Greetings all, and hope you are well and have had a great year. The Executive Council of our specialty section is busy preparing for the annual meeting in San Diego and will be providing some information in this newsletter that should be useful for you. We anticipate a great turn-out for the meeting and hope to see all, especially at the specialty section reception on Monday night. Information on time and venue are included in this newsletter. We also have at least two special events planned and will be providing more information in the Spring newsletter prior to the annual meeting.

First: the Great Debate. We have selected the following statement as the topic for debate: “Peer-reviewed literature can be used to formulate regulatory policy”. This is a hot topic for many in the scientific community and involves several issues. Important is the reliability of the peer review process. Regulatory policy depends on both sound science and data integrity, and peer review is the gate keeper of the system. Another issue relevant to this topic is reproducibility of published studies: a hot topic in science. These and other issues will be addressed in the debate and we will give you the names of our debaters in the Spring.

Another special event is new for RSESS. We plan to have a luncheon on Tuesday in which you will have the opportunity to hear and discuss policy issues with a regulatory specialist from outside the US. Our first guest speaker will be Dr. Beatriz Silva Lima as a representative from Europe who will present and answer questions about current topics in drug development overseen by the European Medicines Agency (EMA). This will be a brown bag lunch open to SOT membership and we anticipate significant interest. More information will be provided prior to the meeting.

RSESS will continue to support travel for students as we have in the past: in 2014 we awarded seven students and post-doctoral trainees with $1500 each to supplement their travel costs to the annual meeting. In addition, we partner with the International Society for Regulatory Toxicology and Pharmacology to provide $500 for one student/post-doctoral trainee in addition to RSESS funds. [continued on p. 5…]
Past-President’s Message

SOT Continues to Assist Congressional Staff/Members with TSCA Reform

by Daland R. Juberg, PhD, FATS

Background

Members of the Society of Toxicology’s Toxic Substances Control Act (TSCA) Task Force continue to meet with members from the House and Senate who have responsibility for modernizing the Toxic Substances Control Act of 1976.

Because of its commitment to “Creating a Safer and Healthier World” and owing to the depth of knowledge amongst its membership relative to chemicals, toxicology, and the assessment of human health risk, the Society created a TSCA Task Force in 2011 that is committed to providing the U.S. Congress with science-based assistance regarding future TSCA reform. Specifically, the TSCA Task Force is committed to providing 1) education and discussion on scientific topics important to legislation and 2) insight on how the constant evolution of toxicology and risk assessment can be utilized to ensure the best protection of public health and the environment. Consistent with this objective and the expertise of the Society’s members, the following guidelines have been established regarding engagement on TSCA reform with Congressional representatives.

- We are willing to explain and clarify the science of toxicology and methodologies for assessing hazard and risk to anyone in Congress engaged in TSCA reform. Our input may include personal visits, training sessions or briefings, and non-confidential and transparent written responses to questions.

- We will facilitate connections between Congressional representatives and members of the Society who have specific expertise that may be needed. To the extent that there may be a range of views on any particular topic, we will seek to represent the full range of scientifically-credible views.

[continued on p. 6…]
Career: Regulatory Toxicology
By Hilary Sheevers, PhD

RSESS council is happy to report that many members of RSESS are young, and early in their careers. I am often asked by students, post doctoral candidates, and people early in their career how to train for a career in regulatory toxicology. Toxicologists generally train for years in academia and in a laboratory, and have little experience to help them refocus their careers in regulatory toxicology. In general, no set of course work is offered in graduate level toxicology programs in regulatory toxicology. Some short courses are offered in regulatory toxicology. Examples include:

- Continuing education and symposiums at SOT
- The American College of Toxicology CE and symposiums at their annual meeting, and a 1-week course in regulatory toxicology at different locations and times
- Regulatory meetings, such as the Drug Information Association (DIA) and the Regulatory Affairs Professionals Society (RAPS) annual conferences
- Continuing Education classes in universities, such as the CE courses offered through Harvard’s School of Public Health
- Master of Advanced Studies (MAS) in Advanced Human Toxicology, (Module: Risk Assessment and Regulatory Toxicology) University of Genève & SCAHT – Swiss Center for Human Toxicology
- German Society of Pharmacology and Toxicology, post graduate qualification (Fachtoxikologe DGPT) includes Regulatory Toxicology and Risk Assessment modules.

The bottom line, however, is that there is no straightforward US professional degree or certification in regulatory toxicology, and toxicologists are left to figure it out on their own. Besides attending meetings and courses, people most often get started by taking a job as a

Global Regulatory Toxicology:
First Stop EU

RSESS announces the first — and hopefully annual — luncheon sponsored by RSESS. We will invite a non-US regulatory toxicologist to join us at the annual SOT meeting. This year, Dr. Beatriz Silva Lima, former chair of the safety working party of EMA, will give a presentation on EU nonclinical pharmaceutical development, as well as a Q&A session at a brown bag luncheon on Tuesday. Please note the annual meeting program for exact time and location. Thanks to Annette Koerner for developing this new RSESS offering.
FDA: Rethinking “Same”  
by Ken Hastings, DrPH, DABT, Fellow ATS

On Oct. 10, 2013, Activas voluntarily withdrew its Abbreviated New Drug Application (ANDA) for generic Wellbutrin, following a determination by the Office of Generic Drugs (OGD), CDER, FDA that the product was not bioequivalent (BE) to the reference product (and therefore not therapeutically equivalent, TE). On April 14, 2014, OGD posted a Request for Proposal to study pharmacokinetic and pharmacodynamic (PK/PD) parameters associated with generic metaprolol. OGD is also seeking outside help with other approved generic products (valproic acid, tacrolimus). These actions suggest that OGD has begun to question standards for establishing bioequivalence needed to deem a generic drug as therapeutically equivalent to already existing products.

In all of the cases listed above, concern was driven by adverse event reporting and other public input. The original standard for bioequivalence (that various PK parameters should be demonstrated to be within 80 – 125% of those for the reference product) was established for immediate-release (IR) formulations intended for oral administration. The critical parameters were oral bioavailability, T\textsubscript{MAX}, C\textsubscript{MAX}, and AUC. The ANDA applicant was not required to conduct comparative efficacy studies. In sum: a small group of normal, healthy subjects received either the proposed generic or the reference product, PK values were obtained, and comparisons made (usually the study subjects received both test articles in a cross-over design). Over the years, this approach has been subject of criticism (e.g. for “narrow therapeutic index” drugs), but has been maintained as the gold standard.

The paradigm is now under scrutiny. There are a number of reasons for this: the emergence of modified-release (MR) formulations, ANDAs submitted for complex drug substances, and biosimilars. In the case of MR formulations, the key issue appears to be “dose dumping”: simply put, the generic doesn’t work as intended, and the required BE studies failed to predict this. Thus, OGD is going “outside FDA” to find out why. (In the case of generic MR metaprolol, the safety implications are especially significant.)

FDA/CDER has released several draft guidances in the last year that address BE and TE issues in addition to product specific guidances for BE determinations. An example is the recently published “Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations” (draft, March 2014), which is a valuable guide to current thinking. However, this guidance also highlights problems with current methodology. Interested parties should expect changes, and there are a number of indicators of this. First: OGD, which was a sub-office within the Office of Pharmaceutical Sciences (OPS), has now been elevated to a “super office” directly reporting to the Center director (Dr. Janet Woodcock). Second: the generic user fees authorized under FDASIA will provide significantly greater resources for OGD. Finally, the chemistry reviewers in OGD are being moved to the new Office of Product Quality Assessment (OPQA). The results will likely be: (1) enhanced scientific expertise within OGD. In the past, when there were significant safety and/or efficacy issues associated with an ANDA, expertise (consult reviews) came from relevant Office of New Drugs (OND) review divisions. This will change – OGD is building a science base long needed. (2) Shifting the chemists to the new product quality office implies that the same standards will apply to generics and innovator products – the problems with MR formulations may be related to differences in... [continued on p. 9…]
President’s Message  [continued from p. 1]

Please direct applications for these competitive awards to Suzanne Fitzpatrick, Vice-President of RSESS – the application form is available on the SOT website (go to the RSESS link).

We are also in the process of developing an award for distinguished service to regulatory science. This will be a career achievement award similar to those given by other specialty sections. A work in progress, we hope to be able to announce the specifics and offer the award soon and may be able to provide more information at the annual meeting.

Finally, a personal note concerning current affairs of interest to those of us involved in regulatory policy. RSESS first convened as a group at the 1993 annual SOT meeting, and the first president and one of the founders was a colleague from FDA: Fran Mielach. Many of us may recall the situation in 1993: AIDS was a devastating public health emergency that the scientific community was only beginning to deal with in any effective manner. It was clear at the time that change was needed in how regulatory agencies such as FDA could deal with what were then experimental therapies for a disease for which there was very little to offer. To the credit of SOT, RSESS was formed – in large part – to facilitate interaction between academia, industry, and regulatory authorities to help, through constructive dialogue, expedite discovery and development of pharmaceuticals that would hopefully help bring this public health disaster under control. Thinking back on that time, I think the intellectual partnerships fostered by groups such as RSESS were helpful in important ways that some of our younger colleagues may not be aware. Now, we face a new emergency: Ebola. Once again, the scientific and regulatory community must step up and provide the expertise needed to deal with this public health crisis. The membership of RSESS can be a key actor in responding to this challenge, as it has from the beginning. Just a thought for your consideration.
SOT Continues to Assist Congressional Staff/Members with TSCA Reform [continued from p. 2]

- We will avoid any attempts to advocate for specific positions, interpretations, or application of the science when scientific consensus is lacking. As warranted, consensus may be tested via a subset of members representing the range of views within the Society.

- We will avoid engagement on issues that are not scientific in nature; e.g. issues involving political or legal principles, costs, administration, and we will not engage in drafting of legislative language.

SOT TSCA Reform Principles

Since February 2014, SOT TSCA Task Force members have met with leaders on the House Committee on Energy and Commerce and the Senate Environmental and Public Works Committee to talk about the importance of drafting legislation that is grounded on the best available science. SOT has developed 3 principles that it believes will provide a sound basis for future TSCA reform which include:

- Flexibility in the choice of the most appropriate specific techniques for generating information used in the safety and risk assessment process.

- Authority of the US Environmental Protection Agency to judge when, and how, to apply new techniques and methods for generating information for safety and risk assessment within TSCA.

- Consistent application of scientific terms and concepts throughout the proposed legislation.

Task Force 2014 Activities

- The House Subcommittee on Environment and Economy has distributed two separate drafts seeking input from various stakeholders. In May, the House Democrats on the Subcommittee distributed a red line version for the second draft to indicate changes [continued on next page]
they are seeking to the House draft. Upon release of each of these drafts, the TSCA Task Force has analyzed and developed input/guidance separate letters with SOT Council review) to Congressional members and their staff to address scientific and toxicological issues. Consistent input from the Task Force has centered on intent and use of terms which include, but are not limited to:

1. Best available science
2. Publicly available information
3. Alternative testing methods
4. Safety determination
5. Separation of risk assessment and risk management
6. Defining potentially exposed sub-populations
7. Defining priority substances
8. Weight of evidence
9. Unreasonable risk
10. Mixtures

Since February 2014, the Task Force has held 20 meetings with various Members and their staff. During each session, the Task Force representatives have emphasized the importance of the principles noted above, the toxicologist’s role in implementing TSCA reform legislation, and their willingness to serve as technical advisers to both Democrats and Republicans.

These efforts have been paying off. A review of draft bills that have been released has revealed improvements in language and consistency along the lines of our recommendations and principles in the use of toxicological/scientific terms.

Congressional members and staff are starting to reach out to members of the Society for input separate from the meetings on the Hill. Several Task Force members have responded to technical questions directly from the House Energy and Commerce Committee staff on toxicological and scientific matters.

The Task Force has been invited to develop and present to staff of the House Energy and Commerce Committee a briefing/seminar with Q&A on the essential elements/principles of toxicology and risk assessment. This briefing is planned for early September, 2014.

The Task Force is also engaged in developing educational material on toxicological and scientific terms which will be distributed to Congressional staff and members for use in future drafts of the TSCA reform legislation and will likely be applied to other legislative efforts when the need arises for incorporating sound scientific principles into legislative language. There appears to be a fundamental need for grounding and understanding of scientific terms used in TSCA legislation and as such, the Task Force has recognized this as an opportunity to provide additional guidance.
Career: Regulatory Toxicology  [continued from p. 3]

toxicologist within a regulated industry, such as chemicals, pesticides, foods, or pharmaceuticals. There is also a general skill set, however, that people can develop to make them better and successful candidates in the regulated industries. Below are the skills that I look for in a candidate.

- **Good scientist:** Strong scientific skills and logical thinking are the foundation of a regulatory toxicologist.
- **Relevance:** An innate ability to determine what is relevant to the regulatory strategy and the decisions that need to be made.
- **Fast learner:** Regulatory toxicologists use the skills learned in graduate school or a postdoc to enable them to jump into areas where they have absolutely no experience. They need to read, ask questions, understand a new area, develop strategies, identify gaps, and ask questions no one has thought of in a relatively short amount of time. It is not for the faint of heart!
- **Good communicator:** Regulatory toxicologists quickly and succinctly explain the background around an issue in great detail to their peers, but also at a very high level for management. He or she will also be able to do this in a written form: e.g., a one page executive summary or a 30-100 page fully detailed report where no detail is left unturned.
- **Exquisite attention to detail:** No string can be left hanging in a regulatory development plan, because it will certainly come loose and the plan will fall apart. Every possible problem, unanswered question, inconsistency must be hunted down and dealt with. When this is not done, whole products sometimes fail or are delayed a year or more. Not many careers can survive such errors, and certainly not more than once.
- **Experience:** This is the old catch 22, no one will hire a person without experience, and so how can a person get experience? There is actually a lot a candidate can do about this. I am often amazed when a job candidate states their sincere interest in pharmaceutical drug development and they have not attended things like SOT courses that discuss this area and have never read a guidance, which are carefully hidden (not!) on the internet under “FDA Guidances”. By attending meetings, reading guidances, and talking with colleagues in the field of interest, a job candidate has a big advantage over others at the same level in the job market.

The biggest difference between a research job and a regulatory job in toxicology is that you must be able to understand information on a research level, but also be a generalist and understand how the research applies to the regulatory environment and the development of the product for an employer, be it a company or government. If a scientist is most comfortable being an expert in a single niche area, then the job as a regulatory toxicologist is probably not the right fit. If a scientist also likes to know a lot about everything, and wants to understand how it all fits together, he or she is likely to be a good candidate to work in the world of regulatory toxicology. As a member of RSESS, newsletter readers have likely decided regulatory toxicologist is the right fit for you. So sign up for those SOT CE courses that fit, and if you are at the highly experienced point in your career, please step up and share your experiences and offer or present in symposium and CE classes.
FDA: Rethinking “Same” [continued from p. 4]

standards applied to generics (controversial, but changes in bureaucratic structure at FDA usually mean more than just moving boxes on an organization chart.) (3) Expect the unexpected – for example, we may see post-marketing commitments/post-marketing requirements for generics (at least for certain products) to monitor for adverse effects associated with difficult manufacturing processes (such as those needed for MR formulations).

Finally: biosimilars. Of interest is that biosimilar applications are currently reviewed by the indication-specific division within OND. This may change as well. One thing that is not likely to change is the disparity between the European Medicines Agency (EMA) and FDA on biosimilar approvals. EMA is more concerned with comparable pharmacology, whereas FDA will likely remain much more concerned with physical/chemical comparability. The draft FDA guidances on biosimilars are fairly clear on this point: any structural difference between a proposed biosimilar and the reference product will not be acceptable. The draft guidance “Immunogenicity-Related Considerations for the Approval of Low Molecular Weight Heparin for NDAs and ANDAs” (April, 2014) makes the reason behind this clear: extensive characterization of the product is expected to reduce the incidence of unacceptable immunogenicity. This guidance gives a clue as to why FDA is taking a more conservative approach to establishing biosimilarity compared to EMA: interchangeability. This is a determination made in the European Union by member countries. FDA anticipates making this (pre-emptive) determination: thus, stricter standards.

There may be another change expected for OGD: use of population PK/PD. In fact, this might be an outcome of academic studies with failed generic MR formulations (like metaprolol): the only way to detect clinically significant differences between a generic versus innovator formulation is to sample a relatively large patient population. “Same” for FDA may no longer be adequately assessed in healthy volunteers. ■
RSESS Sponsored 2015 SOT Sessions

Sunday 22-Mar-2015

Continuing Education:

AM04: Safety Evaluation of CNS Administered Therapeutics—Study Design, Dose Routes, and Data Interpretation

AM05: The Future of Developmental and Reproductive Toxicology—Building a Bridge to the Animal Free Zone

AM07: Toxicology and Regulatory Considerations for Combination Products

PM09: Interpretation of Cardiovascular Safety Data in Toxicology Studies

PM11: Skeletal System Endocrinology and Toxicology

Monday 23-Mar-2015

Workshop Session:

Friend or Foe—Challenges and Perspectives for Nonclinical Development of Antibody-Drug Conjugates

Infant Formula Nutrition: Regulatory and Safety Evaluation of Ingredients

The US Tox21 Collaboration: Advances Made and Lessons Learned

RSESS Reception and Great Debate

Tuesday 24-Mar-2015

Workshop Session:


In Vitro Microphysiological Systems—Developing Confidence in Predictive Ability

Regulatory Neurodevelopmental Testing: New Guiding Principles for Harmonization of Data Collection and Analysis

The EDSP Screening Battery: A Work-in-Progress for Prioritizing Compounds for Quantitative Risk Assessment

Understanding and Communicating Uncertainty in Hazard Assessment and Dose Response

RSESS Sponsored Luncheon: Global Regulatory Toxicology: First Stop EU

[continued on next page...]
Wednesday 25-Mar-2015

Informational Session:
Risk Communication and Management in the Era of Social Media and the Internet: Serving Society's Needs with Accurate Information

Roundtable Session:
Epigenetics and Chemical Safety Assessment: Are We Ready?
Should Respiratory Sensitizers Be Listed As Substances of Very High Concern (SVHC) under REACH?
The Future of Carcinogenicity Testing
Will Generally Recognized As Safe (GRAS) Become an Endangered Species?

Symposium Session:
Advanced Approaches for Quantitative Risk Assessment Using Human Data with Applications across Disciplines

Workshop Session:
An Experiment in Collective Wisdom Utilizing Real-Time Audience Input: Weight-of-Evidence Assessment for Chemical-Specific Modes of Action Utilizing Two Case Studies
Strengths and Weaknesses of Mouse Models in Studies of Immunological Effects of Drugs and Chemicals

Thursday 26-Mar-2014

Symposium Session:
Exposure Assessment in the 21st Century: Needs and Challenges Facing High-Throughput Exposure Modeling

Workshop Session:
Painting the Future of Repeat-Dose Systemic Toxicity Testing: Progress from the European SEURAT -1 Project