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Safety pharmacology investigations in toxicology studies: An industry survey

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ABSTRACT

Introduction: The Safety Pharmacology (SP) Society (SPS) conducted an industry survey in 2012 in an attempt to define current industry practices as they relate to inclusion of safety pharmacology (SP) endpoints into Toxicology studies. **Methods**: A total of 361 participants from Asia (9.1%), Europe (19.4%) and North America (71.4%) responded to the survey. The preponderance of respondents were toxicologists (53.2%) followed by safety pharmacologists (27.2%) and scientists involved in the conduct of both disciplines (19.6%). Most participants (58.6%) were from pharmaceutical companies employing more than 500 employees. **Results**: A majority (68.2%) reported having experience in designing, performing or interpreting the SP component of a study when performed as part of a toxicology study. Some participants (42.0%) had submitted data to a regulatory agency where ICHS7 studies were performed as part of a toxicology study rather than as a standalone study. When comparing species that were used in studies in which SP was added to toxicology studies, canines were the most frequently reported animals used for new chemical entities (NCE) whereas non-human (NH) primates were the most frequent for the assessment of biological agents. The most frequent primary motivator for adding ICHS7 SP endpoints to regulatory toxicology studies was to generate additional data to allow for determination of an integrated risk assessment thereby testing Confidence in Safety (CIS) to better manage and/or mitigate risk. The current ability to add safety pharmacology endpoints into regulatory toxicology studies was used to address a specific concern (by 42.1% of respondents) to allow management of risk more effectively (36.8%) or to generate data that contributes to cessation of the progression of a compound (21.1%). For an NCE, SP measurements in toxicology studies were conducted in addition to standalone SP studies (by 40.6% of respondents) or in addition/instead of standalone safety pharmacology studies (by 39.8% of respondents). For biological agents, a majority (74.3%) indicated SP measurements in toxicology were conducted instead of standalone studies as outlined in the ICHS6 guideline while inclusion of SP endpoints in toxicology studies for biological agents in addition to standalone studies was reported by only 25.7% of the respondents. **Discussion**: The survey highlights that obtaining regulatory agreement for the proposed combined SP/Tox study designs may be useful before study conduct in some cases. Respondents suggest that such discussion could occur at the pre-IND meeting before the IND/CTA enabling program.

1. Introduction

Non-clinical drug safety testing encompasses use of a broad range of assays. Recently, application of *in silico* modeling was suggested to complement early safety screening methods (Taboureau & Jørgensen, 2011) in order to supplement standard *in vitro* methods (Bowes et al., 2012) and *in vivo* animal studies using uniform methods in accepted test species. Since the instigation of safety pharmacology as a discipline there has been a greater degree of regulatory oversight in the establishment of validated, specific and sensitive non-clinical screening methods to ensure greater opportunity to detect the hazard potential of NCEs. Despite this, the success rate for drug approvals over the last few decades has been low and only in 2012 did it actually increase — a 15 year high that saw 39 drugs being approved by the FDA, approximately 33% higher than the average yearly approvals for the previous two decades (Mullard, 2013). An International Life Sciences Institute (ILSI) workshop in 1999 examined the strengths and weaknesses in non-clinical studies and their prediction of human toxicity (Olson et al., 2000). Rodent and non-rodent toxicity studies showed a true positive concordance rate of only 71% in

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predicting human toxicity (Olson et al., 2000). Consequently, overarching drug development paradigms must be constantly challenged (Lee, Authier, Pugsley, & Curtis, 2010) and strategies improved to identify safety concerns (Turner, 2009).

Prior to 2000, SP was an ill-defined component of the highly defined industrial 'acute toxicological' process conducted for NCEs. So initially, these studies were usually undertaken by toxicologists, albeit, with study paradigms that differed substantially between each discipline. However, today SP is a unique component discipline of pharmacology that derives its ethos and strategy from roots within discovery biology as well as toxicology (Pugsley, Authier & Curtis, 2008; Pugsley, Gallacher, Towart, Authier & Curtis, 2008). It is concerned with the generation of a risk assessment for NCEs using a wide range of *in vitro* and non-clinical models strategically used at timing from early discovery to late stage safety testing. The current definition of SP is "…those non-clinical studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relationship to exposure in the therapeutic range and above" (see Anon, 2001; Pugsley, 2004; Pugsley, Authier, et al., 2008; Pugsley, Gallacher, et al., 2008). This definition clearly includes 'acute toxicology' study, but has a much broader scope and uses very highly refined data acquisition methods to monitor functional (physiological, biochemical and behavioral) endpoints in validated animal models (Lindgren et al., 2008; Valentin, Bass, Atrakchi, Olejniczak, & Kannosuke, 2005). Thus, single dose SP studies despite being dissimilar to repeat dose toxicology studies (which identify potential end organ toxicities) carry the mandate to provide identification of potential hazards to humans.

It has been suggested that the functional endpoints defined by the developed methods applied in the assessment of SP studies be included into toxicology studies (Luft & Bode, 2002; recently reviewed by Redfern et al., 2013). Such an action may reduce drug attrition through missed or lack of observed toxicity using each study type independently. The integration of relevant SP-related endpoints in repeat toxicology studies could potentially strengthen the overall risk assessment strategy and also represents a potential opportunity to reduce the number of animals used (in keeping with the 3Rs agenda) and thereby limit drug development costs. This approach has been debated for more than a decade (Luft & Bode, 2002) but industry practices remain unmodified and data to support scientific and regulatory acceptability of an integration of SP endpoints into toxicology studies have been mostly anecdotal and without serious consideration.

Thus, the goal of this industry survey was to evaluate current practices relative to the inclusion of SP study endpoints in toxicology studies and also to ascertain from participants on their thoughts regarding the advantages/disadvantages and acceptability of this combination strategy in the non-clinical safety assessment of new drugs.

2. Results

All results are presented as the percentage of total response rate per question, as percentage of total number of scientists that responded to each question or number of responding scientists.

2.1. Study survey demographics

Three-hundred-sixty-one (361) scientists from various fields of expertise (Panel A) and from multiple continents (Panel B) participated in the survey (Fig. 1). A predominance of participants from North America was likely due to the greater proportion of scientists from this geographical region in the population solicited to take this survey. Participants were distributed between diverse organization types (Panel C) and sizes (Panel D) but a predominance of responses from large organizations (>500 employees) was observed. This may be attributed to the larger number of employees from larger companies (*e.g.*, pharmaceutical; contract research organizations) in the global drug development community. Consequently, the results from the survey reflect practices and perceptions of individuals working predominantly in larger institutions. It was interesting to note that a majority of study participants (67.2%) had experience with the inclusion of SP endpoints into toxicology studies (Panel E); however, a majority had never submitted data from combined SP/Tox studies to address the S7 requirements to the regulatory agencies (Panel F). All survey results were included and may represent a limitation as some participants had no experience with inclusion of SP endpoints into toxicology studies.

2.2. SP endpoints in toxicology studies survey results

As anticipated, a greater proportion of the participants had experience with the inclusion of regulatory SP study endpoints into toxicology studies for biologics (59.7%) than with new chemical entities (44.8%). This is in accord with the ICH S6(R1) guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (Anon, 2012) which advocates the incorporation of SP into regulatory toxicology studies. As illustrated in Table 1, most participants include SP measurements at baseline (73.6%) but the timing of post-dosing evaluations was relatively variable. A majority (45.8%) reported always taking measurement study Day 1 (Day 1 = first day of dosing) of the toxicity study, but many (almost 40%) did assessment on Day 2, most likely to avoid confounding influences on Day 1 (*e.g.*, repeated blood sampling). Most participants occasionally stagger the study start (59.6%) in order to measure SP endpoints on the appropriate day (Table 2). Most participants (89.8%) reported that the inclusion of SP endpoints into regulatory toxicology studies did not result in a deviation from GLP compliance. When participants received feedback from regulatory authorities, the agency considered the proposed methodologies acceptable in most cases (only 4 out of 140 respondents had the agency consider the methodology unacceptable, see Table 3) with minor differences across therapeutic areas (Table 4).

When conducting regulatory studies for new chemical entities (NCE), SP endpoints were added to studies using various species (given mouse, rat canine, non-human primates (NHP) and mini-pig as choices) — responding scientists selected canines as the most frequently used species (Fig. 2). This is likely in keeping with both the ICH S7A SP guidance and also the M3(R2) toxicology guidance describing the nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals (Anon, 2009). The NHP was the most frequent non-clinical choice for use in the study of biological agents (Fig. 3), as per the ICH S6 guidance. A broad range of SP endpoints has been added to regulatory toxicology studies when evaluating an NCE. Of all the SP study or endpoint types, the CNS evaluation (functional observation battery or FOB) in the rat was the most frequent addition in studies with NCE, followed by an ECG evaluation in restrained animals (canine and NHP) and respiratory measurements (rat, canine and NHP) (Fig. 4)). For regulatory toxicology studies on biologicals, the SP methodologies used in toxicity studies were similar to those for NCE assessments where ECG in restrained (and jacketed) animals, inclusion of the FOB and respiratory measurements was added to the regulatory toxicology studies by most survey respondents (Fig. 5). Similarly, the number of NHP studies conducted was higher for this class of drugs in development (Fig. 5).

Among the meaningful *advantages* of adding SP endpoints into toxicology studies, a majority of survey participants included that an important/very important feature was a reduction in the overall number of animals (3Rs) used. Similarly, the added value in interpretation that could be derived due to combined experimental endpoints in the same animals was deemed important. However, the increased sensitivity based on group sizes in toxicology studies and assessment after long-term exposure (beyond a single dose) was determined to be the most important advantage for conducting integrated studies (Table 5). Based upon the experience of participating scientists, the most important *disadvantages* of incorporating S7 SP endpoints into regulatory toxicology studies included interference on functional SP endpoints by toxicology-related activities in the room that are