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Overview of the ISRTP October 2014 workshop on GRAS determinations

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ABSTRACT

On October 12–13, 2014 the ISRTP held a very successful *Workshop on GRAS Determinations* in Washington DC that was not only well-attended by seasoned public and private professionals from a wide swath of food safety disciplines but featured a series of very insightful and informative presentations from current and past officials from the US Food & Drug Administration (FDA). To stay true to our international nature as a Society, we had regulatory and industry representatives from Canada and Europe.

ISRTP President Diane McColl gave a short introduction to the goal of the workshop, which was to give the science and regulatory community an opportunity and a forum to respond to recent critiques of the FDA GRAS program published by both the Governmental Accountability Office (GAO) (US GAO, 2010) and public health and environmental non-governmental organizations (NGOs) in recent years (*e.g.*, Pew Charitable Trusts, 2013; CSPI, 2015; Neltner and Maffini, 2014). The critiques center around four assertions: (1) the GRAS exemption established by the 1958 Food Additive Amendments has eclipsed and perverted its original Congressional intent (the "loophole has swallowed the law" contention); (2) FDA needs to modernize the science supporting GRAS determinations and mandate specific testing as is done for pesticides; (3) FDA must ensure all food ingredients are equally safe for the US food supply and initiate cyclical reviews; and (4) mandatory fee-based FDA pre-market approval system should be established in place of the current voluntary GRAS notification system. The first day of the workshop featured several speakers, each from very different backgrounds but all with an enormous command of the principles, methods and data required for making a GRAS determination. A GRAS determination requires two elements: "technical evidence of safety" and "common knowledge." (US FDA, 1997). The "common knowledge" element requires that (1) the pivotal data and information supporting safety be generally available to the scientific community and (2) there exists evidence of a consensus among qualified experts that such data and information establish safety of the intended use. Regardless whether a self-determination of GRAS status is followed by a voluntary GRAS notice or not, the "technical evidence of safety" for a GRAS determination must satisfy a safety standard of the exact same rigor and depth as the safety standard applied to a food additive that undergoes the mandatory FDA premarket petition process. That safety standard requires a reasonable certainty of no harm under the intended conditions of use; it does not now and never has required absolute certainty of no harm. Dr. William Allaben, who enjoyed a very successful 30 + year career with FDA prior to joining the faculty at University of Arkansas Medical Sciences, led off the workshop with a thorough review of the basic scientific and regulatory principles that support GRAS determinations and FDA approval of food additive petitions. Again, these are identical with one simple exception – the "common knowledge" element of a GRAS determination that requires public availability of pivotal supporting data and information and evidence of a consensus by qualified experts that under the conditions of intended use, the substance is safe. In fact, one of the overarching themes of the workshop is that not only is the GRAS determination process held to the same rigorous safety standard used for food additives (and indeed all substances intended to be put in food) but it surpasses the food additive evidentiary standard by virtue of the "general recognition" (or "common knowledge") clause. Barbara Petersen, an internationally recognized expert in dietary exposure and risk assessment and Principal Scientist with the science and engineering consulting firm Exponent, then reviewed the requirements for

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chemical characterization and provided an excellent overview of dietary assessment methods as well as data sources used to support GRAS determinations. Dr. Petersen touched upon another one of the overarching themes from the conference that would be explored more on the second day, that is, the notion that imposing a safety data standard similar to that of pesticides (as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA) would be preferable to the current FDA safety data standard for substances added to foods. Multiple speakers addressed in different ways and to different degrees the fact that pesticide products are designed for very different functionalities than food additives, often display different magnitudes of acute and chronic toxicity, are regulated in very different ways by federal agencies with different governing philosophies, and are ultimately based on the same core set of reliable animal-based tests (acute, subchronic, chronic and specialty endpoint studies such as immunotoxicological or neurodevelopmental studies). The latter point was addressed by the third speaker, Dr. Gary Williams, who reviewed the toxicology data requirements that support GRAS determinations and highlighted some alternative testing approaches that meet the rigorous safety standard yet employ a shorter experimental protocol relative to the typical chronic/carcinogenicity assays used now. Dr. Williams, a professor at New York Medical College and Director of the Department of Pathology Medicine, Food and Chemical Safety Program, also touched an area that saw much discussion throughout the two days: the growing use of non-animal based toxicological methods ("Tox 21 approaches") and how this interfaces (or doesn't interface as the case may be) with the NGO call for FDA to modernize its science. By and large, workshop speakers who addressed this issue all delivered the identical message that, while *in vitro* and *in silico* approaches show promise to reduce testing burden and shorten the overall approval process, these methods are not yet mature enough to do little more than help prioritize subsequent animal-based tests. In addition, while it appears now that the evolution of modern toxicological testing appears headed towards a "systems biology" approach, this may yet be another decade or more in the making.

The second day featured several detailed and insightful presentations that explored both the "technical element" and "common element" (i.e. "general recognition") regulatory standards used for GRAS determinations, informative presentations from industry, academia and the government, and ended with a forward-looking panel discussion. Dr. Michael Dourson, former EPA official and President of Toxicology Excellence in Risk Assessment, started off the second day by reviewing a potpourri of advances in the chemical toxicology and risk assessment world that are used to differing degrees in the food additive toxicology and risk assessment world. Dr. Dourson outlined approaches and considerations that GRAS determinants should employ in order to be protective and current, including introducing the concept of organizing and thinking about biological effects from a "mode of action" perspective – one of the tenets of Tox 21 that everyone agreed was worthwhile (Tox 21 Consortium, 2015). Next, Dr. David Hattan, a longtime employee of the FDA Center for Food Safety and Applied Nutrition, reviewed the history and source materials that FDA relies upon to make its safety determinations and provided some additional insight into how newer toxicological tests are introduced into regulation; thus addressing some of the complexities surrounding the NGO request for FDA to "modernize" its science. Dr. Claire Kruger, recognized expert in scientific, regulatory and strategic issues surrounding foods, consumer products and pharmaceuticals and President of Spherix Consulting Inc., amplified and enhanced the information presented regarding toxicity data requirements by showing that many of these same technical and regulatory procedures (and in many cases, the exact same data) have been used successfully all around the world. Dr. Kruger provided the basis for another one of the overarching messages of the workshop: the procedures in place to incorporate new food additives into the marketplace have been used successfully for many decades and these procedures used worldwide are all grounded in the same well-understood toxicological and risk assessment principles.

Perhaps the highlight for most attendees during the second day was the lunchtime keynote presentation given by Dr. Antonia Mattia, the current Director of Biotechnology and GRAS Notice Review Division (Office of Food Additive Safety, CFSAN) at FDA. She provided a rich history of the GRAS program from the early days of food toxicology at FDA up through the current day, including an overview of most recent critiques from the GAO and NGOs. In trying to address the path forward, Dr. Mattia pointed out some of the key challenges and issues FDA faces in trying to respond to its critics, namely:

(1) the 1997 proposed rule that changed the GRAS process from a premarket petition approval process to a voluntary notification process still guides the GRAS notice process today and has yet to be finalized;
(2) there has been no mandated formal long-term and/or cyclical process to routinely reevaluate GRAS substances over time since the 1958 Food Additives Amendment as FDA lacks the Congressional authority to do so and any such future initiative should apply to all food-related regulatory approvals or notifications (i.e. color additives, food contact substances, food additives, and GRAS listed, affirmed or notified ingredients);
(3) the underlying reasons and process by which GRAS notifications are withdrawn are likely misunderstood by the public and do not necessarily indicate any safety issue with the ingredient
(4) the level of FDA resources and personnel would have to be massively expanded in order to be able to handle the increased workload that would result from reinstituting the premarket GRAS affirmation petition (i.e. pre-1997) process; and
(5) FDA has worked diligently with the GAO to address its concerns and action on all its major recommendations are either completed or well underway (including finalization of the 1997 rule and a post-market review strategy).

Finally, Dr. Mattia shared some of FDA's current thinking and plans in response to recent critiques. Most importantly, FDA is taking the concerns of its critics regarding conflict of interest (COI) policy rather seriously. At the heart of the NGO critique regarding COI is the "common knowledge" requirement for evidence of scientific consensus among qualified experts regarding safety based on available data and its apparent clash with the reality that qualified experts generally are compensated for reviewing data and providing their expert opinion. Critics have also noted that certain experts have participated in an inordinate number of GRAS determinations over the years. Again, this criticism clashes with the reality that those very same experts sat on the Select Committee on GRAS Substances (SCOGS) that reviewed the GRAS/food additive status of hundreds of ingredients at the request of FDA, and were therefore sought out by industry precisely because of this critical experience and high credibility with the agency (US FDA, 2015). Seeking the same expertise that FDA sought and relied upon is not a conflict of interest. Nonetheless, both GAO (US GAO, 2010) and the NGOs urged FDA to issue guidance on COIs (*e.g.,* Pew Charitable Trusts, 2013; CSPI, 2015; Neltner and Maffini, 2014). Given that FDA views the COI issue as relevant for both FDA reviews and GRAS