stating that they are re-evaluating the safety and use of added caffeine in products such as energy drinks. Pterostilbene is a naturally occurring stilbene, which is a dimethylated analog of resveratrol, and has been reported to have wide variety of beneficial health effects. Although co-cystalization of pterostilbene and caffeine has been shown to increase the aqueous solubility of pterostilbene, the effects of

co-crystalizing pterostilbene and caffeine on their respective bioavailabilities is unknown. Therefore, a novel multicomponent crystal of both ingredients in a 1:1 stoichiometric molar ratio was evaluated in animal (rat) and human trials to determine the effect of the co-crystal structure on pharmacokinetic parameters of both ingredients. Co-crystalizing pterostilbene and caffeine may modulate the bioavailability of the two components and allow for a reduction in the amount of caffeine in energy beverage products without noticeably impacting the consumer experience. Additionally, the comparison of pharmacokinetic results between rats and humans will allow for confirmation of the appropriateness of the rat model to assess safety of the co-crystal.

P304

Repeat-Dose Toxicity Studies of 3-Bromopyruvate in Rats Following Oral and Intraperitoneal Administration. *S. Godin*[1], *K. Engelke*[1], *J.F. Geschwind*[2]. Smithers Avanza, Gaithersburg, MD, USA[1]; Johns Hopkins University School of Medicine, Baltimore, MD, USA[2].

The anticancer efficacy of the pyruvate analog 3-bromopyruvate (3-BP) has been demonstrated in tumor models, and inhibits glyceraldehyde-3-phosphate dehydrogenase resulting in a depletion of intracellular ATP and cellular death. Thus, 3-BP may be a potent and promising anticancer agent. Groups of rats were dosed with 3-BP four times/day for 28 consecutive days by oral gavage at doses of 0, 20, 100, and 200 mg/kg/day and for 21 days by 2-hour intraperitoneal (IP) infusion at doses of 0, 0.25, 2.5, and 5 mg/kg. Selected animals were included in each study to evaluate the persistence or reversibility of any toxic effects during a recovery period. Test article-related mortality occurred at oral doses ≥100 mg/kg/day. Other test article-related effects following oral administration included clinical observations involving the lung and abdomen, elevated ALT, acute bromide toxicity, electrolyte imbalances, and macroscopic and mild microscopic changes in the gastrointestinal tract, lymphoid tissues, and lungs. The no-observed-adverse-effect level (NOAEL) is less than 20 mg/kg/day and the highest nonseverely toxic dose (HNSTD) is <100 mg/kg/day. No definitive test article-related mortality occurred following IP dosing. However, a treatment-related decrease in body weight and food consumption, increase in absolute and relative spleen weight, and adhesions/masses along with enlargement/thickening/discoloration of abdominal organs was noted. Microscopic changes included fibroplasia and mixed-cell infiltrate of the peritoneum and abdominal organs, injection site and liver necrosis, mesenteric hemorrhage, and fibrin deposition that were considered local effects. The no-observed-adverse-effect level (NOAEL) is less than 0.25 mg/kg and the highest nonseverely toxic dose (HNSTD) is <2.5 mgkg.

P305

Video-Electroencephalography in Conscious Rats, Dogs and Nonhuman Primates Using Telemetry and Computer Analysis: The Goal Standard to Assess Seizure Liability. *S. Authier*[1], *D. Paquette*[1], *M. Pouliot*[1], *E. Troncy*[2], *R. Forster*[1]. CITOxLAB, Laval, QC, Canada[1]; Faculty of Veterinary Medicine, University of Montreal, St-Hyacinthe, QC, Canada[2].

EEG investigations are occasionally required as follow-up safety pharmacology studies to further characterize adverse neurological effects. Seizure liability studies generally aim to: 1) confirm drug-induced seizures are self-limiting, 2) determine plasma level at seizure onset 3) identify prodromal clinical signs which can be monitored in clinical trials 4) confirm that conventional drugs (e.g. diazepam) can successfully treat drug-induced seizure and 5) confirm the no observed adverse effect level (NOAEL) by absence of paroxysmal activity at lower dose level of the test article. Proconvulsant risk evaluations are routinely conducted in all species including rats, dogs, or NHPs. Cynomolgus monkeys, Beagle dogs and Sprague-Dawley rats were instrumented with telemetry implants with EEG electrode placement based on the *10–20 system* (*C3-O1, Cz-Oz, C4-O2,* or *F3-C3*) combined with an EMG. After 24 h of continuous video-EEG monitoring, animals received an IV infusion of pentylenetetrazole (PTZ) until convulsions were noted. Convulsions were immediately treated with diazepam. A seizure detection protocol with a dynamic spike train threshold was used for the entire EEG monitoring period (total of 44 h). Spectral analysis was performed to quantify the absolute and relative amplitudes of EEG frequency bands (delta, theta, alpha, sigma, and beta waves but also individual frequencies). Spike trains were detected by computerized analysis in all animals. Seizure peak frequency was 3–6 Hz. EEG-video is useful to characterize neurological adverse effects with unpredictable onset. Computerized EEG analysis was a valuable tool for safety pharmacology investigations, including proconvulsant risk assessment, spectral analysis of frequency bands.

P306

Developmental Exposure to Lead and Late Life Neurotoxicity in Rats. *C. Basha Davuljigari*[1], *U. Rani Motuku*[2], *R. Reddy Gottipolu*[1]. Department of Zoology, Sri Venkateswara University, Tirupati, India[1]; Department of Psychology, Sri Venkateswara University, Tirupati, India[2].

A significant variance in log mean treatment costs was observed in different parameters like pseudo cholinesterase levels, type of poison consumed, anticholinergic administered and incidence of intermediate syndrome. The APACHE II Score, prehospitalization period and length of hospital stay had significant correlation with log cost. Among the variables, length of hospitalization had strong correlation with log cost ($r=0.673$, $p<0.001$). For every one-unit increase in prehospitalization period, APACHE II score and length of hospital stay, the log cost increases by INR 1.01, 1.27, and 1.5 respectively.

Exposure to lead (Pb) during early postnatal development can lead to late life cognitive deficits. The present investigation envisages the immediate and/or long-term toxic effects of Pb on the synatposomal acetylcholinesterase activity (AChE) and acetylcholine (ACh) levels in different brain regions (hippocampus and cerebellum) and spatial memory of rats at PND 45, 4, 12, and

18 months age rats. Further, we have evaluated the protective effect of a mixture of essential elements (calcium, zinc, and iron) against Pb-induced long-term effects on cholinergic system and behavior. Male rats were lactationally exposed to low level Pb (0.2%) or Pb acetate together nutrient metal mixture (0.02% Ca, Zn and Fe) in drinking water of the mother from postnatal day (PND) 1 to PND 21. Exposure to Pb resulted in significant decrease in the activity of AChE and increase in ACh levels in both cerebellum and hippocampus at PND 45, 4, 12, and 18 months age rats. Pb-exposed rats exhibited significant deficits in spatial reference memory acquisition, reversal and working memory performance in the Morris water maze (MWM) at all selected age groups of rats. Alterations in cholinergic system, spatial memory and tissue Pb levels were greater at PND 45. Further, essential nutrient supplementation together with 0.2% Pb significantly reversed the Pb-induced alterations in brain chemistry and behavior. In conclusion, the results indicate that early life exposure to Pb produces long-term neurotoxicity in rats and essential metal nutrient supplement (Ca, Zn, and Fe) provides protection against Pb-induced toxicity.

P307

Studies of the Mechanism of Zinc Toxicity in Olfactory Neurons. *H. Hsieh[1], J. Deng[1], M. Medvedovic[1], M.B. Genter[1].* Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA[1].

Zinc has long been touted as a panacea for the common cold. However, there has been some controversy over whether an intranasal (IN) zinc gluconate gel (Zicam), purported to fight colds, causes anosmia, or the loss of the sense of smell, in humans. Previously, we had shown that zinc gluconate was as toxic as zinc sulfate in an *in vitro* olfactory neuron model, the rat Odora cell line. However, the mechanism of toxicity was not understood. Using RNA-seq analysis, we have shown that cationic zinc causes an up-regulation of oxidative stress-related genes, which have been associated with cell death. The zinc-mediated toxicity initially causes changes in genes involved with the pentose phosphate pathway, which is used to generate NADPH, a criticial co-factor for the generation of the antioxidant glutathione. Additionally, the cell also down-regulates expression of the ryanodine receptor, which is responsible for calcium release from the endoplasmic reticulum and other calcium stores. This may be a protective measure by the cell since increases in intracellular calcium have been linked to apoptosis and necrosis. Inevitably, the cell is overwhelmed by reactive oxygen species (ROS) and dies via a nonapoptotic mechanism, as evidenced by lack of DNA laddering and upregulation of several anti-apoptotic genes (e.g. Bcl2-XL, IAP). In conclusion, zinc toxicity in Odora cells appears to be mediated through oxidative stress in a nonapoptotic manner.

P308

Effects of Cu Nanoparticles and Their Micron and Ionic Analogs in Bacteria. *C. Kaweeteerawat[2], C.H. Chang[1], R. Liu[1], H. Godwin[1].* University of California Center for Environmental Implication of Nanotechnology, Los Angeles, CA, USA[1]; Molecular Toxicology Interdepartmental Program, University of California, Los Angeles, Los Angeles, CA, USA[2].

Nanotechnology has grown rapidly over the past decade, promising benefits in diverse areas of society. However, the rate of toxicological analysis of nanoparticles (NPs) has not kept pace with the rate of development, leading to concerns over the potential biological toxicity and environmental contamination of NPs. Here, we report toxicity ranking as well as mechanisms of toxicity for a series of Cu particles, including nano Cu, nano CuO, nano $Cu(OH)_2$, micro Cu and micro CuO as well as ionic Cu ($CuCl_2$ and $CuSO_4$) in bacteria (*Escherichia coli* and *Lactobacillus brevis*). Fluorescent assays such as PI/SYTO, XTT, DiBAC, and H_2DCFDA were used to measure viability, respiration rate, membrane potential, and ROS production, respectively. IC50 values were calculated from growth inhibition curves, revealing that Cu and CuO NPs are more toxic than their microsized counterparts, with toxicities approaching that of ionic Cu. Strikingly, the NPs showed distinct differences in their mode of toxicity when compared to the Cu ions, highlighting the unique toxicity properties of materials at the nanoscale. Sucrose gradient centrifugation and ICP-MS revealed that the NPs, but not the microsized particles, were internalized by cells. 3D tomography images were constructed from electron microscopy of cells exposed to the NPs, confirming the presence of NPs inside the cells.

400 Series—Toxicology Methods

P400

A Comparison of Capillary Microsampling and Traditional Blood Sampling for the Bioanalysis of the Biotherapeutic Humira® in Sprague-Dawley Rats.

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The use of capillary microsampling has recently emerged as a viable technique to collect and analyze bioanalytical samples in the preclinical setting. This technique has been successfully applied across Charles River sites for the collection and analysis of small molecule bioanalytical samples from rodents. The major objective for the implementation of this technique is to use smaller samples for bioanalytical evaluation in an effort to reduce the number of animals used on studies in accordance with the 3R initiative. The technique allows for full pharmacokinetic profiles from single animals and allows for the correlation of the toxicology data with the exposure data in the main study animals. We have now expanded this technique to also include the development and analysis of a large molecule bioanalytical assessment using the biotherapeutic Humira® as an example. Humira® was administered to Sprague-Dawley rats via subcutaneous injection at 1 mg/kg and macro (0.4 mL K_2EDTA) and micro (32 µL hematocrit capillary tube K_2EDTA) samples were collected at matched time points post administration. The results of the macro- versus microsamples were compared using an ECL-based immunoassay qualified on the Meso Scale Discovery instrument. Although the Cmax varied between 72 hr to 168 hr between animals, the macro and micro sample Cmax times and concentrations were comparable within any single animal. All macro- and microsamples collected were within the expected variability of a large molecule ligand binding assay (≤ 30% variability) demonstrating that capillary microsampling yields comparable pharmacokinetic results to traditional sampling methods.

P401

A Dermal Sensitization Assay Using SkinEthic™ RHE.

G. DeGeorge[1], M. Troese[1]. MB Research Labs, Spinnerstown, PA, USA[1].

International regulatory agencies, as well as animal welfare groups, are seeking *in vitro* assays for assessing the toxicity of chemicals and products. One of the most difficult challenges has been to develop nonanimal tests for skin sensitization. As an outcome of the Sens-it-iv project in Europe, Corsini and colleagues developed an Interleukin-18 (IL-18) response assay in monolayer keratinocytes as an indicator of sensitization in 2009. Here we report release of IL-18 into the culture medium of SkinEthic RHE™ treated with sensitizers, but not with irritants or nonsensitizers. Sensitizer-induced IL-18 release by RHE tissues was observed to occur in a concentration-dependent manner. RHE tissues were exposed to test substances for 24 hours. Data were expressed as a Stimulation Index (SI) calculation. An SI ratio of >2.0 were considered a positive result for dermal sensitization. A range of slight to severe sensitizers, as well as nonsensitizers and irritants were tested. A commercially available ELISA measured IL-18 and tissue viability was determined by MTT. Of the twelve known positive sensitizers tested, ten were correctly predicted. In addition, six of seven irritants and nonsensitizers were correctly predicted. Overall accuracy of the assay was calculated to be 84%. In conclusion, an *in vitro* assay for dermal sensitizers was developed in SkinEthic™ RHE, using IL-18 as an endpoint. This assay is promising for identification of sensitizers with high accuracy and predictivity.

P402

A Feasibiliyt Project: Long-Term Intraventricular CSF Sampling in a Cynomolgus Monkey via a Port Catheter System.

S. Korte[1], J. Sternberg[1], C. Rose[1], B. Niggemann[1]. Covance Laboratories GmbH, Münster, Germany[1].

Multiple lumbar, *cisterna magna* or intraventricular (IVT) cerebrospinal fluid (CSF) samplings (by needle tab) in NHP(Nonhuman Primates) is often limited by the number of sedations allowed due to animal welfare reasons within 48hrs. An implanted lumbar port catheter system often only has a reduced (in our experience ~70%) success rate for CSF withdrawal through the port, as small catheter holes easily can be blocked. An IVT port catheter system was used to test an alternative for multiple samplings in nonsedated animals. For the proper location of the stereotaxic space a template atlas of the macaque brain was used. The presented study demonstrates the successful IVT surgery in one cynomolgus monkey, and the results of multiple CSF samplings over a time period of +6 months. During this time the animal was in good clinical condition with the port system accessible at any time. The CSF could be obtained directly through the port on several occasions and, based on evaluation of albumin, chloride, inorganic phosphate, sodium, calcium, glucose, potassium, total protein, as well as of cell count parameters (white and red blood cell count), demonstrated less contamination as no needle was required interfering with blood vessel. In conclusion, intraventricular port surgery was well tolerated, and did not result in any adverse effects over a time period of +6 months. The access was used for CSF sampling in the conscious monkey. The obtained CSF was of high quality, and therefore this method can be recommended for further studies, using higher animal numbers.

P403

A Study of the Alphatrak Glucometer for Use in Nonclinical Laboratory Testing.

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The AlphaTRAK glucometer is designed for use on animal models but its reliability for use on nonclinical safety studies has not been evaluated. This study compared blood glucose values obtained using the AlphaTRAK with a standard validated clinical chemistry analyzer. Blood was collected from two sites in dogs (jugular and cephalic veins), rats (jugular and tail veins), and monkeys (femoral vein and hand prick). The ReliOn Confirm glucometer was also included in assessment for monkeys only as the AlphaTRAK does not have a calibration specifically for monkeys. The mean

differences between AlphaTRAK and chemistry analyzer values ranged from 6 to 14 mg/dL (average difference of 10.5 mg/dL) in dogs, from 2 to 19 mg/dL (average difference of 12.75 mg/dL) in rats, and from 39 to 53 mg/dL (average difference of 47.5 mg/dL) in monkeys. Mean differences between ReliOn Confirm and chemistry analyzer values in monkeys ranged from -5 to 5 mg/dL (average difference of 0.25 mg/dL). There were no significant differences in blood glucose values based on collection sites when compared to the same method of analysis in dogs and monkeys; however there were significant differences in blood glucose values from different collection sites in rats. Data suggests agreement between AlphaTRAK glucometer and chemistry analyzer for dogs and rats and between the ReliOn glucometer and the clinical chemistry analyzer for monkeys. Either site could be used for blood collection in dogs and monkeys for glucose testing; however only the same collection site should be compared for rat studies.

P404

A Test Drug Screening Panel Assessing Catalepsy, Body Temperature, Nociception, and Motor Activity in Wistar Han Rats. *J. Toot[1], M. Hackman[1], T. Pringle[1], M. Bennett[1], P. Atterson[1].* WIL Research, Ashland, OH, USA[1].

Test drugs acting via the cannabinoid receptor elicit characteristic changes in various physiological and behavioral endpoints including increased catalepsy, decreased body temperature, decreased nociception, and decreased activity. The test drug screening panel utilized by WIL Research includes an evaluation of catalepsy (CAT), body temperature (BT), thermal analgesia (TA), and spontaneous motor activity in a novel arena (MA). Therefore, objectives of this study were to establish the ability of a synthetic tetrahydrocannabinol, WIN55 212-2 (WIN), to serve as a positive control drug and also to generate historical control data of known stimulants, sedatives, and hallucinogens. Adult male Wistar Han rats were assigned to study (n=6–10/group) and administered the test drug by IP or SQ injection (as appropriate). Animals were tested prior to and at approximately 0.5, 1, 2, 4, 6, and 24 hours following dose administration. The positive control drug, WIN, was administered at dosage levels of 0, 0.1, 5, and 10 mg/kg in a 5% DMSO/Saline vehicle. Following administration WIN at 5 and 10 mg/kg, animals exhibited increased CAT, decreased BT, and increased MA for generally up to 2 hours (5 mg/kg group) or longer (10 mg/kg group), with the 0.1 mg/kg group failing to show similar robust changes. The resulting data from the positive control drug supports the validity of the methodology, general procedures, and sensitivity of the screening panel utilized at WIL Research.

P405

Cardiovascular Effects in Three Known Compounds Using the HD-S11 Implantable Telemetry Device: Proof of Concept. *M. Coffee[1], J. Hemker[1], P. Atterson[1], R. Lindquist[2], B. Main[2], M. Kesselem[2].* WIL Research, Ashland, OH, USA[1]; Data Sciences International (DSI), St. Paul, MN, USA[2].

This study was conducted to evaluate the cardiovascular effects of a well-characterized β-adrenergic agonist (isoproterenol; ISO), antagonist (propranolol; PRO), and L-type calcium channel blocker (verapamil; VER) in awake and freely moving animals using a novel implantable telemetry device (HD-S11) developed by Data Sciences International (DSI). The HD-S11 offers enhancements as compared to the T11M2-C50-PXT implant by way of reduction of environmental interference, battery life monitoring capabilities, serial number traceability and auto-configuration of calibration input via digital data as well as improved ECG and blood pressure signal quality. The goal of this study was to evaluate the performance of this novel implantable telemetry device using three known positive control materials.

Adult rats (Sprague-Dawley, four males) were surgically implanted with DSI HD-S11 implants. A cross-over design was used to evaluate vehicle and various test compounds within the same animals. Following the surgical recovery period, the animals were given a single dose of sterile water, ISO (10 mg/kg), PRO (50 mg/kg), and VER (15 mg/kg) by oral gavage with approximately 3 days between dosing. Arterial blood pressure (systolic, diastolic, and mean), pulse pressure, heart rate, electrocardiographic (ECG) waveforms (consisting of PR, QRS, RR, and QT intervals), and body temperature were collected continuously from approximately one hour prior to administration of vehicle or test article through approximately 24 hours post-dosing.

Following data review, we demonstrated the data collected via the HD-S11 implant are in agreement with the literature, and nicely displayed the expected low and high sympathetic tone in conscious, freely-moving SD rats.

P406

Characterization of Jacketed External Telemetry-Blood Pressure (JET-BP) in Dogs Administered Three Positive Controls. *J. Kremer[1], A. Bills[1], N. Hanke[1], C. Michael Foley[1], M. Osinski[1].* Covance Labs, Madison, WI, USA[1].

Nonclinical safety studies are increasingly combining cardiac safety endpoints to discover potential liabilities on cardiovascular function. This trend for more thorough cardiovascular nonclinical safety evaluations is prudent given the high attrition rate due to unexpected cardiovascular liabilities of potential therapeutics discovered in late-stage clinical trials or post-market approval (Redfern, 2010).

Methods: Jacketed external telemetry with an implanted miniature blood pressure transmitter (JET-BP) was used to characterize the tolerability, functionality, and sensitivity of this study design in dogs. Thirty-six male or female beagle dogs (n=6 dogs/sex/group) were administered control (RO water) or etilefrine (1, 10 mg/kg), sotalol (3, 30 mg/kg), and hydralazine (1, 10 mg/kg) on separate days.

Results: All three positive controls elicited the expected pharmacologic responses that were statistically different at the high and low doses. Etilefrine administration resulted in higher blood pressures (up to 84 mmHg, 56%), pulse pressure, and heart rate (56 bpm, 68%). Sotalol administration resulted in prolonged PR and QTc intervals (47 msec, 22%) and decreased blood pressures, pulse pressure, and heart rate (-27 bpm, -25%). Hydralazine administration resulted in decreased blood pressures (-25 mmHg, -16%), pulse pressure, and elevated heart rate (51 bpm, 51%). Retrospective power analysis confirmed this study design was able to statistically differentiate minor (~5–15%) changes in ECG and BP parameters, comparable to an internal

study using implanted telemetry devices (Mitchell, 2013).

Discussion: This characterization study indicates that JET-BP in dogs offers a scientifically-robust method to evaluate test articles for potential cardiovascular liabilities.

P407

Comparison of *In Vitro* Cardiac Electrophysiological Assessments on the ACEA xCELLigence and Axion Maestro Platforms. *A. Kauss[1], H. Uppal[1], D. L. Misner[1].* Department of Safety Assessment, Genentech Inc., South San Francisco, CA, USA[1].

Cardiotoxicity liabilities persist as a major cause of clinical and preclinical drug attrition today. Recent advancements in both biological models and electrophysiological technologies allow for faster and longer-term *in vitro* methodologies to assess beat rate alterations. Both the xCELLigence from ACEA and the Axion Maestro systems are label-free, electrode-based, high-throughput platforms to detect cardiomyocyte beating *in vitro* though detection of impedance and voltage, respectively. To evaluate each system, we used a set of four potent anticancer molecules with potent effects on cell viability (IC50s under 10nM), along with one structurally similar but biologically inactive molecule as a negative control, and determined the effects on human stem-cell-derived cardiomyocytes. Both platforms were able to facilitate the multiple-day experiments required to detect significant changes in beating over time. In these time course studies, both systems showed that the most toxic doses had dramatic effects on cardiomyocyte functionality, ultimately stopping beat rate entirely, and doses closer to the IC50s had more intermediate effects of reduced beat rate and amplitude. In contrast, the inactive molecule was benign, demonstrating specificity of the compounds' effect. Measurements from both systems were sensitive enough to detect on-target, time-dependent and mechanism-specific responses. Additionally, the Maestro-detected spike slope, as well as T wave position, which allowed for assessment of repolarization periods (QT intervals), which helped further discriminate the mechanisms of functional toxicity versus viability effects across molecules.

P408

Cultured Porcine Cornea Assay Using Confocal Microscopy for High Resolution Detection and Quantification of Submild Ocular Irritation. *M. Piehl[1], M. Carathers[1], E. Ryan[1], W. Hahn[1], G. DeGeorge[1].* MB Research Laboratories, Spinnerstown, PA, USA[1].

A critical need exists for a nonanimal ocular irritation assay that is sensitive to sub-mild ocular irritation. We have developed a novel assay, PorFocal, which can quantify individual dead corneal epithelial cells in porcine corneas using confocal microscopy. PorFocal uses phosphate buffered saline (PBS) as a negative control and 0.01% benzalkonium chloride (BAK) as a positive control. In 17 experiments, 0.01% BAK always caused more cell death than PBS, and statistically ($p<0.05$) more in 15 of 17 replicates. The PorFocal assay detected a significant dose-response with BAK dilution series treatment. Treatment with 0.01% BAK-preserved lubricant eye drops showed a significant 3-fold increase in cell death versus the preservative-free version. To examine the potential of the PorFocal to detect human eye sting of a known stinging chemical (avobenzone), we compared a low avobenzone (LA) to a high avobenzone (HA) sunscreen. The HA caused significantly more cell damage (7-fold increase) than the LA. We compared PorFocal to an industry standard 3D reconstructed human tissue (RhT) ocular irritation assay. The RhT detected four of nine materials while the PorFocal assay detected eight of nine materials tested as statistically different ($p<0.05$) from PBS values. Overall, this indicates a great degree of sensitivity with PorFocal assay, heretofore not attainable by existing methods.

P409

Development of a Curved Stratified, *In Vitro* Model to Assess Ocular Biocompatibility with Contact Lenses. *A.M. Wright[1], C. Postnikoff[2], R. Pintwala[2], S. Williams[2], D. Hileeto[2], M. Gorbet[2].* ALCON, Johns Creek, GA, USA[1]; University of Waterloo, Waterloo, ON, Canada[2].

Purpose: To further improve *in vitro* models of the cornea, this study focused on the creation of a three-dimensional, stratified, curved epithelium; and the characterization and evaluation of its suitability as a model for biocompatibility testing. Methods: Immortalized human corneal epithelial cells were grown to confluency on curved cellulose filters for seven days, then differentiated and stratified using an air-liquid interface for seven days before testing. Varying concentrations of a commercial ophthalmic solution containing benzalkonium chloride (BAK), were tested on the model. A whole balafilcon A lens soaked in phosphate-buffered saline (BA PBS) was also used to assess biocompatibility and validate the model. Both a viability assay and flow cytometry were performed on cells to investigate changes in integrin expression and cell death. Results: The reconstructed curved corneal epithelium was composed of 3–5 layers of cells. Increasing concentrations of BAK showed dose-dependent decreased cell viability and increased integrin expression and cell death. The BA PBS combination appeared to be very biocompatible with no adverse change in cell viability or integrin expression. Conclusions: The stratified, curved, epithelial model proved to be sensitive to distinct changes in cytotoxicity and is suitable for continued assessment for material biocompatibility testing of contact lenses. In this model, patient use on the cornea is replicated by the entire lens in close contact with the superficial layer of the epithelial 3D-curved model. Flow cytometry can provide quantitative analysis of cell response to biomaterials or cytotoxic compounds for both the supernatant and adherent cell populations.

P410

Development of a Method for Intradermal Dose Administration in the Minipig. *T. Ramani[1], M. Savidge[1], G.M. Hoffman[1], C. Willard-Mack[1], C.S. Auletta[1].* Huntingdon Life Sciences, Somerset, NJ, USA[1].

This presentation describes a procedure developed for intradermal administration into the skin of laboratory minipigs for a preclinical safety evaluation study. This is not a common route of administration for this species and required some investigative work to develop an appropriate method, one that would accurately administer the test article to the desired area (intradermal) of a minipig and allow for appropriate animal restraint and handling. Issues addressed were: dose site, dose volume, number of

injections, equipment and administration procedure, including animal restraint and handling. Initial attempts to administer 0.1 mL intradermally into the skin of the back and sides, using a standard 1 mL syringe and 28 to 31gauge needle to the skin of the back or sides of a minipig were unsuccessful because of the skin density. Subsequently, the skin in the axillary and inguinal areas was identified as skin for which intradermal injections could easily be made. The injection procedure could not be performed on a conscious animal, due to the reactions of the minipig, the location of the dose site and the need for multiple injections. Therefore, it was necessary to perform injections under sedation (intramuscular Telazol). There were no adverse effects of this sedation and animals recovered rapidly. Injections were well-tolerated. Microscopic examination from saline-treated sites revealed no abnormalities. Additional evaluations of these procedures would be necessary for studies of longer duration.

P411

Development of a Targeted Biomarker Assay to Predict Developmental Toxicity Using Induced Pluripotent Stem Cells. *J. Palmer[1], L. Egnash[1], A. Smith[1], K. Conard[1], P. West[1], R. Burrier[1], E. Donley[1], F. Kirchner[1].* Stemina Biomarker Discovery, Inc., Madison, WI, USA[1].

Assessment of potential developmental toxicity of new chemicals is both resource intensive and time consuming. Large numbers of laboratory animals are required and the predictive value of these decades-old tests has been challenged. Availability of more predictive developmental toxicity screens would reduce costs and increase pharmaceutical and chemical safety. Using two metabolites previously identified in human embryonic stem (hES) cells as indicators of developmental toxicity, a metabolic biomarker-based *in vitro* assay utilizing human induced pluripotent stem (iPS) cells was developed to identify the concentration of test compounds which may perturb cellular metabolism in a manner indicative of teratogenicity. iPS cells are derived from the genetic manipulation of human somatic cells. These cells are being investigated for use in place of hES cells by many researchers due to the moral, ethical and political controversies surrounding their use. Human iPS cells are phenotypically and genetically similar to hES cells in many respects (i.e. morphology, proliferation, gene expression). We tested 31 compounds with known teratogenicity in both hES and iPS cells in the new targeted biomarker assay. The predictions (teratogen vs. nonteratogen) as well as the concentration a compound was predicted teratogenic at were compared between the two cell lines. In hES cells, the assay was over 90% accurate in predicting the teratogenic potential of these compounds. These results are highly concordant with the results obtained in iPS cells. The transition of the targeted biomarker assay to iPS cells harnesses the predictive power of the hES cells without the ethical controversy surrounding them.

P412

Development of an *In Vitro* Preclinical Cellular Assay to Predict Induction of Cytokine Storm by Therapeutic Antibodies. *G. Strizheva[1], U. Warrior[1].* Eurofins Panlabs, Inc, Bothell, WA, USA[1].

Cytokine storm (Hypercytokinemia/Cytokine Release Syndrome) is an acute immune reaction consisting of a positive feedback loop between cytokines and immune cells, resulting in severe inflammation and organ failure. A clinical trial of immunotherapeutic anti-CD28 antibody TGN1412 in 2006 demonstrated the importance of thorough preclinical screening and need for more sensitive assays to predict cytokine storm. In that study, 6 healthy volunteers suffered from hypercytokinemia at doses 500-fold less than the lowest dose tested in nonhuman primates (NHP), showing the failure of standard preclinical safety approaches of that time. We have developed an *in vitro* assay to evaluate biologics for induction of cytokine storm. Frozen human and NHP PBMCs are cultured with test articles and assayed for cytokine production and cell proliferation. Anti-CD28 superagonist antibodies, which have been shown to be similar in mechanism as TGN1412, are used as a positive control. Human PBMC produced substantial amount of cytokines, such as IL-2, IL-6, IFN-gamma, TNF-alpha and MIP-1-alpha, compared to isotype control or untreated cells, while PBMC from NHP were nonresponsive. The increased production of key pro-inflammatory cytokines in response to stimulation with anti-CD28 antibodies is accompanied by increased PBMC proliferation, while no proliferation increase is detected in isotype-treated or unstimulated cells. We also tested anti-CD3 antibodies (OKT3 and UCHT1) on PBMC from seven healthy donors which showed difference between these clones in the pattern of induction, dependent on the method of antibody presentation to cells. This confirms necessity of testing novel antibody agents in different *in vitro* testing approaches.

P413

eCiphrCardio: A High-Throughput Multiwell Microelectrode Array (MEA) Assay for Cardiotoxicity Prediction. *S. Qin[1], J. Gilbert[1], C. Strock[1].* Cyprotex US, Watertown, PA, USA[1].

Cardiotoxicity is one of the most common reasons for drug attrition. Current *in vitro* cytotoxicity assays identify only the most overtly toxic compounds, while assays to measure more specific liabilities such as hERG and other ion channels fail to detect a response which relies on a combination of endpoints or a delayed response due to expression. Toxicity determination relies heavily on the later preclinical phase animal studies which have much higher costs associated and can have species specific results which may not model human responses. Therefore, an ideal assay for predicting cardiotoxicity would involve screening earlier on a platform which measures the field potential in human cardiomyocytes. The recent development of iPSC-derived cardiomyocytes and the multiwell MEA by Axion Biosystems have made the development of this assay possible.

eCiphrcardio is a multiwell MEA assay which measures the field potential of iPSC-derived cardiomyocytes. This provides a summation of the effects of the compounds on all channels, receptors, and pathways which affect cardiac function. This data is extracted to report effects of test compounds on the different

phases of the heartbeat. The endpoints reported are field potential duration (QT), beat rate, fast Na amplitude and slope, as well as Early After Depolarizations (EAD). The assay is label free so action potentials can be monitored over multiple time points and days to measure effects which are delayed through turnover or expression changes (i.e., hERG trafficking effects).

P414

eCiphrNeuro: A High throughput Assay to Detect Neurotoxic Compounds in Early Drug Discovery. *J. Bradley[1], H. Luithardt[1], J. Gilbert[1], C. Strock[1].* Cyprotex US, Watertown, MA, USA[1].

Seizurogenic neurotoxicity produces significant drug attrition during drug discovery. Currently available *in vitro* assays cannot predict this toxicity due to the failure of general cytotoxicity assays to predict sublethal target-specific electrophysiological liabilities. Ion channel and receptor activity assays can be used to predict some seizure potential, but these only focus on specifically measured targets for prediction and may miss a response which relies on a combination of endpoints. Most evaluation of seizure inducing compounds occurs later in preclinical development in *in vivo* studies, which have much higher costs. Therefore, the development of a high-throughput *in vitro* assay to screen compounds for seizurogenic potential would lead to evaluating compounds earlier at lower cost and greater reliability. Here we demonstrate the use of a 48-well multielectrode array (MEA) to screen for seizurogenic compounds using rat cortical neurons. Spikes were measured and the results were computed for mean firing rate, synchrony, and spike train organization (inter-spike and burst statistics) using custom Matlab scripts and NeuroExplorer. All of the seizurogenic compounds, including $GABA_A$ antagonists, showed significant changes in MFR, synchronization, and spike train and burst organization, while all of the negative controls were ineffective. Glutamate, the excitatory neurotransmitter, showed a robust increase in activity. Neuroinhibitory molecules such as Domoic Acid, a neurotoxin, GABA (GABA agonist), Tetrodotoxin (sodium channel blocker) and TEA (potassium channel blocker) were also tested and found to block activity. These results illustrate the power of a high-throughput rat cortical neuron MEA assay for predicting compound induced neural toxicity.

P415

Effect of Analgesic Administration on the Guinea Pig Maximization Test. *D. Rice[1], L. Anderson[1], J. Gass[1].* Baxter Healthcare, Round Lake, IL, USA[1].

Guinea pig maximization tests have been associated with inflammation at induction sites due to the use of 1-chloro-2, 4-dinitrobenzene (DNCB) as a positive control and Complete Freund's Adjuvant (CFA). To alleviate the potential for pain and distress, we evaluated the use of the analgesic, buprenorphine hydrochloride (HCl). Analgesics can modulate the inflammatory response and may interfere with the detection of contact sensitization. The purpose of this study was to determine if the administration of buprenorphine HCl would affect the results of the guinea pig maximization test. DNCB and Rubbercare® Gloves were used as test articles. The experimental design was consistent with the procedures described in ISO 10993- 10 and the guinea pig maximization test, with additional parameters evaluated. The experimental design consisted of 10 groups with each group receiving different concentrations of the test articles with or without analgesic treatment. Twenty-four to 30 hours after topical induction, the groups treated with buprenorphine HCl were given 0.06 mg/mL every 12 hours for a total of three doses. Three animals per group were terminated on study day 10 for hematology, coagulation and histologic evaluation of treatment sites. Clinical observations, hematology, coagulation and histopathology of treatment sites were similar in groups treated with and without analgesics. At least 60% to 100% of animals in each group were sensitized with no difference between corresponding groups with or without analgesic treatment. Based upon the results of this study, the use of bupenorphine HCl did not interfere with the results of the guinea pig maximization test.

P416

Electrophysiologic Characterization of Human Adult Cardiac Stem Cells from Cellular Dynamics International (iCell® Cardiomyocytes) and Axiogenesis AG (Cor.4U®). *R. Numann[1], Y. Yue[1], J.K. Gibson[1].* Ionic Transport Assays, Inc., St. Louis, MO, USA[1].

To determine differences in cellular electrophysiology, human adult-induced pluripotent cardiac stem cells were cultured using the media and methods provided by the appropriate vendor. Both iCell® Cardiomyocytes and Cor.4U® cardiac cells were plated onto 8 mm coverslips at 10,000 to 20,000 cells per well. Cells were recorded from days 6–19 for Cor.4U® cells and from days 11–52 for iCell® Cardiomyocytes. Both cell lines showed similar distributions of three different cardiac cell types. In recordings from fifty Cor.4U® cells, 60% were ventricular-like, 22% were pacemaker-like, and 18% were atrial-like. Recordings from fifty iCell® Cardiomyocytes gave 57% ventricular-like, 28% pacemaker-like, and 15% atrial-like. iCell® Cardiomyocytes and Cor.4U® cells gave stable ventricular-like action potentials (resting membrane potential, RMP, > -60 mV, action potential duration at 90% of the peak, APD90, > 400 msec). Recordings using the gramicidin perforated patch clamp technique showed little change in ventricular-like action potential waveform during 30 minutes of recording (RMP, APD90, peak amplitude, upstroke velocity). High-quality ventricular-like action potential recordings were first seen from day six with Cor.4U® cells and after 13 days in iCell® Cardiomyocytes. Ventricular-like paced action potentials were subsequently recorded from days 6–10 and 11–19 in Cor.4U® cells and days 13–21 and 25–52 in iCell® Cardiomyocytes. These data demonstrate that, in the conditions described above, Cor.4U® cells quickly reach a mature steady state after 6–10 days in culture; whereas, iCell® Cardiomyocytes are mature at days 13–21 but continue to grow until day 52.

P417

Established Method to Assess Cardiorespiratory Parameters in Inhalation Safety Pharmacology Studies in Conscious Dogs. *C.M. Kelly[1], T. Ziegelhofer[1], J. Sentz[1], M. Miyamoto[1], J. Sheehan[1].* Huntingdon Life Sciences, E. Millstone, NJ, USA[1].

A critical but challenging aspect of inhalation cardiorespiratory safety pharmacology studies is the collection of high quality cardiovascular and respiratory data immediately prior to, during and immediately after dose in order to recognize any acute effects of the inhaled test article. This poster describes methods for achieving successful study outcomes, including factors that

must be considered in the design and execution. Effects of proper habituation to equipment and carefully scheduled study activities were assessed based on the overall character of cardiorespiratory response from three different studies. Prior to data collection, all animals were surgically implanted with telemetry transmitters and habituated to the exposure/data collection system. Telemetry data were collected continuously for 2 hours while animals were in their home cage, after transfer to the exposure suite for 0.5 hours prior to air or vehicle exposure, during the one hour exposure, 0.5 hour after exposure and for 24 hours postdose. Each study used a different vehicle and an air (sham) control was administered for assessment of the vehicle effect. Administration of the vehicle produced no effects on blood pressure, heart rate, body temperature, respiratory rate, and tidal and minute volume, when compared to the air control in all three studies. These data confirm we have developed a reliable method of collecting cardiorespiratory parameters in inhalation safety studies.

P418

Evaluation of Pachymetry Data for the Measurement of Corneal Thickness in Cynomolgus Monkeys. *S. Korte*[1], *C. M. Luetjens*[1], *B. Niggemann*[1]. Covance Laboratories GmbH, Münster, Germany[1].

Measurement of corneal thickness (CT) is a standard tool in the regulatory driven safety evaluation of ocular drugs. New equipment (here: Accutome AccuPach VI, Accutome/ADI, The Netherlands) needs to undergo an *in vivo* validation for utilized ultrasound technology. In this study the data of 12 cynomolgus monkeys (*Macaca fascicularis*, 4.0–8.6 kg, 6–9 years) underwent multiple readings for CT within 30 minutes in the late afternoon under a light sedation using ketamine hydrochloride and topical instillation of a local ophthalmic anesthetic (proxymetacain) into both eyes. The results of the method are considered acceptable if the CV is below 25%. Intra- and inter-run precision were determined for the right and left eye. Key elements for successful measurements are the accurate positioning and orientation of the probe on the eye surface, measurement on the same location of cornea (central), to keep the orientation of the probe perpendicular to the eye globe (inline with visual axis) and to keep the animal eyes moist whilst sedated to avoid drying the cornea due to obstructed twinkling. A manually blink of the eye before reading is supporting a uniform tear film. In conclusion, the obtained results achieved a mean intra-run precision between 5.3 and 6.9% and an inter-run precision between 1.5 and 1.9%. The mean concordance between staff was 97.9 and 98.3%. Average results were between 411.3 and 418.7 µm and therefore lower than comparable monkeys measured by Kodamo, 2010 (men 580–616 µm, n=8,5–7 years) using optical coherence tomography (RTVue-100, Optovue, Inc., Meridianville, AL, USA).

P419

Evaluation of Two Glucometer Models in Rats. *C. Li*[1], *M. Zamfir*[1], *M. Vezina*[1]. Charles River Laboratories, Senneville, QC, Canada[1].

Blood glucose (GLU) is a common endpoint in diabetic toxicology models and clinical monitoring of animals. Handheld models are convenient for real-time GLU determination, but provide limited numerical data when values fall outside the device's range. Accurate numerical data for GLU levels can be generated via the Roche/Hitachi Modular Analytics analyzer; however, limitations include a minimal required blood volume, timeliness of obtaining data, limited available blood volume due to species type, and number of allowable blood volume draws. A novel device, StatStrip® Xpress™ Glucometer (Nova Biomedical), was compared to a standard handheld glucometer and the Modular Analytics to determine if its performance was suitable for preclinical studies. Fifteen brown Norway rats were given streptozocin at 60 or 55 mg/kg by intravenous injection on Day 1 to induce a diabetic condition (>250 mg/dL). GLU was measured using blood from the tail vein with a Bayer® Contour™ glucometer on Days 2, 3, 5, and 8. Additional GLU measurements were performed on five rats using the StatStrip® Xpress™ with jugular vein blood collected on Days 3, 4, and 8. Remaining blood volume was analyzed on the Modular Analytics for comparison purposes. The Contour™ detected GLU levels ≤595.8 mg/dL, but values >600 mg/dL were presented as Hi. The StatStrip® Xpress™ presented values ≤866 mg/dL. Values obtained from the Modular Analytics were comparable to the StatStrip® Xpress™. The StatStrip® Xpress™ provided an accurate extended range of detection for preclinical test system monitoring with the benefits of real-time results and minimal blood volume requirements.

P420

Gaseous Distension of the Gastrointestinal Tract in Mice Associated with Restraint Tube Configuration in an Inhalation Study. *N. Macri*[1], *T. Ramani*[1], *S. Cracknell*[1], *J. Damiano*[1]. Huntingdon Life Sciences, E. Millstone, NJ, USA[1].

Gaseous distension of the gastrointestinal tract (GDGIT) due to aerophagia has been described in a variety of species including rodents, rabbits, horses and humans. In rodents and rabbits GDGIT has been associated with obstructive proliferative lesions in the nose and nasopharynx and experimental occlusion of the nostrils. We conducted a chronic inhalation study in mice in which a high rate of GDGIT was initially observed. The original configuration of the restraint tubes, used to hold mice during exposure, was a parallel sided structure with metal end bars and mesh screens to prevent animals from escaping into the exposure system. Observation of the restrained animals suggested that they were chewing the metal bars during exposure. We hypothesized that a combination of chewing activity and extended neck posture caused by the tube restraint resulted in aerophagia and subsequent GDGIT. Modifying the restraint tubes to incorporate tapered end caps of sufficiently low diameter to prevent the animals from exiting and removing the metal end bars and mesh screens resulted in significantly decreased mortality from GDGIT. To our knowledge GDGIT has not been associated with exposure system components in inhalation studies. Here we demonstrate a unique pathogenesis for GDGIT in mice related to restraint tube

configuration. We believe that morbidity and mortality from GDGIT can be minimized or prevented by the use of tapered end caps without metal end bars or mesh screens.

P421

In-Life Care and Background Information on Fatty Zucker Diabetic (ZDF) Rat Model for Toxicology Study Studies. *A. Prefontaine[1], F. Poitout[1], S. Gariepy[1], C. Copeman[1], B. Lise[1].* Charles River Laboratories, Senneville, QC, Canada[1].

The US FDA recently requested to pharmaceutical companies developing compounds for treatment of diabetes, to perform additional toxicology studies using an insulin-resistant rodent model for Type 2 diabetes in order to identify potential effects on pancreatic structure and function. The male Zucker diabetic fatty (ZDF) rat has proven to be the model of choice for these studies. Specific animal husbandry/handling procedures and background data on this inbred strain play an important role in overall interpretation of toxicity studies. Consequently, compilation of background data of control animals (body weight (BW), food consumption (FC), clinical chemistry parameters along with details of specific husbandry/handling and veterinary care procedures and complications) were compiled. Between 7 and 15 wks of age, ZDF rats show increases in BW and FC. By 15 wks of age, ZDF rat stabilize and maintain their BW and FC at ~400g and 40 g/day, respectively. Glucose, glycated hemoglobin (HbA1c) and insulin levels are elevated by 12 wks of age and glucose and HbA1c continue to increase as compared to insulin levels that are maintained up to 21 wks of age at ~6.5 ng/mL. Specific husbandry and veterinarian care are required for alleviating the increased incidence of swelling, redness and discharge of the prepuce. Given their unusual anatomy, modified restraint procedures are required, especially for blood collection procedure. Based on the accumulated data and implementation of modified husbandry and veterinary care, it is considered that male ZDF rat is a suitable candidate for the conduct of regulatory compliant studies for diabetic compounds.

P422

Mechanistic Nephrotoxicity Monitoring by Targeted Urinary Proteome Measurement Using LC-MS/MS. *M. Gharib[1], L. Di Donato[1], J.D. Smith[2], R. Fryer[2], D. Chelsky[1], L. McIntosh[1], J.A. Phillips[2].* Caprion Proteome, Montreal, QC, Canada[1]; Integrative Toxicology, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA[2].

Current investigative toxicology approaches employ new methods for understanding the mechanisms of toxicity. This study describes an approach leveraging the rapid method development and multiplexing capability of LC-MS based proteomics for the identification of urinary proteins related to drug-induced nephrotoxicity in rats. The objective is to evaluate opportunities to flexibly monitor targeted portions of the urinary proteome for nonclinical toxicology assessments. Urinary biomarkers offer the advantage of noninvasively monitoring nephrotoxic injury. As sample complexity is a significant factor affecting mass spectrometric (MS) quantification of low abundance protein biomarkers, urine also offers the advantage of being a simple matrix. Hence, hundreds of protein biomarkers can be measured in a single assay without immunoaffinity depletion of high and medium abundance proteins and/or fractionation procedures prior to MS. Rats were treated with the known nephrotoxicant cisplatin (CDDP), to model acute renal injury. Each group of Sprague-Dawley rats (n=8 per group) were dosed with CDDP (1 or 3 mg/kg/day) or saline vehicle. Urine samples were subjected to a protein precipitation procedure followed by multiplexed targeted LC-MRM/MS analysis. High-purity stable-labeled peptides were used as internal standards to determine the concentration of several well-studied urinary anchor biomarkers. Individual protein abundance was corrected for urine volume and creatinine level. The relative LC-MRM/MS response of these anchor biomarkers provided results comparable to conventional immunoassay results. These results suggest flexible measurement of multiple protein analytes using quantitative LC-MRM/MS approaches that provide a rapid biomonitoring solution for investigative toxicology studies.

P423

Method-Validation and Assessment of Immunotoxicity Potential for New Drugs. *P. Mendoza[1], I. Lenthéric[1], L. Canut[1], V. Reig[1], D. Dickel[2], P. Sagelsdorff[2], E. Fernández[2].* Harlan Laboratories, S.A., Spain, Santa Perpetua de Mogoda, Spain, UK[1]; Harlan Laboratories, Ltd., Switzerland, Itingen, Switzerland[2].

Keyhole Limpet Hemocyanin (KLH) is a large and highly glycosylated protein well-known for its immunogenic potential and widely used as an antigen for the study of primary T-cell-dependent antibody response (TDAR). Harlan Laboratories has established and validated a method across two different sites (Harlan Laboratories Ltd. and Harlan Laboratories S.A.) to evaluate the possible effects on the immunoresponse caused by a drug in Wistar or SD Rats after 2-week daily intravenous treatment administration of KLH at 500 µg/kg.

To determine the primary immune response, rats treated daily with CPA (cyclophosphamide) or with vehicle (distilled water) were immunized with KLH on day 10. After KLH administration, anti-KLH IgM levels in treated animals were quantified by ELISA and compared to the anti-KLH IgM levels found in untreated immunized rats (control group).

Harlan Laboratories has established a historical data bank of untreated rats, which can be used to evaluate the immunotoxicological effect on animals treated with different drugs. Different studies will be presented for discussion.

This validation procedure will be extended to other species such as dog, mouse, and monkey.

P424

Normal Physiological and Pathological Values for the Sinclair Miniature Swine. *D. Brocksmith[2], L.D. Brown[1], A. Stricker-Krongrad[1], B.C. Hanks[1], J. Liu[1], G.F. Bouchard[1].* Sinclair Research Center LLC, Auxvasse, MO, USA[1]; Sinclair BioResources LLC, Auxvasse, MO, USA[2].

The miniature swine are increasingly recognized as a nonrodent model in regulatory toxicology. The Sinclair miniature swine (SMS) is the oldest strain of miniature swine developed for research and one of the smallest breeds. The similarities between the cardiovascular, renal, and digestive systems make the miniature swine a suitable animal to model the human counterpart. The miniature swine are also the most recognized species for dermal toxicology. The SMS has other attractive traits that make them a good substitute to model humans. They are omnivorous, easy to handle, prone to obesity, and will develop atherosclerosis and dyslipidemia if fed a high-fat diet. All routes of compound administration can be used with miniature swine. The SMS should be considered as one of the nonrodent species in systemic toxicity testing. In an effort to generate a database on baseline information about the normal physiological status of the Sinclair miniature swine, we reported physiological data from normal intact and naïve three-month-old Sinclair miniature swine of both genders. The normal physiological data gathered includes growth parameters, hematology, serum chemistry, coagulation profile, urinalysis, ECG rhythm and segment intervals, and organ weights.

P425

Normal Physiological Ranges for Hanford Miniature Swine. *M. Ross[1], L. D. Brown[1], D. Unterreiner[1], B. C. Hanks[1], D. Brocksmith[2], T. Madsen[1], J. Liu[1], G. F. Bouchard[1].* Sinclair Research Center LLC, Auxvasse, MO, USA[1]; Sinclair BioResources LLC, Auxvasse, MO, USA[2].

The miniature swine have been increasingly recognized as a nonrodent model in regulatory toxicity. Members of the US FDA have even published on the use of miniature swine as an alternative to canine and nonhuman primates in regulatory toxicity. The similarities between the cutaneous, cardiovascular, renal, and digestive systems make the miniature swine a suitable animal to model the human counterpart. The miniature swine are also the most recognized species for dermal toxicology. The Hanford miniature swine (HMS) has other attractive traits that make them a good substitute to model humans. They are omnivorous, easy to handle, prone to obesity, and will develop atherosclerosis and dyslipidemia if fed a high fat diet. With the advent of new techniques, all routes of compound administration can be used with miniature swine. The HMS should be considered as one of the norodent species in dermal toxicity testing. In an effort to generate a database on baseline information about the normal physiological status of the Hanford miniature swine, we report expanded physiological data from normal intact and naïve juvenile and young adult miniature swine of both genders. The normal physiological data gathered includes growth parameters, hematology, serum chemistry, coagulation profile, urinalysis, ECG rhythm and segment intervals, and organ weights.

P426

Procedural Enhancements to Refine the Method of Dog Restraint for Inhalation Studies. *S. Moore[2], M. Timothy[2], S. Hawes[2], S. Cracknell[1], J. Damiano[1].* Huntingdon Life Sciences, E. Millstone, NJ, USA[1]; Huntingdon Life Sciences, Huntingdon, UK[2].

Huntingdon Life Sciences pioneered the use of minimal restraint methods for dogs used in inhalation toxicology studies in 2001 and has routinely employed these methods for every study performed since that time with great success. As part of Huntingdon Life Sciences commitment to animal welfare, this poster provides information on further refinements of this methodology and presents revisions to the habituation procedures that have been demonstrated to further improve animal welfare, compliance and study outcomes. Modifications include the earlier introduction of the facemask and compressed air supply in the 14 day habituation period and a more gradual increase in the duration of restraint. Introduction of these refinements has resulted in improved animal compliance particularly during first 7 to 14-days of inhalation exposure. These changes have the potential to improve both animal welfare and quality of study data.

P427

Simultaneous Automated Blood Sampling and Radiotelemetered Physiological Measurements in Cynomolgus Macaques. *D. Hopper[1], P. Kruzich[1], S. Kurtz[1], B. Gien[1], M. Swaab[2], D. Singer[2], D. Sarazan[2], R. Sun[1], T. DeGraw[1].* BASi, Mount Vernon, IN, USA[1]; DSI, St. Paul, MN, USA[2].

Preclinical cardiovascular safety studies commonly use radiotelemetry in large animals, such as cynomolgus macaques (cynos) but require toxicokinetic measurements in separate animals to avoid disruptions in physiologic measurements from handling. Challenges with use of cynos include signal interference during procedures, and increases in stress markers (*e.g.,* cortisol) due to handling. A proof of concept study was conducted whereby automated blood sampling (Culex-L) was coupled with radiotelemetry (DSI) to compare automated versus manual blood sampling during physiological measurements in cynos. Four female cynos implanted with telemetry devices and intra-carotid catheters were dosed twice with 175 mg/kg of moxifloxacin (Moxi), an antibiotic with QT prolongation liability. Blood samples for measurement of Moxi and cortisol were collected either manually or via the Culex-L on different days, while physiological parameters were recorded. Moxi concentrations were similar for both sampling techniques. Cortisol concentrations were markedly elevated during the manual collections phase. Automated collection was associated with fewer room disturbances and less technician time. Challenges encountered with Culex-L and radiotelemetry included missed plasma samples, resolved by revising component connections between the Culex-L and the animal, and complete telemetry data drop-out due to loss of digital signal to receivers, addressed by adjusting receiver placement. This study established the feasibility of collecting simultaneous blood samples by the automated Culex-L while recording physiological measurements by radiotelemetry in caged, tethered cynos. Markedly less animal stress was incurred by automated sampling as demonstrated by lower cortisol concentrations and fewer physiological data dropouts.

P428

Targeted Animal Safety: Radiotelemetry Implanted Felines. *K. Kearney[1], R. Hamlin[2], P. Atterson[1].* WIL Research, Ashland, OH, USA[1]; QTest Laboratories, Columbus, OH, USA[2].

There are vast amounts of cardiovascular data readily available for many animal models commonly employed in preclinical research, while limited data (specifically cardiovascular) are available for animal models extending beyond rodents, canines, minipigs, and nonhuman primates.

The purpose of the current investigation was to assess the feasibility of using telemetry implanted cats for targeted animal safety studies designed to evaluate continuously acquired cardiovascular data. The data presented was collected from telemetry implanted cats over 24-hour periods following subcutaneous injection of Dipyridmole. Data were analyzed for diurnal variations in cardiovascular endpoints. ECG intervals were additionally investigated and are presented. Animals exhibited sinus rhythms with subtle respiratory sinus arrhythmias. Additional evaluation of the QT vs HR plots are discussed, and demonstrate potential inadequacies in standardized QT-correction formulae for use in cats. These data effectively demonstrated the use of telemetry implanted cats for the purpose of evaluating cardiovascular liability for pharmaceuticals administered in felines.

P429

Use of a Cyclophosphamide-Induced Model of Immunosuppression to Validate Commercially Available Assays for the Evaluation of T-Cell Dependent Antibody Response (TDAR) in the Nonhuman Primate. *A. Aulbach[1], J. Rose[1], J. Coash[1], B. Zeigler[1], K. Nelson[1], Y. Q. Xiao[1], S. E. Boley[1].* MPI Research, Inc., Mattawan, MI, USA[1].

Current regulatory guidelines require functional immunotoxicity testing of new drugs that have demonstrated the potential for effects on the immune system as determined by evaluation of standard lymphoid and hematopoietic endpoints. T-Cell Dependent antibody response (TDAR) testing is endorsed by regulatory agencies as a first-line immune function test for new drug candidates; however, there are few commercially available methods. We conducted a study designed to result in robust primary and secondary antibody responses to the TDAR antigen, Keyhole Limpet Hemocyanin (KLH) in the nonhuman primate (NHP). Immunization of naïve NHP with KLH resulted in statistically significant ($p<0.01$ or $p<0.05$) increases in anti-KLH IgM and IgG antibody concentrations beginning by 7 to 14 days post-immunization. A separate group of animals dosed with cyclophosphamide exhibited diminished anti-KLH IgM and IgG antibody responses relative to immunized control animals demonstrating the ability of these methods to distinguish between antibody responses of immunocompetent and immunocompromised animals. We performed a fit-for-purpose method validation of commercially available ELISA methods which included inter/intra-assay precision and accuracy, dynamic range, specificity, determination of LLOQ/ULOQ (lower and upper limit of quantification), dilutional linearity/parallelism, spiked recovery, and stability. All intra/interassay precision and accuracy runs resulted in %CV and %RE <18%. The range of quantification was determined to be 12.5–400 ng/mL for IgM and 0.94–30 ng/mL for IgG. In summary, we were able to perform a fit-for-purpose method validation on commercially available ELISA methods for the determination of anti-KLH IgM and IgG antibody concentrations in response to a standard immunization protocol.

P430

Use of the Göttingen Minipig As a Model of Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression. *R. Seals[1], D. Hopper[1], N. Suttles[1], W. Jo[2], S. Basu[2].* BASi, Mount Vernon, IN, USA[1]; Dow Pharmaceutical Sciences, Inc., Petaluma, CA, USA[2].

The objective of this study was to characterize and validate a model of HPA axis suppression in Göttingen minipigs using Ultravate Cream® (0.05% halobetasol propionate). Topical corticosteroids can produce reversible HPA axis suppression. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria may occur in some patients while on treatment. Ultravate Cream was applied to 10% of the body surface area of six male minipigs once daily for seven consecutive days at an application rate of 0.005 or 0.01 g/cm^2.

Basal serum cortisol concentrations were measured on Days -1, 3, 5, and 7, and at 1, 2, and 3 weeks after the last dose. On Day 8 and 4 weeks after the last dose, a cosyntropin stimulation test (Cortrosyn®; 0.25 mg IM) was conducted and blood collected within 15 minutes prior to and 30 minutes after stimulation.

In this study, clinical criteria for HPA axis suppression were used, i.e., prestimulation or basal serum cortisol concentrations ≤ 5 µg/dL and/or 30 minutes postcosyntropin stimulation cortisol concentrations ≤ 18 µg/dL. Based on prestimulation cortisol concentrations on Day 8, 1/3 animals at 0.005 g/cm^2 and all three animals at 0.01 g/cm^2 had HPA axis suppression. Poststimulation concentrations on Day 8 indicated that only one animal from each group was suppressed. Group mean stimulated cortisol concentrations were 26% lower in animals at 0.01 g/cm^2 when compared to animals at 0.005 g/cm^2 (18.5 and 25.1 µg/dL, respectively). Basal cortisol concentrations returned to pretest values on Day 14. Based on these results, the Göttingen minipig could be used as a model of HPA axis suppression.

P431

Validation of a Flow Cytometry-Based Method to Detect the Degranulation and Cytolytic Function of Cynomolgus Monkey CD^8+ Cytotoxic T-Lymphocytes. *D. Wilkins[1], K. Hallett[2], R. Ardelean[1], R. Young[1], C. Satterwhite[1], J. Blackbourne[3].* Charles River Laboratories, Reno, NV, USA[1]; University of Wisconsin, Madison, WI, USA[2]; Eli Lilly and Company, Indianapolis, IN, USA[3].

Several methods are available to assess the function of lymphocytes; however, the methodologies available for CD8+ cytotoxic T-lymphocytes (Ctx) are limited. Ctx are crucial components of the adaptive immune system, therefore, methods that assess the function of Ctx in the context of preclinical safety studies are increasing in demand. We developed and validated a flow cytometry assay that measures degranulation and target killing, two hallmarks of Ctx function. Degranulation was assessed by the expression of CD107a on Ctx, and killing activity of Ctx was assessed by the percentages of CFSE+/7AAD+ (killed) P815 target cells after incubation with PBMCs and stimulation (PMA or anti-CD3) or control conditions (mIgG1κ). Validation parameters included precision, stability, reproducibility, and range of

response. PBMCs from 10 naïve cynomolgus monkeys (5 per sex) were assessed for reproducibility over three independent assays. The reproducibility was acceptable, with % CV values less than 30%, and male and female animals presented with mean percentages of 53.5% and 38.6% CD3+/CD8+/CD107a+ cells (degranulated) and 43.2% and 32.3% CFSE+/7AAD+ (killed) P815 target cells following anti-CD3 stimulation, whereas the mean control values for each population were less than 6% and 10% for male and female animals, respectively. Stability assessments demonstrated that PBMC samples must be isolated, cultured, and labeled on the day of blood draw; however, labeled samples can be stored up to 22 hours at 2-8ºC prior to cytometer acquisition. Collectively, these data demonstrate a precise and reproducible method suitable for use on preclinical toxicology studies for the assessment of Ctx function.

P432

Comparative Analysis of Methodologies Assessing QT Risk in Large Animal Models. *K. Kearney*[1], *K. Landis*[1], *P. Atterson*[1]. WIL Research, Ashland, OH, USA[1].

The ICH S7B guidelines were established to assess the potential of new chemical entities to affect ventricular repolarization and proarrhythmic risk. In some instances, pharmaceuticals causing delayed repolarization (prolongation of the QT interval) have been associated with proarrhythmic episodes including, but not limited to, torsadogenicity. This biomarker (QT duration) has thereby been viewed as a determining endpoint for the evaluation of cardiovascular risk assessment in large animal models.

Factors may influence the QT duration independent of pharmacological action. The guidelines acknowledge the non linear, inverse relationship, to heart rate; and further suggest methods of accounting for variables. The purpose of the current investigation was to evaluate different methodologies of QT corrected for changes in heart rate (QTc) using standardized correction models as well as individualized correction factors in large animal models (canine, nonhuman primate, and minipig).

As not all episodes of prolongation assume proarrhythmic or torsadegenic risk, a measure of QT instability was used as secondary tier of evaluation to further define QT risk in the presence of delayed repolarization.

P433

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500 Series—Safety Evaluation Pharmaceuticals

P500

An Enantiomerically Pure Formulation of Esmolol Attenuates Hypotension and Preserves Efficacy in Dogs. *J. McKee[1], B. Rabinow[1], J. Daller[1].* Baxter Healthcare Corporation, Round Lake, IL, USA[1].

BREVIBLOC® (esmolol HCl) is a selective beta-1 adrenergic receptor antagonist for the treatment of supraventricular tachycardia and intra- and postoperative tachycardia and/or hypertension, and is currently marketed as a racemate (RS). The S-enantiomer (S) has been shown to be two times more efficacious than RS on an equal weight basis (mcg/kg/min) in lowering drug-induced elevations in heart rate, suggesting that S possesses the beta-1-blocking activity of RS, and that the R-enantiomer (R) is without pharmacodynamic effect. Hypotension is the most frequently reported adverse event in patients receiving esmolol HCl. The aim of this study was to investigate whether R contributes to the hypotension by comparing RS to S. Mongrel dogs were anesthetized and instrumented to obtain direct blood pressure and heart rate. RS and S (equal to one-half of RS on a mcg/kg/min basis) were infused separately for 15 minutes, each at multiple infusion rates (N=4–7). Immediately following each infusion, a bolus dose of isoproterenol was given to assess the effectiveness of RS and S to block the increase in heart rate, and to assess their potential to induce hypotension. Hypotension was evaluated at the end of the infusion and just prior to isoproterenol. The S-only formulation of esmolol exhibited less hypotension compared with RS while maintaining the same degree of heart rate control over a broad range of infusion rates (figure). In summary, these data indicate that in the dog the R-enantiomer provides no apparent efficacy (heart rate control) and contributes significantly to the hypotension associated with esmolol HCl.

P501

Assessment of Pharmacological Effects and Toxicities of Allopurinol When Administered Alone or in Combination with a Urate Transporter 1 Inhibitor in Rats and Relevance to Humans. *R. Yan[1], C. Jaramillo[1], K. Tieu[1], D. Zhou[1], Z. Shen[1], S. Baumgartner[1], L. Yeh[1], C. Wilker[1].* Ardea Biosciences, Inc (A Wholly Owned Subsidiary of AstraZeneca PLC), San Diego, CA, USA[1].

Allopurinol, a xanthine oxidase (XO) inhibitor and first-line therapy for gout, blocks the conversion of hypoxanthine/xanthine to uric acid (UA) in the final step of purine metabolism in man, thus lowering serum UA (sUA). In animals, sUA is maintained at low levels as UA is further metabolized to allantoin by uricase, which is not present in humans. Nonclinical safety assessment of allopurinol was previously conducted in the 1960s. Recent rat studies with allopurinol using current standards showed allopurinol increased urinary excretion of hypoxanthine/xanthine by 10- to 260-fold, an expected pharmacological effect of XO inhibitors. This effect was seen in humans but at significantly less magnitude of 4- to 10-fold increase at 300 mg qd allopurinol dosing. Allopurinol in rats induced kidney toxicity characterized by tubular nephropathy due to xanthine crystal formation as seen previously and is characteristic of XO inhibitors. Allopurinol/oxypurinol exposures in rats at toxic doses were lower than that in humans, providing no safety margin for human risk assessment. Allopurinol human toxicity is known to be associated with hypersensitivity syndrome, which is not predicted by rats. Based on the current data, using rats as models to predict human toxicity remains challenging. Additionally, sUA lowering may be improved in humans when combining a XO inhibitor with urate transporter 1 (URAT1) inhibitors, such as lesinurad, through increasing urinary excretion of UA. Co-administration of allopurinol with lesinurad for 13 weeks in rats did not result in new or increase allopurinol-induced toxicities even though allopurinol/oxypurinol exposure increased with the addition of lesinurad.

P502

Behavioral, Cardiovascular, and Bioanalytical Changes Associated with Morphine Dependence in Cynomolgus Monkeys. *J. Toot[1], B. Rodriguez[1], K. Landis[1], M. Beck[1], P. Atterson[1].* WIL Research, Ashland, OH, USA[1].

The US FDA and EMEA dependence potential guidelines for novel drugs able to cross the blood-brain-barrier require physical dependency assessments to be conducted as part of an abuse liability program. Although the rodent is the most commonly used animal model in these assessments, testing in the NHP may be necessary depending on the drug class, mechanism of action, and metabolic profile of the test drug. The objectives of this study were to: 1) assess neurobehavior, body weight, and food consumption changes following treatment, 2) monitor plasma morphine levels, and 3) assess dependence potential during morphine withdrawal. Morphine sulfate was administered to 5 Cynomolgus males (that were implanted with telemetry probes) at 3–6 years of age on an escalating (1, 2, 4, and 5.6 mg/kg/day) dose regimen by BID subcutaneous injection over a period of 4 weeks, followed by a 2-week withdrawal phase. During the treatment and withdrawal phases, all animals were monitored for body weight (BW), food consumption (FC), neurobehavioral observations (FOB) and cardiovascular parameters (CP). Blood was collected prior to and following each morphine escalation, and during withdrawal. During treatment, BW and FC remained stable, with FOB, CP, and bioanalytical parameters exhibiting changes consistent with increased morphine exposure. Following the cessation of treatment, classic withdrawal effects involving BW, FC, and CARDIO, along with noted masking of behaviors and elevated levels of agitation were present. These results support the validity of the methodology, model, and general procedures utilized by WIL Research as part of the NHP physical dependence testing paradigm.

P503

Biodistribution of Reolysin® (Pelareorep) in Sprague-Dawley Rats to Support the Use of This Orphan Virus As an Investigational Drug for Cancer Treatment.

R. Tavcar[2], R. Chakrabarty[1], H. Tran[1], A. Hagerman[1], S. Serl[1], B. Thompson[1], M. Coffey[1], I. Boulay[2], M. Bigras[2], A. Parenteau[2], R. Forster[3], F. Debra[2]. Oncolytics Biotech Inc., Calgary, AB, Canada[1]; CiToxLAB North America, Laval, QC, Canada[2]; CiToxLAB France, Evreux, France[3].

Reolysin® (pelareorep) is a clinical formulation of the human Reovirus Type 3 Dearing strain. The clinical safety and efficacy of Reolysin® as an oncolytic therapy in humans is being tested on an assortment of cancer indications as a mono and/or combination therapy. Reovirus has many inherent characteristics that make it a potential candidate for virotherapy, including: the rapid and natural spread through the haematogenous route, the ability to overcome immunological barriers thereby reaching tumor sites, and being replication-competent. The purpose of this study was to elucidate the biodistribution pattern of Reolysin® in healthy Sprague-Dawley rats. Following a single 15-minute intravenous infusion (at dose levels of 6.5E+07, 6.5E+08 and 6.5E+09 viral particles/animal, based on an average body weight of 225 grams) via the tail vein in Sprague-Dawley rats, the levels of virus genome were determined in 16 organs/tissues by RT-qPCR (Reverse Transcriptase-Quantitative Polymerase Chain Reaction) over a 336 hr follow-up period. Maximal reovirus RNA levels were observed in the spleen, indicating its involvement in viral uptake and clearance, followed by heart, ovaries, tail (infusion site), liver and lungs. All the organs/tissues demonstrated unquantifiable levels of reovirus genome at the end of the follow-up period, suggesting substantial to complete viral clearance. Several studies in the last decade have described the use of reovirus for treating ovarian cancers. An increase of reovirus genome in ovaries at 24-hr postinfection was noted. The results will aid in the design of additional exploratory clinical trials for Reolysin®.

P504

Calcium Chloride-Stimulated Plasma Calcitonin and Thyroid C-Cell Mass, Hyperplasia, and Neoplasia in Rats following Twice Weekly Subcutaneous Injection of Dulaglutide for 52 and 93 Weeks.

R. Byrd[1], S. Sorden[2], T. Pienkowski[2], R. LaRock[2], J. Wijsman[1], H. Smith[1], J. Blackbourne[1], T. Rosol[3], G. Long[4], J. Vahle[1]. Eli Lilly and Company, Indianapolis, IN, USA[1]; Covance Laboratories Inc, Madison, WI, USA[2]; The Ohio State University, Columbus, OH, USA[3]; Experimental Pathology Laboratories Inc, Sterling, VA, USA[4].

Dulaglutide (DU) is a once weekly long-acting human GLP-1 receptor agonist (GLP-1RA) in Phase 3 clinical development. The tumorigenic potential of DU was evaluated in a 2-year carcinogenicity study in Crl:CD (SD) rats injected twice weekly with subcutaneous DU doses of 0, 0.05, 0.5, 1.5, and 5 mg/kg (0.5-, 7-, 20-, and 58-fold the human AUC, respectively). DU treatment increased thyroid C-cell hyperplasia and neoplasia in rats similar to other long acting GLP-1RAs[1,2,3]. Diffuse C-cell hyperplasia and C-cell adenoma were increased at ≥0.5 mg/kg, and C-cell carcinomas were numerically increased at 5 mg/kg. However, like other long acting GLP-1RAs[1,2,3,4], C-cell neoplasia was not associated with decreased survival. The NOEL for C-cell hyperplasia and neoplasia was 0.05 mg/kg. A separate 52-week study in Crl:CD (SD) rats assessed C-cell volume using morphometric and calcium chloride-stimulated plasma calcitonin measurements. Rats received twice weekly subcutaneous injections of 0 or 5 mg/kg DU (58-fold the human AUC) for 52 weeks. DU increased focal C-cell hyperplasia; however, increases in C-cell volume did not precede the identification of focal C-cell hyperplasia. Consistent with the lack of morphometric changes in C-cell volume, no effects of DU were found on diffuse C-cell hyperplasia or on basal or calcium-stimulated plasma calcitonin. These data indicate that diffuse increases in C-cell volume in rats do not occur early during chronic treatment with DU.

[1]Knudsen et al. *Endocrinol* 2010; 151(4):1473–1486.

[2]US FDA. *BYDUREON SBA* 2012.

[3]EMA. *Lyxumia EPAR* 2012.

[4]Parks and Rosebraugh. *NEJM* 2010; 362(9):774–777.

P505

CLS1001 Suprachoroidal Injectable Suspension of Triamcinolone Acetonide Is Well Tolerated in the Albino Rabbit.

R. Verhoeven[1], K. Viaud-Quentric[2], F. Cacciamani[2], S. Patel[1]. Clearside Biomedical, Alpharetta, GA, USA[1]; Iris Pharma, Nice, France[2].

Purpose: To evaluate the ocular tolerability and toxicokinetics of CLS1001 Suprachoroidal Injectable Suspension (40 mg/mL triamcinolone acetonide, TA) in a GLP study in the New Zealand White rabbit.

Methods: On Day 0, rabbits (4/sex/group) were administered a single bilateral suprachoroidal injection of vehicle or CLS1001 (4 mg TA) using a 33g 750µm Clearside Biomedical microneedle. Clinical observations, body weights, food consumption, slit lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure assessment (IOP), central corneal thickness (CCT), electroretinography (ERG), serum chemistry and hematology, and systemic exposure were assessed up to 13 weeks postdose. Animals were sacrificed on Day 1 and Week 13 for macroscopic observations at necropsy and ocular histopathology.

Results: There were no treatment- or administration-related adverse effects on body weight, food consumption, clinical observations, serum chemistry and hematology, ophthalmic examinations, CCT, or ERG. A mild, transient increase in IOP of 2–3 mmHg was observed in the CLS1001 group when compared with vehicle; this resolved by Week 13 and was not considered adverse. Systemic exposure to TA was minimal, and similar to that observed after intravitreal injection. Suprachoroidal administration of vehicle or CLS1001 did not induce adverse effects as assessed at necropsy or by ocular histopathology.

Conclusion: A single bilateral suprachoroidal injection of CLS1001 Suprachoroidal Injectable Suspension using a Clearside Biomedical proprietary microneedle was well tolerated in the albino rabbit and resulted in limited systemic exposure to TA. These data suggest that administration into the suprachoroidal space using a microneedle may be a safe, nonsurgical option for ocular drug delivery of TA.

P506

Evaluation of Background Data from rasH2 Mice Used in 26 Week Carcinogenicty Studies. *P. Mansell[1], K. Bonnette[2], A. Adamou[1], J. Jolette[1], L. Kangas[1], M. Morse[2].* Charles River Laboratories Pre Clinical Services, Senneville, QC, Canada[1]; Charles River Laboratories Pre Clinical Services, Spencerville, OH, USA[2].

The ICH Harmonised Tripartite Guideline Testing for Carcinogenicity of Pharmaceuticals S1B recognizes the use of additional *in vivo* models to assess carcinogenetic potential in rodents as an alternative to the conventional 2 year bioassay. Data from rasH2 (CByB6F1-Tg(HRAS)2Jic) mice housed in two conventional nonbarrier facilities, was evaluated. Endpoints included survival, body weight, food consumption and incidence of common neoplastic lesions. The study designs incorporated a positive control group receiving N-Nitrosomethylurea (NMU) in addition to appropriate vehicle controls. Survivability in controls after 26 weeks ranged from 88 to 100%, survival in positive controls was as low as 6%. Control body weights ranged from 32.1g (SD 3.26) in males to 25.2g (SD 1.57) in females. Bodyweights in the positive control were between 10–6% lower than the male and female controls, respectively. Food consumption ranged from 6.4 g/animal/day (SD 0.33) in males to 6.2 g/animal/day (SD 0.59) in females with lower consumption being noted in the positive control. Spontaneous neoplastic lesions in controls were limited to lung (bronchioloalveolar adenoma) and spleen (hemangiosarcoma) in males and systemic lymphoma in females. Mice administered NMU developed high incidences of forestomach squamous cell papillomas/carcinomas or malignant lymphomas. Based on the high levels of survivability in controls, the stable growth patterns and the presence of characterized neoplastic tumor profiles, the rasH2 mouse model continues to be an appropriate alternative model for the assessment of carcinogenic potential of pharmaceuticals.

P507

Evaluation of Serum Amylase and Lipase, Expanded Pancreatic Histology and Histomorphometry in Zucker Diabetic Fatty (ZDF) Rats following Twice Weekly Subcutaneous Injections of Dulaglutide for 13 Weeks. *A. Usborne[1], R. Byrd[1], J. Blackbourne[1], J. Sullivan[1], J. Meehan[2], F. Poitout-Belissent[2], A. Prefontaine[2], J. Vahle[1].* Eli Lilly and Company, Indianapolis, IN, USA[1]; Charles River Laboratories, Preclinical Services Montreal, Senneville, QC, Canada[2].

Dulaglutide (DU) is a once weekly long-acting human GLP-1 receptor agonist (GLP-1RA) in Phase 3 clinical development. GLP-1RA therapy has been implicated as a risk factor for acute pancreatitis in diabetic humans. Studies examining exocrine pancreatic structure in rodents have yielded conflicting results ranging from no discernible effects to evidence of pancreatic inflammation and/or proliferation of ductal epithelium. The effects of DU doses of 0.5, 1.5, and 5 mg/kg (3-, 8-, and 30-fold the human AUC, respectively) in male Zucker diabetic fatty (ZDF) rats were examined on serum enzyme biomarkers, glucose, hemoglobin A1c (HbA1c), and pancreatic morphology. At termination, pancreata were collected, fixed, processed, serially trimmed, and embedded. Pancreatic sections (≥6/rat) were stained with hematoxylin/eosin. Adjacent sections were stained using immunohistochemistry with an epithelial marker (cytokeratin 19), and either a proliferation marker (Ki67) or an apoptosis marker (TUNEL). Efficacious reductions in glucose and HbA1c occurred at all DU doses. Modest increases in total and pancreatic amylase activities, but not lipase, occurred at all doses without individual microscopic inflammatory correlates. Microscopic DU-related changes included increased incidence/severity interlobular ductal epithelium without ductal cell proliferation (≥0.5 mg/kg), increased acinar atrophy with/without inflammation (≥1.5 mg/kg) and increased incidence/severity of neutrophilic acinar pancreatic inflammation (5 mg/kg); only the latter finding was considered adverse. These data indicate that DU treatment was associated with a modest exacerbation of the spontaneous lesions of the exocrine pancreas that occur in the ZDF rat model.

P508

Genotoxic Assessment of Rosuvastatin by the Comet Assay *In Vitro*. *A.A. Berber[1], S. Yilmaz[2], H. Aksoy[1].* Sakarya University, Sakarya, Turkey[1]; Ankara University, Ankara, Turkey[2].

Rosuvastatin is one of the drugs called statins and it is synthetic lipid-lowering agent. In this study, we investigated the genotoxic effects of rosuvastatin in human peripheral lymphocytes by using *in vitro* comet assay. For this purpose, peripheral venous blood was collected from healthy nonsmoking adults, two males and two females aged 20–22 years. The isolated lymphocytes were treated 0.0625, 0.125, 0.25, 0.5, and 1 µg/mL concentrations of rosuvastatin for 1 hr. In this assay, significant increases in comet tail length and tail moment were observed at 0.0625, 0.5, 1 µg/mL concentrations. The comet intensity was significantly increased in all concentrations except 0.0625 µg/mL. According to these results, rosuvastatin is clastogenic in isolated lymphocytes *in vitro*. Further studies should be conducted in other test systems to evaluate the full genotoxic potential of rosuvastatin.

P509

Immunosafety of Furfural Exposure in Rodents. *A. Katz[1], J. Wagar[1], A. Burke[2], G. Burger[3], E. Bunting[3], S. Somera[3].* toXcel, LLC, Gainesville, VA, USA[1]; WIL Research, Ashland, OH, USA[2]; Agriguard Company, LLC, Cranford, NJ, USA[3].

Furfural (2-furaldehyde; CAS 98-01-1) occurs ubiquitously in nature and it is classified as GRAS (FEMA No. 2489) for direct food additive use as a flavoring agent. It is also used as a solvent and it has a wide variety of industrial applications. Furfural has recently gained prominence in the US as an effective soil nematocide and fungicide for turf and ornamental uses. Over the course of many years of investigation of its safety for manufacturing workers, formulators, applicators and the general public, an extensive database is available from which to assess potential toxicity to mammalian target organ systems with a high level of confidence. Existing data from acute, subchronic and chronic toxicity studies in rodents, as well as specialized testing to assess immunological parameters, provides the foundation for a thorough evaluation of immune response to furfural exposure. Parameters examined from repeated dose toxicity studies included absolute and relative lymphoid organ weights, hematological determinations, and histopathological examinations of lymphoid tissues. Specialized testing was also conducted with furfural administered via gavage at dosage levels up to and including 80 mg/kg/day for 28 consecutive days in male SD rats, in accordance with US EPA Health

Effects Guideline OPPTS 870.7800; this assessment included peripheral blood phenotyping, a splenic antibody forming cell (AFC) assay for T-cell dependent antibody response to sheep RBCs, and a natural killer (NK) cell assay for evaluation of innate immune response. Results of all studies showed no significant adverse effect on immunological function from exposure to furfural.

P510

Induction of Severe Hemophilia A in Cynomolgus Monkeys Using Antihuman FVIII Antibody. *J. Forget[1], L. Huard[1], F. Poitout[1], A. Sehgal[2], B. Lise[1].* Charles River, Montreal, QC, Canada[1]; Alnylam Pharmaceuticals Inc, Cambridge, MA, USA[2].

The availability of an animal model for a specific disease is a considerable advantage for product development and efficacy assessment. Therapies designed to restore or enhance the clotting activation have the potential to cause exaggerated thrombosis leading to hemorrhages and potentially death when tested in normal individuals. We have developed a model that establishes a transient and severe hemophilia condition induced by Factor VIII deficiency. Deficiencies in Factor VIII result in a bleeding disorder termed hemophilia A. Hemophilia was induced by once weekly intravenous injections of antihuman FVIII antibody (Ab) at increasing doses until the maximum inhibition level of FVIII activity (<1%) was reached. Factor FVIII activity, activated clotting time (ACT), and coagulation parameters [activated partial thromboplastin time (APTT), and prothrombin time (PT)] were monitored in two cynomolgus monkeys/sex. Administration of FVIII Ab elicited dose-related decreases in FVIII activity at doses ≥1,000BU/kg with almost complete inhibition at 20,000BU/kg, four hours postinjection. The effect partially reversed two days after the FVIII Ab injection and FVIII activity was back to pretreatment level by one week. Correlating increases in ACT were observed at ≥1,000BU/kg(+125%) and APTT increases at ≥10,000BU/kg(+192%), four hours postinjection. There were no clinical observations noted with FVIII Ab administration or effects on food consumption and bodyweight. This model presents an advantage for animal safety due to its transient nature as oppose to a permanent hemophilia condition. These results suggest that administration of FVIII Ab every two days at a dose level of 20,000BU/kg would be sufficient to maintain the hemophilic condition over multiple days.

P511

Intestinal Toxicity Caused by a Small Molecule Tankyrase Inhibitor in Mice Is Reversible. *Y. Zhong[1], P. Katavolos[1], T. Nguyen[1], J. Boggs[1], A. Sambrone[1], D. Kan[1], M. Merchant[1], E. Harstad[1], D. Diaz[1], M. Zak[1], M. Costa[1], M. Schutten[1].* Genentech, South San Francisco, CA, USA[1].

Tankyrase inhibitors are being studied as potential treatment for colorectal cancer (CRC), which is frequently associated with activated WNT signaling. TNKS inhibition reduces Wnt signaling by stabilizing Axin leading to destruction of β-catenin. However, Wnt/β-catenin signaling is critical for intestinal tissue homeostasis and Tankyrase inhibitors have been shown to cause intestinal toxicity in mice. The purpose of the current study is to investigate the reversibility of this intestinal toxicity. A small molecule Tankyrase inhibitor was administered orally (QD) to CD-1 mice at 0 (vehicle), 25 or 100 mg/kg for 14 days, and the reversibility of the intestinal toxicity was assessed after 7 or 14 days of recovery. Toxicity assessments included mortality, clinical observations, body weights, clinical pathology, organ weights and macroscopic and microscopic anatomic pathology. Tankyrase inhibition caused dose-dependent intestinal toxicity after 14 days of dosing. At 25 mg/kg/day (AUClast = 41.8 hr*μM, tolerated), the intestinal toxicity was minimal-mild and comprised of villus blunting, epithelial degeneration and mild enteritis, which was fully reversed after 14 days of recovery. In contrast, at 100 mg/kg/day (AUClast = 75.2 hr*μM) the intestinal toxicity was moderate-marked, characterized by multifocal-regional necrotizing and ulcerative enteritis of primarily the small intestine leading to premature deaths in some animals. After 14 days of recovery, the intestinal toxicity was partially reversed with evidence of crypt and villus regeneration, mildly blunted villi, and/or scarring/inflammation of the submucosa. In conclusion, the intestinal toxicity caused by tolerated doses of Tankyrase inhibitors is expected to be fully reversible after adequate recovery.

P512

Investigation of Control Animal Exposure to Test Article in a Cynomolgus Monkey 90-Day Oral Toxicity Study. *C. Brynczka[1], R. Sanchez[2], R. Rush[3].* Gradient, Cambridge, MA, USA[1]; Seaside Therapeutics, Cambridge, MA, USA[2]; Idenix Pharmaceuticals, Cambridge, MA, USA[3].

Preservation of the naïve state of control animals within a toxicity study is a fundamental requirement for the adequate assessment of test article effects. In a 90-day toxicity study performed on a small molecule by oral gavage in the cynomolgus monkey, plasma test article concentrations above the lower limit of quantitation and approaching pharmacologically active exposure levels were detected in study control animals at sequential toxicokinetic sampling time points. An investigation eliminated gavage, formulation, sample preparation, and bioanalysis cross-contamination. Concentration-time plots for individual control animal plasma concentrations presented evidence of test article distribution/elimination and was suggestive of inadvertent exposure within the vivarium. The test article was administered at dose levels of 50, 250, and 1,000 mg/kg/day in 0.5% methylcellulose, and study group cages were organized in ascending order such that control animals were maintained against the wall opposite to the high dose group. Clinical signs in high dose animals included white feces and was indicative of poor test article solubility in dosing formulation and low gastrointestinal absorption. Alignment of toxicokinetic sampling times to room cleaning intervals determined that daily room cleaning times preceded toxicokinetic sampling. Routine room cleaning included high-pressure rinsing of the cage pan to a centrally located drain. Evidence therefore supported aerosolization of poorly bioavailable test article during room cleaning and subsequent control animal inhalation or oral exposure. These data illustrate the contribution of test article bioavailability to the routine planning of study conduct in order to prevent inadvertent control animal exposure in toxicity studies of prolonged duration.

P513
Withdrawn

P514
Occurrence of Spontaneous Pancreatic Lesions in Normal and Diabetic Rats May Confound the Nonclinical Assessment of Glucagon-Like Peptide (GLP)-1 Elevating Therapies. *K. Chadwick[1], D. Roy[4], A. Fletcher[1], C. Parrula[1], A. Bergholm[5], R. Mangipudy[1], E. Janovitz[2], M. Graziano[3], T. Reilly[3].* Bristol-Myers Squibb, New Brunswick, NJ, USA[1]; Bristol-Myers Squibb, Hopewell, NJ, USA[2]; Bristol-Myers Squibb, Lawrenceville, NJ, USA[3]; Amylin, San Diego, CA, USA[4]; AstraZeneca, Mölndal, Sweden[5].

GLP-1 therapeutics, including GLP-1 receptor agonists and dipeptidyl peptidase (DPP) 4 inhibitors, have glycemic and potential nonglycemic benefits for Type 2 diabetes, but recent publications raised concerns over potential increased risks of pancreatitis and pancreatic cancer. These literature reports have attributed a variety of findings in rodents (including ductular metaplasia, exocrine pancreas degeneration and pancreatic duct abnormalities) to GLP-1 therapeutics. However, extensive toxicology experience with saxagliptin (DPP4 inhibitor) and exenatide (GLP-1 analog) has not demonstrated drug-related exacerbation of pancreatitis or neoplasia, with hundreds of animals being dosed for up to two years at exposure multiples up to 2200x therapeutic levels. We hypothesized that the lesions attributed to GLP-1 therapeutics are commonly observed in the absence of drug treatment, similar to those in control animals. Therefore, we endeavored to characterize the incidence of spontaneous pancreatic lesions in 3 rat strains (Sprague-Dawley [SD], Zucker diabetic fatty [ZDF] and HIP rats [rats expressing human islet amyloid polypeptide]; n=36/group) under different feeding conditions (normal or high fat diet) over a 4-month period. Pancreatic findings in all groups included focal exocrine degeneration, atrophy, inflammation, ductular cell proliferation and/or observations in large pancreatic ducts similar to those described in the literature with an incidence of exocrine atrophy/inflammation in SD (42% [HF]–72% [norm] of rats) > HIP (39%) > ZDF (6%). These data indicate that pancreatitis is a common background finding in rats. Thus, many of the pancreatic lesions that are described as resulting from GLP-1 elevating therapies occur regularly in untreated normal and diabetic animals.

P515
Preclinical Studies of SB 9200 for Hepatitis Treatment. *R. K. Iyer[1], J. Marquis[1], M. Harter[2], L. Cochrane[2].* Spring Bank Pharmaceuticals, Milford, MA, USA[1]; MPI Research, Mattawan, MI, USA[2].

SB 9200 is a novel dinucleotide with potent antiviral activity against multiple HCV genotypes as well as against wild type and resistant variants of HBV. SB 9200 activates RIG-I and NOD2, the cytosolic proteins involved in virus detection, causes the activation of the IFN signaling cascade and induction of antiviral state in cells. Studies were conducted in rats and cynomolgus monkeys to evaluate the pharmacokinetics, potential toxicity and safety of orally administered SB 9200. These studies included dose range-finding and 14-day repeat-dose toxicology studies in rats and monkeys, and safety pharmacology including a cardiovascular study in monkeys, and neurobehavioral and respiratory studies in rats, and an *in vitro* hERG assay in HEK cells. Overall, SB 9200 was well tolerated in all studies. Major toxicological findings were limited to mild increases in ALT and triglycerides following 14 days of repeat dosing at 360 mg/kg/day to monkeys. These changes were reversible at the end of the 14-day recovery period. In conclusion, SB 9200 is a potent antiviral agent with an excellent safety profile and is currently being evaluated in human clinical trials against HCV.

P516
Pulmonary Arterial Hypertension in Rats Induced by Combination of Semaxanib and the Presence of a Low Oxygen Environment: Time Course of Pulmonary Artery Pressure Increases Measured by Telemetry. *J. Huang[1], L. Neves[1], P. Senese[1], M. Gralinski[1].* CorDynamics, Chicago, IL, USA[1].

Previous work from our labs has demonstrated development of increased terminal pulmonary artery pressures, hypertrophy of pulmonary arterial vascular smooth muscle, and proliferation of the endothelial vascular lumen in rats following extended exposure to hypoxia and VEGF-receptor antagonist. We have also reported the efficacy of bosentan and sildenafil in this preparation. In this study we continue to describe this model by evaluating the time course of PAH development using telemetry catheters implanted in the pulmonary artery. Male Sprague-Dawley rats (240–370 gms) were surgically instrumented with telemetry catheters in the pulmonary artery, allowed to recover, then kept in their home cages inside a hypoxic room. Baseline atmospheric oxygen (21%, Chicago, IL—600 ft above sea level) was reduced to 11.5% (15,500 ft above sea level equivalency) using an oxygen scrubbing generator. Prior to placement inside the room, each rat received a single dose of semaxanib (200 mg/kg, s.c.). Rats were maintained in hypoxia for six weeks and pulmonary artery pressures were recorded daily via telemetry. During the course of six weeks hypoxia following semaxanib treatment, systolic pulmonary artery pressures (SPAP) increased on a daily basis. Baseline values for SPAP (pre-hypoxia) were 36 ± 2 mm Hg. At 14, 28, and 42 days into the study, SPAP was 77 ± 8 mm Hg, 114 ± 11 mm Hg, and 131 ± 6 mm Hg respectively. In summary, this data can support the timing selection to initiate intervention treatment in the context of hypoxia/semaxanib-induced pulmonary arterial hypertension in the rat.

P517
RBP-8000: A Dose Escalation Cocaine Interaction Study in Male Sprague-Dawley Rats. *D. McGee[1], S. Godin[2].* Reckitt-Benckiser Pharmaceuticals, Richmond, VA, USA[1]; Smithers Avanza, Gaithersburg, MD, USA[2].

The purpose of this study was to evaluate the toxicity resulting from administration of cocaine by intraperitoneal injection route followed by intravenous dosing of RBP-8000, a cocaine esterase, to rats. Thirty-six male rats were assigned to study (6/group) and treated on Study Day 1 with cocaine (80 or 160 mg/kg) followed approximately three minutes later by iv injection of RBP-8000 (3 or 10 mg/kg) or placebo. Rats were observed continuously following cocaine administration until recovery or death. Cageside observations, physical examinations, body weight, food

consumption, serum chemistry and hematology were evaluated. Rats were euthanized and necropsied on Day 15. There were no RBP-8000-related effects on mortality, gross pathology or organ weights. Mortality occurred in 3/6 and 5/6 rats following 80 mg/kg and 160 mg/kg, doses of cocaine respectively, without RBP-8000 treatment. Mortality from 80 mg/kg cocaine was reduced to 1/6 with 3 mg/kg or 10 mg/kg RBP-8000. Mortality following 160 mg/kg cocaine was 5/6 and 3/6 with 3 and 10 mg/kg RBP-8000, respectively. Postdose observations were typical of cocaine with the incidence and severity reduced following RBP-8000. Body weight loss was reduced and food consumption tended to be higher as compared with cocaine-only controls. AST and ALT were lower in RBP-8000 groups compared to cocaine controls. Improved survival, food consumption, body weight changes and postdose observations, as well as a better liver enzyme profile when compared to controls that received only cocaine, demonstrated RBP-8000 compatibility in the presence of cocaine, and confirmed a rescue effect of RBP-8000 for cocaine toxicity.

P518

Rodent Toxicology Studies for a Novel Anticancer Agent, SOR-C13. *J. Stewart[1], J. Daniels[2], M. Luksic[2], G. Goodfellow[2], T. Ilenchuk[1].* Soricimed Biopharma Inc., Moncton, NB, Canada[1]; Intrinsik Health Sciences Inc., Mississauga, ON, Canada[2].

Soricidin is a proprietary, 54-mer peptide that was isolated from the sub-maxillary saliva gland of the Northern Short-tailed Shrew. SOR-C13 is a novel 13-mer synthetic peptide based on the first 13 amino acids of the C-terminus of soricidin. SOR-C13 inhibits the function of TRPV6 [the 6th member of the transient receptor potential (TRP) vanilloid cation channel group] and selectively induces apoptosis and inhibits cell proliferation in cell lines from ovarian and breast cancers as well as a number of other tumor types. Xenograft studies in mice have confirmed the *in vivo* effect of SOR-C13 as a single agent against ovarian and breast cancer tumors, and have also provided evidence of enhanced activity in combination with carboplatin/paclitaxel (ovarian cancer model) and paclitaxel (breast cancer model). As part of the program undertaken to support entry into clinical trials, a GLP-compliant 28-day IV toxicity study of SOR-C13 was conducted in Sprague-Dawley rats (n=10/sex/group). Animals were treated with SOR-C13 at dose levels of 0, 100, 200, or 400 mg/kg/day (0, 600, 1,200, or 2,400 mg/m^2/day, respectively) for 28 consecutive days. SOR-C13 was generally well tolerated. At 400 mg/kg/day, there were adverse clinical signs of decreased activity, shallow respiration, blue or pale skin, paws, muzzle, and/or mucous membrane, with slight to moderate swelling of the paws. Overall, a NOAEL was established at 200 mg/kg/day (1,200 mg/m^2/day) and the dose Severely Toxic to 10% of the animals (STD10) was >400 mg/kg/day (>2,400 mg/m^2/day) which corresponded to a mean combined sex AUC of 8,005 µg•min/mL).

P519

Short-Acting and Long-Acting Buprenorphine Therapeutic Drug Levels following Single Subcutaneous Administration in Diabetic Yucatan Miniswine. *B. C. Hanks[1], S. Schlink[1], L. D. Brown[1], M. Luna[2], Y.S. Liu[2], J. Liu[1], A. Stricker-Krongrad[1], G. F. Bouchard[1].* Sinclair Research Center LLC, Auxvasse, MO, USA[1]; KCAS LLC, Shawnee, KS, USA[2].

Sustained analgesia for animals involved in potentially painful procedures is required for animal welfare and ethics. Buprenorphine HCl (BUP) is routinely used in swine on a BID basis (dose range 0.05–0.2 mg/kg im, sc, or iv). We designed a study to assess buprenorphine analgesics in a cross-over design in four diabetic Yucatans weighing approximately 30 kg. For BUP, animals were dosed subcutaneously (left flank) with either 0.01 mg/kg (low-dose) or 0.02 mg/kg (high-dose), while for BUP SR the dose was either 0.12 mg/kg (low-dose) or 0.24 mg/kg (high-dose) s.c. Washout was set at 9d before animals were redosed. For BUP, blood samples were collected at predose, 0, 15, 30, 60, 120, 240, and 480 minutes (8 timepoints targeted). For BUP SR, samples were collected at predose, 0, 30, 60, 90, 240, and 480 mins, and 12h, 24h, 48h, 72h, and 96h (12 timepoints targeted). Buprenorphine was analyzed in K_2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (quantitation range 50 to 5,000 pg/mL). Results were reported in picograms/mL of plasma. BUP peaked at 2192 pg/ml (high-dose) or 842 pg/mL (low-dose). BUP drug was onboard for 240–480 mins (above 0.1 ng/mL efficacious threshold). BUP SR peaked at 1795.5 pg/ml at 240 mins (high-dose) and 1532 pg/mL at 30 mins (low dose). BUP SR was present in plasma for 96 hrs (above 0.1 ng/mL). In conclusion, data show that these dose levels provide plasma levels of drug for analgesia (>0.1 ng/mL) for 8 hr (BUP) or for at least 96 hr (BUP SR).

P520

Subchronic Oral Toxicity Study of 2-Deoxy-D-Glucose (2-DG) in F344 Rats with a 15 Day Recovery Period. *N.R. Bordelon[3], A.J. Koester[3], T.P. Arndt[3], S.P. Hong[3], A.M. Brys[3], K.M. Patton[3], T.P. Sutula[2], P.S. Joshi[1].* National Center for Advancing Translational Sciences (NCATS), Besthesda, MD, USA[1]; University of Wisconsin, Madison, WI, USA[2]; Battelle Memorial Institute, Columbus, OH, USA[3].

2-Deoxy-D-glucose (2DG), a glucose analog, is being developed as a novel anticonvulsant and disease-modifying remedy for epilepsy patients. A study was conducted to determine its toxicity when gavaged BID for 45 days followed by 15 days recovery. Rats (five/sex/group/sacrifice point) were assigned to either vehicle or three dose groups (50, 125, or 375 mg/kg BID) with day 7, 14, 21, 45, and 60 sacrifice time points. Separate TK animals were assigned for TK analysis. High-dose group was discontinued on day 22 due to mortality with clinical signs of lethargy, rough coat and reduced feces. On day 8 and 15, high-dose male rats had significantly reduced body weights. C_{max} and AUC_{last} values increased dose dependently with slight accumulation on day 45 compared to day 1. Decrease in red blood cells, hemoglobin, and hematocrit with increase in reticulocytes was noticed in males from high-dose group on day 14. In females, decreased hematocrit in both mid- and highdose groups was observed on day 21. Alanine aminotransferase and aspartate aminotransferase levels were elevated throughout dosing in high- and middose groups corroborating with hepatocellular damage. Plasma NT pro-

BNP levels increased from day 14 and were generally associated with cardiac histopathology (vacuolar degeneration). Observed toxicity appeared to be reversible. In conclusion, male rats seem to be more sensitive to 2-DG toxicity. No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 50 mg/kg for 2DG administered BID by oral gavage. (Supported by NCI-SAIC Contract No. HHSN261200800001E, and NINDS under BrIDGS Program).

P521

Test Article Conservation during the Conduct of *In Vivo* Lead Optimization Respiratory Safety Assessment Studies Using a Capsule Based Aerosol Generation System. *S. Moore[1], R. Goodway[1], S. Cracknell[3], G. Paul[2], J. Damiano[3].* Huntingdon Life Science, Huntingdon, UK[1]; GlaxoSmithKline, Ware, Hertfordshire, UK[2]; Huntingdon Life Sciences, E. Millstone, NJ, USA[3].

In both clinical and nonclinical environments the inhaled delivery of drug substances to conscious subjects will require larger quantities of the test article than other routes of administration. This difference is greatest for dry powder formulations where charge and proximity effects are most pronounced, but is also due to the losses and inefficiencies in the delivery device and aerosol delivery system. Minimizing such losses, particularly when conducting *in vivo* lead optimization studies in rodents, can reduce the cost of drug development. Decreasing the amount of test article required enables the conduct of investigations utilizing the inhaled route earlier in a development program, when the test article is most likely to have limited availability and greatest cost. Over a period of three years GSK Inhaled Sciences has collaborated with HLS to design and develop aerosol generation methods to minimize powder usage for inhaled delivery to conscious nonclinical species. The principle alternative delivery methodology that has been commonly employed, intra-tracheal insufflation, achieves particulate deposition dissimilar to conscious inhaled delivery and can produce artifactual toxicological and pharmacological outcomes. The results of work sponsored by GSK Inhaled Sciences and performed by HLS to characterize an existing capsule-based aerosol generator and design and manufacture an alternative instrument are presented. If further work is successfully concluded, the instrument developed will facilitate the use of the inhaled route earlier in *in vivo* lead optimization studies, so increasing the quality of candidate drugs and reducing compound attrition precipitated by findings in later more resource intensive *in vivo* studies.

P522

Thyroid C-Cell Morphology, Morphometry and Serum Calcitonin in Male Monkeys following Twice Weekly Subcutaneous Injection of Dulaglutide for 52 Weeks. *J. Vahle[1], R. Byrd[1], J. Blackbourne[1], S. Sorden[2], T. Ryan[2], T. Pienkowski[2], J. Wijsman[1], H. Smith[1], T. Rosol[3].* Eli Lilly and Company, Indianapolis, IN, USA[1]; Covance Laboratories Inc, Madison, WI, USA[2]; The Ohio State University, Columbus, OH, USA[3].

Dulaglutide (DU) is a once weekly long-acting human GLP-1 receptor agonist (GLP-1RA) in Phase 3 clinical development. Long acting human GLP-1RAs, including DU, have caused hyperplasia/neoplasia of thyroid Ccells in rodent carcinogenicity studies. Monkey studies of GLP1RAs have not identified changes in the thyroid; however, group sizes were small (≤5/sex/dose). The present study was designed to determine if DU altered C-cell mass in monkeys. Male cynomolgus monkeys (20/group) were subcutaneously injected with 0 or 8.15 mg/kg DU twice weekly for 52 weeks (~500-fold the human AUC). Basal and calcium gluconate-stimulated serum calcitonin concentrations were obtained at 3, 6, 9, and 12 months. At termination, thyroids were weighed and sectioned every 500 µm using uniform random sampling. C-cell volumes were measured in calcitonin-labeled sections using automated image analysis. Light microscopy and Ki67 labeling for cell proliferation were also performed. DU treatment did not increase serum calcitonin and had no effects on thyroid weight or light microscopic appearance, C-cell proliferation, or absolute or relative C-cell volume. As expected, C-cell volumes in control monkeys were low compared to control rats in a companion study. This study represents a comprehensive evaluation of monkey thyroid C-cells following dosing with a GLP-1RA with large group size (n=20) and measurement of multiple relevant parameters. The lack of effect of chronic administration of high doses of DU on monkey thyroid C-cells is consistent with other monkey studies of GLP-1RAs and suggests that monkeys are much less sensitive than rodents to the effects of GLP-1RAs on thyroid C-cells.

P523

Unexpected Pituitary Pathology after Chronic Administration of MEDI412, a High Potency Anti-IgE Antibody. *M. McFarlane[1], W. Iverson[2], J. Bluemel[2].* MedImmune, Cambridge, UK[1]; MedImmune, Gaithersburg, MD, USA[2].

Elevated serum IgE levels play an important role in certain diseases such as allergic asthma or atopic dermatitis. Biotherapeutics like omalizumab targeting the IgE axis have shown promising results in clinical practice. MEDI4212, a high affinity human IgG1 antibody, targeting soluble IgE with more than 50-fold improved affinity over omalizumab, does not cross-link receptor-bound IgE. MEDI4212 binds to cynomolgus monkey, but not rodent, IgE with comparable affinity to human IgE. Repeat-dose studies in cynomolgus monkeys were conducted to establish the safety profile. No noteworthy finding was observed in the IND-enabling 4 week study up to 150 mg/kg administered once weekly. In contrast, hypertrophy of the pituitary gland was seen in all females at 150 mg/kg (high dose) and in 2/3 animals at 50 mg/kg (low dose) in the 6-month study after once weekly administration. This finding was still present at the end of a 13-week recovery period in high-dose group only, but no down-stream functional effects in endocrine organs were observed. Investigative studies confirmed the absence of hyperplasia and demonstrated that MEDI4212 did not bind to circulating female pituitary hormones. MEDI 4212 did not enrich in pituitary glands and direct interaction of MEDI4212 or endogenous IgE with pituitary cell function seems contrary to its pharmacology. Although no clear mechanism of action could be identified in these follow-on studies, a NOAEL of 50 mg/kg once weekly is proposed based on (1) lack of functional consequences, (2) low-grade severity of the lesion and (3) slight trend towards recovery.

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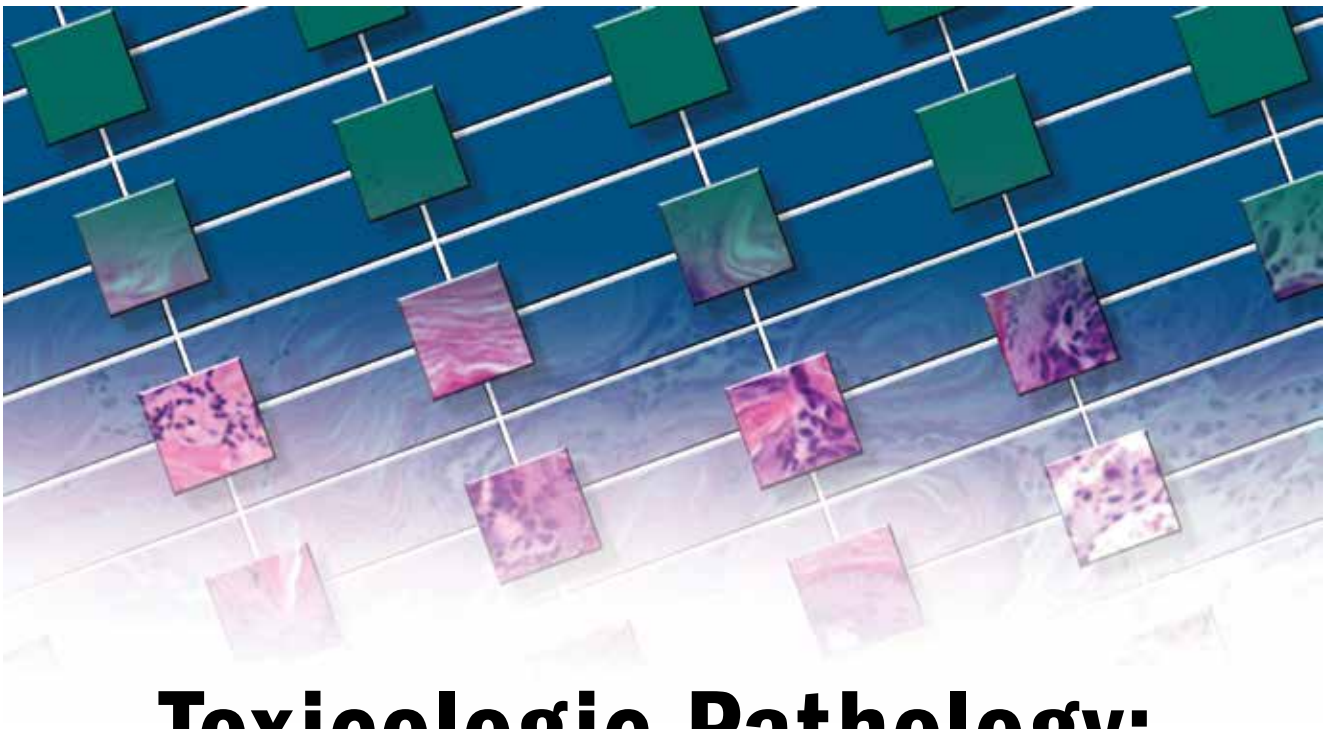

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Email: jturner@otosciencelabs.com
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Website: www.pacificbiolabs.com

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WuXi AppTec partners with our customers to provide a wide range of IND/NDA enabling toxicology and laboratory services that meet global regulatory standards. As part of our integrated portfolio offering, our preclinical services are designed to shorten the time and lower the cost of drug and medical device R&D.

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Xenometrics LLC, is a nonclinical contract laboratory. Our areas of expertise are safety pharmacology, ADME, toxicological testing and discovery support services designed to address pertinent pharmaceutical drug discovery and safety issues. As a company, we strongly believe that quality should never be compromised. Consequently, our experienced scientists are dedicated to providing reliable, dedicated testing, and timely results.

Exhibit Hall Map

Nelson W. Wolff Ballroom B&C

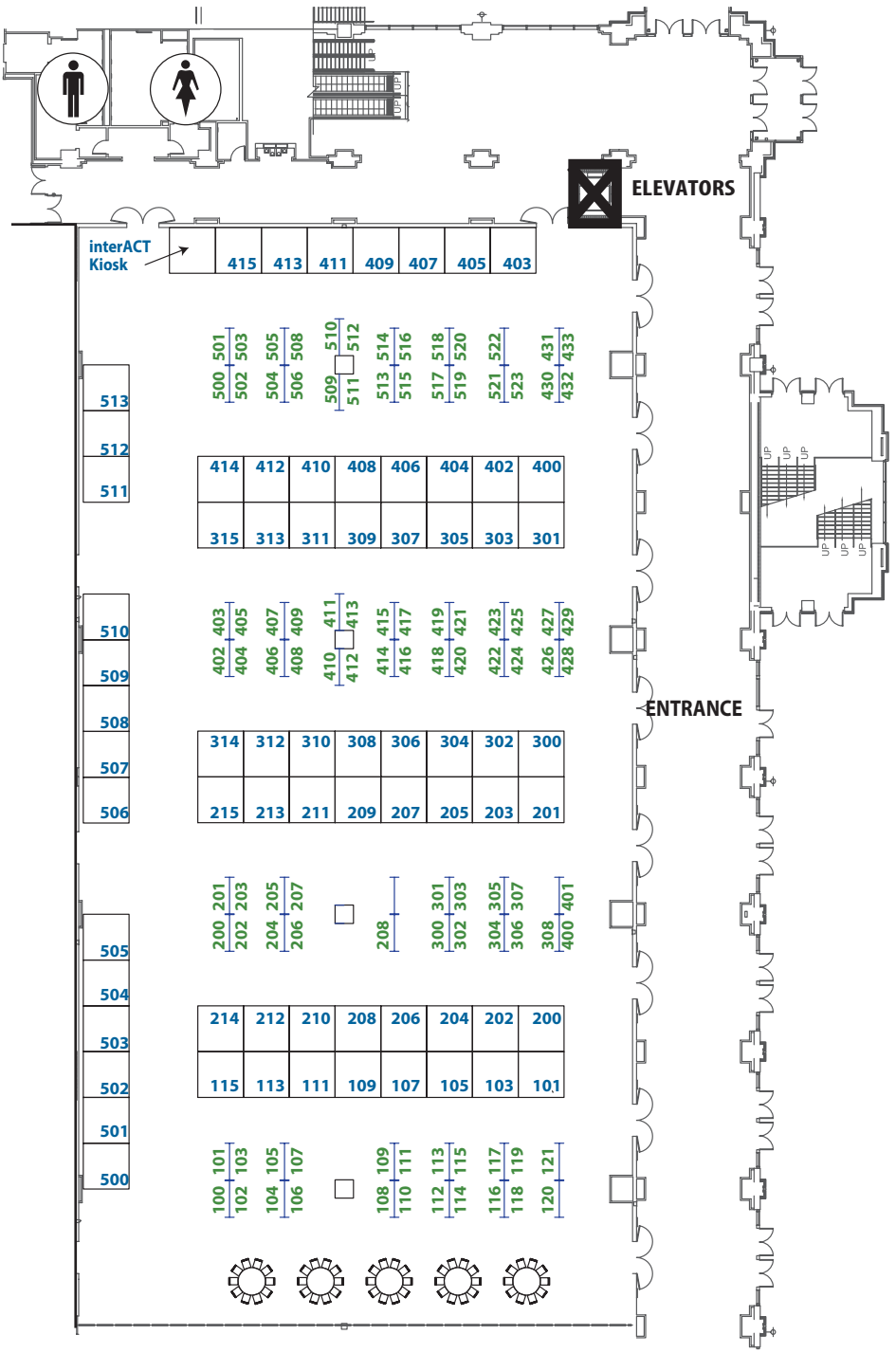

EXHIBIT INFO

Exhibitor-Hosted Programs

Exhibitor-Hosted Programs are commercially supported educational sessions held in conjunction with the ACT Annual Meeting. Programs are open to all meeting attendees.

Changes in Preclinical Safety Evaluation for Cardiotoxicity: Removal of the E14 Clinical Guidance by 2015—An Opportunity and a Challenge

Wednesday, November 6
7:00 AM–7:55 AM
Cibolo 4

Presented by: **Battelle Memorial Institute**

An interactive presentation outlining the proposed additions to preclinical cardiovascular safety pharmacology that could be used to negate the need for a clinical thorough QT study (TQT). The focus will be a test strategy that relies on the use of stem cell-derived cardiomyocytes, and bridging studies from a single cell to the isolated *ex vivo* heart model to a fully integrated *in vivo* system (e.g., telemetered animal models) for both arrhythmogenicity and contractility.

Carcinogenicity WOE and the rasH2 Mouse BioAssay

Wednesday, November 6
12:00 Noon–12:55 PM
Cibolo 4

Presented by: **BioReliance Corporation**

As proposed by ICH S1, the rasH2 Transgenic Mouse Carcinogenicity assay should be a component of the WOE of a Sponsor's CAD requesting waiver of a rat 2-year study. Presentation will include an overview of ICH S1, and historical control data confirming rasH2 mouse as a predictor of carcinogenic risk.

Assays to Monitor T-Cell Functions: How and When to Apply to Toxicology Studies

Wednesday, November 6
12:00 Noon–12:55 PM
Cibolo 2

Presented by: **Charles River**

Experimental therapies are targeting T-cells to activate or inhibit their functions. Several assays were developed to understand the efficacy and pharmacodynamics of these therapies and any off-target effects. This session will address the assays to assess the number and functions of T-cell subsets and how/when these endpoints should be applied to toxicology studies.

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