FDA Genetic Toxicology Workshop
How many doses of an Ames-positive/Mutagenic (DNA Reactive) Drug can be safely administered to Healthy Subjects?
November 4, 2019

Workshop Organizers (Drs. Timothy W. Robison [timothy.robison@fda.hhs.gov] and Aisar Atrakchi [Aisar.atrakchi@fda.hhs.gov])

Location: Building 2, Room 2031
[Overflow: Building 51, Room 1300 (if needed)]

- Full Day Public FDA Workshop
- Includes a panel of outside experts
- Large Room to accommodate FDA and Public audience

Workshop Design

Several Divisions/Offices have raised questions regarding the number of doses of a Ames-positive (DNA-reactive) drug that can be safely administered to healthy subjects. Per the ICH S2 (R1) Guidance, "Because positive results in the Ames test are thought to indicate DNA reactivity, extensive follow-up testing to assess the in vivo mutagenic and carcinogenic potential would be warranted to assess the potential risk for treatment of patients, unless justified by appropriate risk-benefit analysis." Healthy subjects receive no benefits from treatment with an Ames-positive drug and could potentially be exposed to significant health risks. Does this safety concern of an Ames positive drug only apply to chronic administration or does it also extend to a small number of doses? There is a general lack of published scientific literature or guidance documents directed toward the cancer risk or other potential health concerns associated with a small number of doses of an Ames-positive drug.

Several Review Divisions seem to allow a single dose of an Ames-positive (DNA-reactive) drug in healthy subjects; however, others do not allow any dosing and yet others may allow more than 1 dose. Therefore, there is a need to address these differences between Review Divisions regarding repeat dosing with an Ames-positive drug to healthy subjects.

<u>Use of Healthy Subjects in clinical trials with investigational drugs</u>.
Healthy subjects are commonly enrolled into First-In-Human (FIH) phase 1 clinical trials of new drug candidates.

- Studies are typically short (few days up to 2 weeks)
- Treatment may be continuous or intermittent (e.g., washout period of 5 half-lives between doses)
- Receive no benefits and potentially exposed to significant health risks
- Patients will be enrolled in longer phase 2 and 3 trials

Advantages of conducting trials with healthy subjects include:

- investigation of pharmacokinetics (PK)/bioavailability in the absence of other potentially confounding drugs
- data not confounded by disease
- Identification of maximum tolerated dose
- reduction in patient exposure to ineffective drugs or doses
- rapid subject accrual into a study

The supporting nonclinical data package for a new IND includes

- pharmacology studies (in vitro and in vivo)
- safety pharmacology studies (CNS, cardiovascular, and respiratory)
- secondary pharmacology studies
- TK/ADME studies (in vitro and in vivo)
- 14- to 28-day toxicology studies in a rodent and non-rodent
- standard battery of genetic toxicity studies (in vitro Ames bacterial reverse mutation assay and in vitro mammalian cell genetic toxicity assay; [An in vivo micronucleus assay is not required until the start of Phase 2 trials])
- specialized toxicology studies as needed

    - Toxicology studies are used to
        - select clinical doses that are adequately supported by the data
        - assist with clinical monitoring
        - Genetic toxicity studies are used for hazard identification

Generally, most drugs found to be positive for mutagenicity (i.e., Ames-positive) outside of oncology indications are not developed

In the U.S., a drug with positive *in vitro* Ames bacterial mutagenicity test may still be administered to healthy subjects enrolled in a single-dose study

- trial participants must be made aware of the study results in the Informed Consent.

Pharmacokinetic studies typically require at least 2 to 4 doses (e.g., cross-over study)

- Risks with a small number of repeat doses?
- Intermittent (washout period between doses) or continuous dosing

Does this safety concern of an Ames-positive drug only apply to chronic administration or does it also extend to a small number of doses?

- e.g., 1, 2, 3, or 4 doses [a washout period of 5 half-lives might separate each dose]?
- the worst case might be 14 daily doses?
- Lack of published scientific literature or guidance documents directed toward the cancer risk or other potential health concerns associated with a small number of doses of an Ames-positive (DNA-reactive) drug in Healthy Subjects.

- Results of rodent carcinogenicity studies with a new drug candidate are typically not available until late in development or with a marketing application.
- Primarily rely on the results of the standard battery of genetic toxicity studies during IND development.

The workshop seeks to address the question of how many doses of an Ames-positive (DNA reactive) drug could be administered to healthy subjects without significantly increasing their cancer risk.

CDER is seeking advice from a Panel of Experts.

Morning Presentations (8:30am to Noon):

1. **Introduction: How many doses of an Ames-Positive/Mutagenic (DNA Reactive) Drug can be safely administered to Healthy Subjects?** Dr. Timothy W. Robison,

2. **FDA Requirements for the Protection of Healthy Subjects in Phase 1 Clinical Trials** Dr. Kevin Prohaska

3. **Considerations for a Genotoxic API in Clinical Trials: Healthy Subjects or Patients?** Dr. Bob Dorsam

4. **Literature review for data relevant to administering one or a few doses of a DNA reactive drug to healthy subjects** Drs. Dayton Petibone and Jennifer Shemansky

Break:

5. **Do the Steps between Genotoxin and Cancer Create Thresholds of Dose or Time?** Dr. Douglas Brash

6. **Setting Allowable Exposures to Ames-positive Candidate Drugs**
   Dr. Kenny S Crump

Afternoon Panel Discussion (1:00 to 4:00 pm):

Panel Discussion to discuss presentations and answer a list of specified questions

Panelists (8 total)

FDA Moderator, Dr. Aisar Atrakchi (CDER, FDA)

1. Dr. Alan Boobis

   Professor of Toxicology (emeritus), Imperial College London. He retired from his position at the College as Professor of Biochemical Pharmacology and Director of the Public Health England/Department of Health-supported Toxicology Unit in June 2017, after over 40 years. His main research interests lie in mechanistic toxicology, drug metabolism, mode of action and chemical risk assessment. He has published over 250 original research papers (H-factor 80). He is or has been a member of several national and international advisory committees; including current chair of the UK Committee on Toxicity, member of the WHO Study Group on Tobacco Product Regulation (TobReg), FAO/WHO JECFA (veterinary residues) and FAO/WHO JMPR (pesticide residues). He is a member and a past chair of the Board of Trustees of ILSI and HESI. He is a fellow of several learned societies and has received a number of awards, including Officer of the British Empire (OBE).

2. Dr. Douglas Brash

   Professor of Therapeutic Radiology and Dermatology at Yale University. He received his BS in Engineering Physics from the University of Illinois. For his PhD in Biophysics he adapted DNA damage and repair methods to the in vivo situation following carcinogen treatment and during aging, studying with RW Hart, who subsequently directed the FDA's National Center for Toxicological Research. His postdoctoral research at Harvard with William Haseltine applied the new DNA sequencing technology to measure the locations and amounts of UV-induced DNA photoproducts at individual nucleotides – finding that mutations arise at DNA lesions rather than UV elevating random genomic instability. At the National Cancer Institute, he identified the mutagenic UV photoproducts in E. coli and human cells. Upon moving to Yale his lab used the distinctive UV mutation signature to identify genes mutated by sunlight in causing skin cancer; showed that one of these genes, p53, is needed for UV-induced apoptosis to remove cells that otherwise would lead to cancer; and found that this apoptosis also drives clonal expansion of mutant cells once they arise. The lab also discovered that normal-appearing skin contains p53-mutant cells that are already proliferating as clones, with people harboring 60,000 clones occupying 5% of their sun-exposed epidermis. Recently the lab showed that UV-triggered chemical excitation of electrons in melanin, "chemiexcitation", generates mutagenic DNA photoproducts long after UV exposure ends. These results contribute to what is perhaps the best picture available of how a human carcinogen works. Current interests include blocking the carcinogenic reactions of melanin and using unrepaired DNA photoproducts as objective genomic dosimeters of past UV exposure to be used in predicting future skin cancer risk and targeting precision prevention.

3. Dr. Kenny Crump

   Holds a B.S. in Electrical Engineering from Louisiana Tech University, an M.A. in mathematics from the University of Denver, and a Ph. D. in mathematics from Montana

State University. Dr. Crump's research primarily involved development and application of statistical methodologies for quantitative assessment of health risks from exposures to toxic substances. These methodologies have been used by regulatory agencies in the U.S. and Europe for setting exposure standards for toxic chemicals. Dr. Crump is an author of more than 150 peer-reviewed scientific publications and book chapters.

Dr. Crump served on the Environmental Protection Agency Science Advisory Board and Science Advisory Panel, the National Center for Toxicological Research Science Advisory Board, the Mickey Leland National Urban Air Toxics Research Center Science Advisory Panel, the National Institute of Environmental Health Sciences Board of Scientific Counselors, and the National Toxicology Program Board of Scientific Counselors. In addition, he served as an official advisor to the World Health Organization, Health Canada and the Province of Ontario. He served on six National Academies of Science Committees. Dr. Crump is an elected Fellow of the American Statistical Association and the Society for Risk Analysis, and received distinguished achievement awards from both of these organizations.

4. Dr. Robert Heflich –

Division Director, Division of Genetic and Molecular Toxicology
National Center for Toxicologic Research
Little Rock, Arkansas

Robert (Bob) Heflich received a Ph.D. in Microbiology from Rutgers-The State University of New Jersey in 1976, followed by postdoctoral training with Veronica Maher and Justin McCormick at Michigan (now Karmanos) Cancer Foundation and Michigan State University. At MSU Bob studied DNA repair and mutagenesis in normal human fibroblasts. Bob joined the U.S. FDA's National Center for Toxicological Research in 1979, where he is currently Director, Division of Genetic and Molecular Toxicology. His present research involves the development of approaches to measure and analyze mutations in laboratory animals, most recently using the endogenous Pig-a gene as a reporter of mutation in mice, rats, and humans. Other research interests include the development and characterization of relevant in vitro organotypic assays, especially as related to evaluating the risks associated with inhaled substances. Bob has published over 200 papers in peer reviewed journals, has served as Editor-in-Chief of Environmental and Molecular and Mutagenesis, and participates on several FDA and international committees, including leading the effort to develop an OECD Test Guideline for the in vivo Pig-a gene mutation assay.

5. Dr. Timothy McGovern

Pharmacology and Toxicology Associate Director Office of Drug Evaluation
CDER, FDA

Dr. Timothy McGovern is an Associate Director for Pharmacology and Toxicology in the Office of New Drugs (OND) at the Center for Drug Evaluation and Research, US Food and Drug and serves a member of the Pharmacology/Toxicology Senior Leadership Team within OND. In this role, he interacts with nonclinical review teams in OND review divisions regarding the review of IND, NDA, and BLA submissions and conducts tertiary reviews of new molecular entities that have been submitted for marketing approval. He participates in the development of policy and guidance related to nonclinical and regulatory issues including FDA and International Council for Harmonization (ICH) initiatives. He is a standing member of CDER's Executive Carcinogenicity Assessment Committee and a member of the Genetic Toxicology Subcommittee. Dr. McGovern is the current Rapporteur for ICH Q3C (Residual Solvents) Expert Working Group (EWG) and

a member of the EWGs for ICH M7 (DNA reactive impurities) and Q3D (Elemental Impurities). His formal training is in the area of inhalation toxicology.

6. Dr. Miriam C. Poirier

   Scientist Emeritus, National Cancer Institute, NIH

   Dr. Miriam C. Poirier is currently a Scientist Emeritus at the National Cancer Institute (NCI), NIH, Bethesda, MD. From 1997 to 2015 she was Head of the Carcinogen-DNA Interactions (CDI) Section in the Center for Cancer Research, NCI. In 1964 she received an MSc degree in Oncology from the University of Wisconsin, Madison, as a student of James and Elizabeth Miller, and in 1977 she obtained a PhD in Microbiology from Catholic University, Washington DC. Having joined NCI in 1971, she became an NCI independent investigator in 1979. Dr. Poirier pioneered the use of antisera specific for DNA modified with carcinogens to probe the persistence and consequences of human DNA adduct formation. Her studies have extended to polycyclic aromatic hydrocarbons, cisplatin, tamoxifen and antiretroviral nucleoside reverse transcriptase inhibitors. Dr. Poirier has served on committees for the US-FDA, the US-EPA, the AACR, and the International Agency for Research on Cancer Monograph Series. During the past two years she has served as Program Chair and President of the Environmental Mutagenesis and Genomics Society (EMGS). She is author/co-author of 274 publications and recipient of the EMGS Alexander Hollaenender Award and the Genetic Toxicology Association Excellence in Science Award.

7. Kevin A. Prohaska, D.O., M.P.H., Captain (U.S. Public Health Service Corps):

   Title: Senior Medical Policy Advisor/Bioethics Consultant, FDA

   Dr. Kevin Prohaska is a medical officer in the Office of Good Clinical Practice (OGCP) within the FDA Office of the Commissioner. His work at OGCP includes serving as a senior medical policy advisor with a focus on human subjects' protections including issues related to informed consent and bioethics. Dr. Prohaska is a board-certified Family Practice physician with a diverse professional background that includes academic, clinical, military, and regulatory medicine. Dr. Prohaska started his career in the Commissioned Corps in 2000 as a medical review officer for the FDA Office of New Drugs. From there he moved to the Office for Human Research Protections where he served as a medical policy analyst and as the acting Executive Director of the Secretary's Advisory Committee for Human Research Protections (SACHRP). In May 2008, Dr. Prohaska returned to the FDA to serve as the Director of the Division of Safety Compliance and was responsible for the management of the Center for Drug Evaluation and Research (CDER) compliance oversight programs for institutional review boards, Radioactive Drug Research Committees, FDA's Risk Evaluation and Mitigation Strategies Program, and Post-marketing Safety Reporting program. Since May 2014, Dr. Prohaska has been at OGCP where he focuses the majority of his efforts on the bioethical review of clinical investigations involving adult subjects and policy development related to human subjects' protections and good clinical practice.

8. Dr. Errol Zeiger

   Responsible for designing, implementing, and managing the NTP's genetic toxicity testing program, and evaluating the test data. Authored or co-authored more than 230 publications, and co-edited the Handbook of Carcinogenic Potency and Genotoxicity Databases. Served as a consultant to the OECD in Paris for toxicology test guidelines and guidance documents, and supervising in vivo validation studies for endocrine disrupting chemicals.

QUESTIONS/Discussion Issues:

1. How many doses of an Ames-positive drug (DNA reactive drug) can be safely administered to Healthy Subjects?
- 1, 2, 3, or 4 doses

2. If studies in healthy subjects are acceptable with a mutagenic drug, how should such studies be designed?
a. Is continuous daily dosing acceptable? If so, for how long?
b. If dosing is intermittent, how many doses would be acceptable?

3. For generic drug products, the results of the full battery of genetic toxicology and carcinogenicity studies are often stated in the Reference Listed Drug's label. Should a weight-of-evidence approach be used to decide whether a compound should be tested in bioequivalence studies with healthy subjects?
a. If yes, which test results should receive greatest consideration in the WOE assessment?
b. Are there any other factors relating to genetic toxicology that should be considered when determining if a study should include healthy subjects in bioequivalence studies?

4. Certain drugs may be clastogenic, but not mutagenic. Should consideration be given to the mechanism of action of genotoxicity in designing studies in healthy subjects?

5. The ICH S2 (R1) Guidance provides recommendations for follow-up to a positive in vitro mammalian cell clastogenicity assay. If a drug is mutagenic (Ames-positive; artifactual increases have been excluded), are there follow-up studies to assess risk that should be conducted prior to conducting studies in healthy volunteers?
a. Would a 28-day transgenic rodent mutation assay that includes a Pig-a endpoint be acceptable? (If the Pig-a endpoint is positive, there would be no need to proceed with the tissue analysis in the TRG assay. However, if the Pig-a endpoint is negative, the tissue evaluation should proceed)
b. Alternatively, should a 26-week TgrasH2 mouse carcinogenicity assay or a 2-year rodent carcinogenicity study be requested?

6. Can you provide guidance for a path-forward for development of a DNA-reactive drug?
a. Mechanism of action
b. Structural considerations (e.g., functional groups on the molecule)
c. Read-across comparisons to similar molecules with known safety information
d. Observed genotoxic response (e.g., mutation, clastogenic, aneugenic)
e. Follow-up assays as described in Question 6 (e.g., alternative in vivo gene mutation test or two-year rodent bioassay).
f. Allow microdosing of such drug without any follow up assessment.

7. Are there drug classes or specific drugs (e.g., targeted to the epigenome) that should never be administered to Healthy Subjects?