Contemporary Concepts in Toxicology Proposal

Title: Science based decision making to enhance regulatory success
Type: Virtual - 4x1hr webinars

Skeleton summary (Each webinar includes 10 mins Q&A and learning summary)**:**

Webinar 1

1. Ruth Roberts, AstraZeneca (25 mins). *Regulatory toxicology testing for small molecules: strategies and outcome analysis*
2. Laura Andrews, Genzyme (25 mins). *Risk assessment of 'traditional' biologics*

Webinar 2

3. Mary Jane Hinrichs, MedImmune (25 mins). *Risk assessment of humanised monoclonal antibodies and antibody-drug conjugates*
4. Scott P. Henry, PhD, ISIS Pharmaceuticals (25 mins). *Risk assessment of oligonucleotide constructs*

Webinar 3

5. David Jacobson Kram, Consultant (25 mins) *Regulatory Authority experience with diverse APIs and preclinical safety assessments supporting FTIH*.
6. David Jones, MHRA (25 mins). "*Case-by-Case" Regulatory toxicology testing in Drug Development in Rare or Debilitating Disease*

Webinar 4

7. Kathryn L Chapman, NC3Rs (25 mins). *New approaches in regulatory toxicology: why we need to change*
8. Thomas Hartung (Johns Hopkins) (25 mins) - *Roadmap for animal--free drug testing*

Overview

Diversity is increasing in the biological targets, pharmacological strategies, and types of chemistry being investigated in first time in human (FTIH) studies; similarly, there is growing information, guidance and experience to protect volunteer/patient safety. In response, regulatory toxicology strategies have diversified and evolved from those practiced only a decade ago reflecting advances in science and technology and the experiences of individuals and organizations. **This CCT will address how we understand and work with this diversity both now and in the future to bring important new (and safer) medicines to patients.**

The CCT will focus on 4 key areas: small molecules, traditional biologics, innovative biologics and nucleotide constructs. For each of these we will address the relevant aspects of science and technology, strategic and tactical issues (study design, species selection, target organ toxicity profiles), and regulatory guidance relevant to safety assessment, including approaches in rare diseases. There will also be a future focus as we consider new directions in the field, including reducing or moving away from animal testing. This CCT will be of broad interest to academic, industry, regulatory, and consultant toxicologists who wish to be updated in this critical and evolving area.

This CCT could potentially run every other year as guidelines and scientific thinking evolves.

This CCT is based on a highly successful workshop that took place at SOT 2014 entitled 'Science-based preclinical safety assessment: decision making to enhance regulatory success' but with some modifications; an academic and a government sector speaker have been added to provide balance and a regulatory future focused perspective.

Structure: The intention is to deliver the content as 4 successive webinars with a Q&A panel session at the end of the last webinar. The moderator for each webinar can accumulate key questions and learning points to be shared and built into a course commentary and/or Q&A.

Webinar 1 (1 hour):

Moderator: Mary Jane Hinrichs (MedImmune)

Ruth Roberts, AstraZeneca (25 mins)
Presentation Title: Regulatory toxicology testing for small molecules: strategies and outcome analysis
Presentation Description: This presentation will provide an introduction and perspective on target organ toxicity profiles for small molecules then explore how these regulatory toxicology strategies originally developed for traditional pharmacological targets and small molecule chemistries are faring when applied to more challenging targets and more sophisticated chemistries. In these cases, rat and/or the dog may not be the most appropriate test species - specifically, the dog may be inappropriate due to excessive sensitivity that prevents exploration of a full dose response; in these cases the non-human primate could be more appropriate. Other examples include when the species choice for safety assessment is driven by a test compound which is not pharmacologically active in the dog but maybe in non-human primates.

Laura Andrews, Genzyme (25 mins)
Presentation Title: Risk assessment of 'traditional' biologics
Presentation Description: This presentation will address the issues and challenges presented in preclinical risk assessment of pharmacological targets and molecular constructs produced by recombinant technologies such as hormones and cytokines where multiple pre-clinical test species may be inappropriate. As the activity of the biologic therapeutic is frequently species specific, the selection of appropriate animal models or surrogates is crucial to generating useful data. Some animal test systems have been refined to alleviate the inter-species issues, and alternative in vitro strategies have also been identified which could significantly reduce or eliminate testing. The focus of this presentation is to discuss and disseminate the problems and potential solutions associated with the development and safety testing of biological-based products.

Q&A, learning summary: 10 mins

Webinar 2 (1 hour):

Moderator: Ruth Roberts (AstraZeneca)

Mary Jane Hinrichs, MedImmune (25 mins)
Presentation Title: Risk assessment of humanised monoclonal antibodies and antibody-drug conjugates
Presentation Description: This presentation will address the issues and challenges presented in preclinical risk assessment of human pharmacologic targets and human-specific molecular constructs wherein the selection of appropriate pre-clinical test species presents unique challenges and solutions. The specific types of novel biologic drug platforms to be covered include humanized monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and Fc-mutated monoclonal antibodies. The discussion will highlight the unique characteristics of each type of platform that lead to challenges in study design and species selection. In addition, specific case examples will be presented to highlight the strategic thinking required when evaluating the safety of new biologic technologies.

Scott P. Henry, PhD, ISIS Pharmaceuticals (25 mins)
Presentation Title: Risk assessment of oligonucleotide constructs
Presentation Description: This presentation will address issues and challenges presented in risk assessment of intracellular targets and nucleotide constructs such as antisense and microRNAs, concentrating on safety aspects of tissue uptake and assessment of effects related to both the chemical platform and the intended pharmacology. Given the receptor for antisense oligonucleotides is typically RNA rather than proteins, relaying on Watson-Crick base-pair interactions, interspecies difference in sequence homology must be taken into consideration in the design of nonclinical studies. Likewise the pharmacodymic assessment for an intracellular target is challenging. Plasma exposure of oligonucleotides can be achieved by a number of methods, but must be related to tissue concentration to provide a direct assessment of pharmacologic activity. An example of a safety/pharmacodynamics relationship for an antisense inhibitor of Factor XI that incorporates mouse, monkey and human data will be presented.

Q&A, learning summary: 10 mins

Webinar 3 (1 hour):

Moderator: Mary Jane Hinrichs (MedImmune)

David Jacobson Kram (25 mins), Consultant
Presentation Title: Regulatory Authority experience with diverse APIs and preclinical safety assessments
supporting FTIH.
Presentation Description: This presentation will address regulatory issues and challenges associated with novel pharmacologic targets and new molecular chemistries balancing support for innovation in drug discovery while insuring volunteer/patient safety. Most first in human studies are performed in healthy volunteer subjects. Because there is no risk/benefit paradigm for this population, FTIH trails have a high bar for safety. Uncertainty around safety can result when a novel target is being explored, when a sponsor is testing a first in class

molecule and/or when the drug target does not exist in experimental species. Various strategies for dealing with these situations will be discussed such as the MABEL approach, microdose testing, and surrogate molecules

David Jones (25 mins) Medicines and Healthcare products Regulatory Agency (MHRA) UK

Presentation Title: "Case-by-Case" Regulatory toxicology testing in Drug Development in Rare or Debilitating Disease
Presentation Description: This presentation will provide an introduction and perspective on "case by case" approaches for drug development, focusing on rare diseases and severely debilitating diseases with a lack of current therapeutic options. In these cases a far more flexible approach for the supporting non-clinical studies than currently described in ICH guidelines is required. Studies may be conducted in animal models of disease, rather than standard laboratory species, GLP compliance may not be possible and platform studies to cover a multitude of similar products can be appropriate. In extreme cases, it may be that no non-clinical safety studies are appropriate.

Q&A, learning summary: 10 mins

Webinar 4 (1 hour):

Moderator: Ruth Roberts (AstraZeneca)

Kathryn L Chapman, National Centre for Replacement, Reduction and Refinement of Animals in Research (NC3Rs, UK) (25 mins).
Presentation Title: New approaches in regulatory toxicology: why we need to change
Presentation Description: This presentation will focus on current and future approaches to regulatory toxicology and how these can be effectively integrated into the drug development pathway. Approaches which increase confidence in new strategies and study designs, for instance, using cross-company experience and data-sharing will be covered. The limitations of using a default approach to drug development and the advantages of using a science-based approach will be discussed within the context of current regulatory guidelines. Case studies will include topics such as monoclonal antibody and biosimilar development, microsampling and toxicokinetics, the use of recovery animals and animal models in safety pharmacology.

Thomas Hartung (Johns Hopkins) (25 mins)
Presentation title: Roadmap for animal-free drug testing
Presentation Description: This presentation will challenge the current paradigm in drug toxicity testing in the assessment and protection of public health. By using and furthering the translation of concepts of evidence-based medicine to toxicology (evidence-based toxicology), this presentation will describe the systematic assessment of the quality of all tools for regulatory toxicology and the development of new approaches based on annotated pathways of toxicity (the Human Toxome).

Learning summary (Mary Jane Hinrichs and Ruth Roberts) 10 mins

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Expected outcomes:

We anticipate written output consisting of the frequently asked questions and answers plus a summary of key learning points and themes to be made available to delegates after the CCT. Subject to speaker agreement the slides could be made available as a resource.

Level of interest:

This session at SOT 2014 had a high level of interest with subsequent requests to 'do something similar again'.

Access and pricing structure

Given that Specialty Sections provide complimentary access to webinars, the CCT Conference Committee is recommending that these webinars be provided free-of-charge to members and non-members.

Based on audio rates of approximately $1 for USA participants and International participant rates of $3 to $4 per hour, it's anticipated that each one-hour webinar will cost between $1000 to $1500. For this participants can ask questions and can also have subsequent access to the presentation materials, recordings, Q&A and learning points. Or Council could consider 'listen only' options which will reduce the overall expense to approximately $500 to $600 per webinar. The CCT Conference Committee is requesting up to $6000 for these four webinars. The funding would be over-and-above their current budget. For 2015-2016, the Committee will request funding to host webinars.