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Original article

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

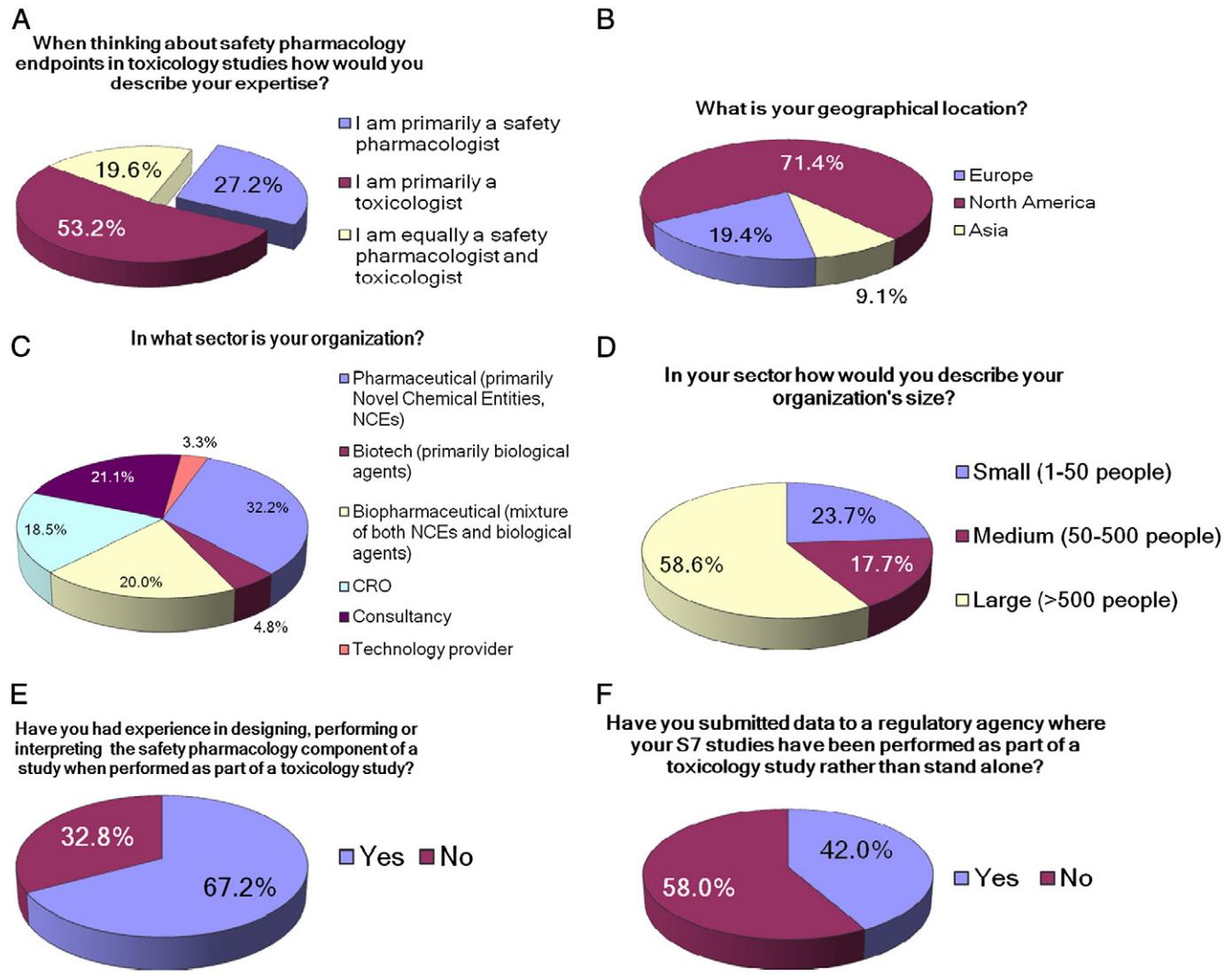

Fig. 1. Incorporation of SP study endpoints into toxicology studies: survey demographics. Panels A–F describe the characteristics of those responding to the survey in terms of expertise (A), geographical location (B), organization affiliation (pharmaceutical, biotechnology, biopharmaceutical, consultancy or technology provider), size of the organization (D), experience of incorporation of SP endpoints into toxicology studies (E) and regulatory submission of S7 safety data derived from combined studies (F).

unavoidable due to the nature of the toxicology study (Day 1 of dosing). Similarly, there were concerns regarding the sensitivity of SP endpoints incorporated into toxicity studies which may be insufficient to provide an acceptable assessment (Table 6). The most frequent primary motivator for adding SP endpoints to regulatory toxicology studies answered by scientists in the survey was to generate additional valuable data to allow an integrated risk assessment, thereby enhancing the Confidence in Safety (CIS) assessment, to identify, manage, and/or mitigate risk (Table 7). The ability to add SP endpoints onto regulatory toxicology studies was used to address a specific concern (42.1%), to allow management of risk more effectively (36.8%) or to generate data that contribute to halt the progression of a compound (21.1%).

For NCEs, survey respondents indicated that SP measurements in toxicology studies were conducted *in addition to* standalone SP studies (by 40.6%) or in addition or instead of standalone SP studies (by 39.8%). For biological agents, a majority indicated SP measurements in toxicology were conducted instead of standalone studies (74.3%) while inclusion of SP in toxicology studies for biological agents in addition to standalone studies was reported in 25.7%.

Table 1
Study day(s) SP endpoints are measured in toxicology studies.

On what study day(s) do you measure safety pharmacology endpoints in your toxicology study (Day 1 = first day of dosing)?		
Answer options	Response percent	Response count
Baseline	73.6%	156
Day 1	45.8%	97
Day 2 to avoid interferences from study activities on Day 1	39.6%	84
Last week of dosing	61.3%	130
After the last dosing	39.6%	84
During week 1 for biological agents	30.7%	65

Table 2
The need to stagger the study start in order to measure SP endpoints.

Have you needed to stagger the study start in order to measure safety pharmacology endpoints on the appropriate day?		
Answer options	Response percent	Response count
Never	26.1%	57
Occasionally	59.6%	130
Routinely	14.2%	31

Table 3
Regulatory authority feedback regarding methodology used when incorporating SP study endpoints into toxicology studies.

If you have received feedback from regulatory authorities what did it indicate?				
Answer options	This methodology was considered acceptable by the agency	This methodology was NOT considered acceptable by the agency	The agency suggested modification(s) to the design	Response count
ECG in restrained animals	15	0	1	16
ECG implanted telemetry	15	1	0	16
ECG jacketed animals	12	0	2	14
Arterial pressure with indirect measurement (cuff)	15	1	0	16
Arterial pressure with implanted catheter *e.g.* ear artery	5	0	0	5
Arterial pressure with implanted telemetry device	13	1	0	14
Functional observation battery	26	1	0	27
Respiratory measurement	21	0	1	22
Renal assessment	9	0	0	9
GI assessment	9	0	0	9

Table 4
Regulatory authority feedback by therapeutic area regarding methodology used when incorporating SP study endpoints into toxicology studies.

When receiving feedback on inclusion of SP endpoints into toxicology studies, was the view of the regulatory agency influenced by the therapeutic area?					
Answer options	My organization has experience with the following therapeutic areas	Methodology accepted	Methodology NOT accepted	Modifications to methodology required	Response count
Oncology	46	38	1	0	50
Anti-inflammatory	29	20	0	0	31
GI	16	9	0	1	18
CV	29	19	0	0	31
CNS	32	19	0	0	35
Anti-bacterial/anti-viral	22	14	1	0	24

2.3. Comments from participants to the industry survey

A total of 428 comments were received from the participants during this industry survey and the topics most frequently reported are briefly summarized. A number of participants suggested that the inclusion of SP study endpoints into toxicology studies is generally acceptable to low risk situations (*i.e.*, for biological agents with high affinity to the efficacy target and low incidence of off-target binding and potential or toxicity) or when a higher risk/benefit ratio is acceptable (*e.g.*, during the development of oncology products where ICH S9 (Anon, 2010) states that "Conducting stand-alone SP studies to support studies in patients with advanced cancer is not required. In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials appropriate SP studies described in ICH S7A and/or S7B should be considered". In the absence of a specific risk, such studies will not be called for to support clinical trials or for marketing.). Some participants also suggested that inclusion of SP endpoints into toxicology studies was valuable in order to obtain an early safety assessment profile of a drug candidate.

Participants reported that for an IND submission, they believed that a standalone cardiovascular safety study was preferred with the incorporation of SP endpoints for other core battery systems (*i.e.*, CNS and respiratory) into the rat toxicology study (presumably for an NCE). Some survey comments emphasized the value of obtaining regulatory feedback (acceptance) of proposed combined SP/Tox study designs *before* the IND/CTA enabling program is conducted. Although the specific circumstances were not identified, it is plausible that regulatory feedback could assist the non-clinical safety assessment in some cases.

The ability to evaluate SP endpoints after repeated dosing (and hence drug exposure) and resulting cumulative effects was reported by many to be advantageous to the development program. This

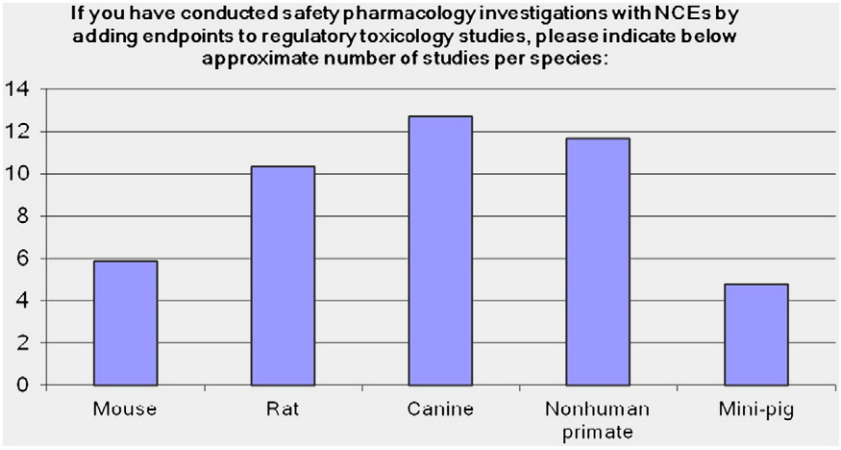

Fig. 2. Number of studies conducted in different non-clinical animal species per year in which SP endpoints were added into regulatory toxicology studies for a New Chemical Entity (NCE).

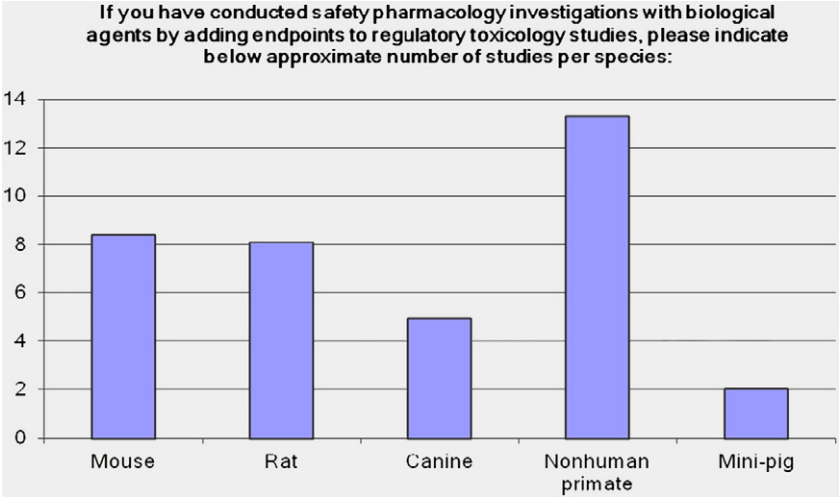

Fig. 3. Number of studies conducted in different non-clinical animal species per year in which SP endpoints were added into regulatory toxicology studies for a biological agent.

advantage was reported for both subchronic (≤3 month) or chronic (≥6 month) toxicology studies. More specifically, a number of participants reported using jacketed external telemetry (JET) methods to evaluate the ECG after repeat dose administration of the test article. Respondents indicated that from experience, a higher variability of ECG parameters was obtained in jacketed animals compared to surgically implanted devices while heart rate values obtained in the physiological range with JET animals were considered an advantage over data obtained from restrained animals. The reliability of blood pressure data derived from toxicology animals was questioned by a number of the participants while high definition oscillometry (HDO) was reported as a valuable methodology for blood pressure monitoring by others. Some marked reservation exists toward the use of surgically implanted telemetry monitoring devices (as used in SP studies routinely) in toxicology animals. The ability to evaluate functional endpoints (SP-related) and histology or other toxicity measurement endpoints in the same animals was considered an advantage to the use of an integrated SP/Tox study design. A recognized challenge of SP interrogations during toxicology studies is that reported functional changes could be due to direct consequences to developing organ toxicity (*e.g.* cardiovascular or CNS) or an indirect effect (or secondary response) to drug-induced general toxicity (morbidity), which is the main objective of toxicity studies.

Logistical considerations were raised by several survey participants concerned with loss in the sensitivity of the SP model endpoints due to the numerous activities ongoing in the animal room during the conduct of toxicology studies. In this context, the selection of proper SP endpoints for use in these studies was deemed important to minimize interference from toxicology activities. Parallel groups in an isolated (quiet) environment (separate study room) for SP measurements were suggested as options, but this effectively translates into a separate sub-study where the gains (advantages) of an integrated study design, compared to individual (dedicated) SP studies, could be reduced to the point of being pointless. The expertise of the personnel (scientific and technical) was highlighted as a success factor for conducting combined SP/Tox studies by a number of participants and training of both technical and scientific staff was reported as an important element to ensure quality is maintained by the use of such a study design. Communication among the team (*e.g.* pre-study meeting, daily communication with technical staff) was listed as a key point to harmonize SP and toxicology procedures in the same study. Additionally, adequate animal acclimation prior to monitoring of functional endpoints in toxicology

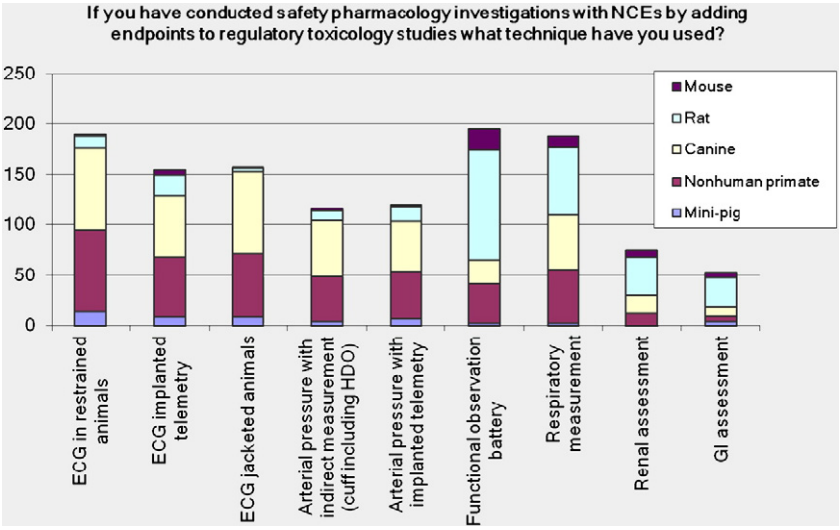

Fig. 4. Methods used in different non-clinical animal species in which SP endpoints were added into regulatory toxicology studies for an NCE.

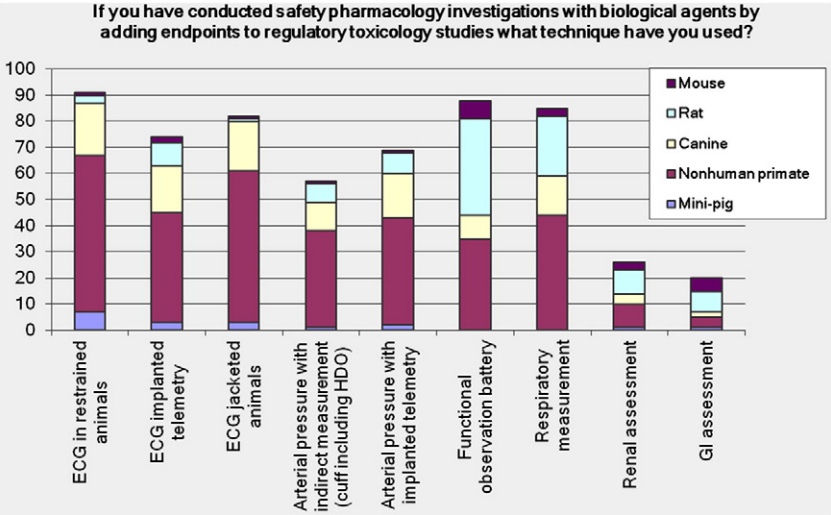

Fig. 5. Methods used in different non-clinical animal species in which SP endpoints were added into regulatory toxicology studies for a biological agent.

studies was reported as an essential element for the implementation of this strategy. Lastly, the onset of severe toxicity could lead to unscheduled loss of animals, or the unanticipated inability to capture data on pre-selected study days, which can compromise data integrity, and the interpretation of overall study findings.

Survey comments included the fact that scientists should understand the mode of action and significance (or lack thereof) of the potential toxicity or change in functional endpoint for humans — this was considered a driver for requests to conduct studies with combined SP/Tox endpoints. The decision to opt for a combined SP/Tox design was reported to be complicated by risk aversion in the current economic environment while continuing development and hence improvement in available technologies was considered a facilitator of such approach.

3. Discussion

Functional adverse effects remain an important cause of drug failure (Pugsley, Authier, et al., 2008; Pugsley, Gallacher, et al., 2008; Valentin & Hammond, 2008) and strategies that compromise quality may present a negative risk benefit ratio in the overall drug development plan (Pugsley, Authier, et al., 2008; Pugsley, Gallacher, et al., 2008). While most participants confirmed having some experience with combined SP/Tox study designs, most had never submitted such data to regulatory authorities. Justification for the relatively limited number of submissions to regulators may reside with the three most reported disadvantages of combined SP/Tox designs which included interference of sensitive functional SP endpoints by toxicology activities, insufficient sensitivity to provide an acceptable assessment

Table 5
Responses characterizing the *advantages* of adding S7 SP endpoints into regulatory toxicology studies.

Based on your experience, which of the following do you consider a meaningful advantage of adding S7 safety pharmacology endpoints to regulatory toxicology studies					
Answer options	Very important advantage	Important advantage	Modest advantage	Not an advantage	Response count
Increased sensitivity due to increased number of treated animals and assessment after repeat dosing	43	73	35	19	170
Overall reduction in number of animals used (3Rs)	57	68	40	16	181
Added value interpretation due to combined experimental endpoints in same animals	52	71	41	14	178
Practice acceptable to regulatory agencies	42	53	56	17	168
Cost savings on overall program development	43	40	69	23	174
Allows better risk mitigation by enabling more diverse evaluation panels for core battery systems	29	61	57	24	169

Table 6
Responses characterizing the *disadvantages* of adding S7 SP endpoints into regulatory toxicology studies.

Based on your experience, which of the following do you consider a meaningful disadvantage of adding S7 safety pharmacology endpoints onto regulatory toxicology studies					
Answer options	Very important disadvantage	Important disadvantage	Modest disadvantage	Not a disadvantage	Response count
Interferences on functional safety pharmacology endpoints by toxicology related activities in the room are unavoidable	41	55	52	26	174
Safety pharmacology investigations in toxicology studies could have significant interferences on toxicology endpoints and parameters.	13	35	67	59	173
Assignment of safety pharmacology expert technical staff to conduct investigations in toxicology studies is problematic	15	27	62	68	172
Sensitivity of safety pharmacology in toxicology is insufficient to provide an acceptable assessment in most programs	31	47	46	47	171
Safety pharmacology in toxicology represents a risk during regulatory submission as it is not an industry standard	15	25	72	58	169

Table 7
Responses describing the primary motivating factor for adding S7 SP endpoints into regulatory toxicology studies.

In your organization, what is the primary motivator for adding S7 safety pharmacology endpoints to regulatory toxicology studies?				
Answer options	Primary motivator	Not a motivator	Unsure	Response count
Where appropriate as an alternate to standalone safety pharmacology studies to address ICH S7 requirements and so save money.	71	65	31	167
To address the 3Rs.	86	53	26	165
To generate additional valuable data to allow an integrated risk assessment thereby testing Confidence in Safety (CIS) to better manage and/or mitigate risk.	111	40	22	173

in most programs and the fact that combined study designs represent a risk as it is currently not the industry standard. The current survey highlights the fact that while the addition of SP endpoints into toxicology studies is common for those studies involving rodents as the non-clinical species it appears to be even more frequent in non-rodents, specifically NHP (for both biologicals and NCEs) and to a lesser degree in canines (for NCEs but less for biologicals) (Figs. 2 & 3). The high translational potential of larger species given their phylogenic proximity to humans, may be a motivator to include SP endpoints in non-rodent toxicology studies. Increasing concerns were raised by the scientific community over the translation of data obtained in rodent models to the clinic (Arnett & Viney, 2007; Koboziev, Karlsson, Zhang, & Grisham, 2011; Seok et al., 2013) and toxicology studies in non-rodent species may represent an opportunity to obtain functional evaluations in vital organ systems, in an effort to increase the predictivity of non-clinical safety assays. The relevance of non-rodents specifically in regard to cardiovascular physiology, especially cardiac electrophysiological parameters, *e.g.* for ECG evaluation for QTc prolongation, and the emphasis on screening for cardiovascular liabilities in drug development may also contribute to the frequent addition of SP endpoints into non-rodent toxicology studies. Comments provided by participants highlight the importance of thorough risk assessment in designing combined SP/Tox designs based on 1) characteristics of the test article (*e.g.* NCE or biological agents, PK, drug class), 2) the indication (*e.g.* oncology *vs*. cardiovascular disease, *etc.*) including risk tolerance of the patient population and 3) validation data and estimated sensitivity in conditions that prevail in combined SP/Tox studies. Extensive efforts and resources are continuously being deployed in SP efforts to validate the sensitivity and specificity of various *in vitro*/*ex vivo* and *in vivo* experimental models (Authier, Tanguay, Gauvin, Fruscia, & Troncy, 2007; Authier et al., 2011; Baird et al., 2013; Chui & Vargas, 2009; Guo, Dong, & Guthrie, 2009; Kano et al., 2005; Lawrence, Pollard, Hammond, & Valentin, 2005; Markert et al., 2009; Miyazaki et al., 2005; Omata, Kasai, Hashimoto, Hombo, & Yamamoto, 2005; Sasaki, Shimizu, Suganami, & Yamamoto, 2005; Shiotani, Harada, Abe, Hamada, & Horii, 2007; Vormberge, Hoffmann, & Himmel, 2006). The sensitivity of SP models is recognized as a cornerstone to optimize the study design (Pugsley, Towart, Authier, Gallacher, & Curtis, 2010). At the current time, validation of SP measures in the toxicology study environments represents an area with scarce scientific literature. The publications of these study designs by safety pharmacologists and toxicologists at both pharmaceutical companies and contract research organizations is needed in order to evaluate all aspects of routine novel study designs. Comparative studies outlining the types of studies where SP endpoints have been integrated into acute, subchronic and chronic toxicology studies would be valuable to evaluate potential differences between standalone and integrated SP endpoints.

In conclusion, functional endpoints such as those monitored in SP studies remain an area of prime interest for the drug development industry. In some cases, toxicology studies represent an opportunity to obtain early safety assessments while in other circumstances the potential to add monitoring for a broad range of physiological systems can help address a specific safety concern.

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References

Anon (2001). ICHS7A: Safety pharmacology studies for human pharmaceuticals. *Federal Register*, *66*, 36791–36792.
Anon (2009). *M3(R2): Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals.*
Anon (2010). S9: Nonclinical evaluation for anticancer pharmaceuticals. *Federal Register*, *44*, 10487 (Docket No. FDA/2009/D/0006).
Anon (2012). S6(R1): Addendum: Preclinical safety evaluation of biotechnology-derived pharmaceuticals. *Federal Register*, *77*, 29665–29666.
Arnett, H. A., & Viney, J. L. (2007). Considerations for the sensible use of rodent models of inflammatory disease in predicting efficacy of new biological therapeutics in the clinic. *Advances in Drug Delivery Review*, *59*, 1084–1092.
Authier, S., Gervais, J., Fournier, S., Gauvin, D., Maghezzi, S., & Troncy, E. (2011). Cardiovascular and respiratory safety pharmacology in Göttingen minipigs: Pharmacological characterization. *Journal of Pharmacological and Toxicological Methods*, *64*, 53–59.
Authier, S., Tanguay, J. F., Gauvin, D., Fruscia, R. D., & Troncy, E. (2007). A cardiovascular monitoring system used in conscious cynomolgus monkeys for regulatory safety pharmacology. Part 2: Pharmacological validation. *Journal of Pharmacological and Toxicological Methods*, *56*, 122–130.
Baird, T. J., Bailie, M., Patrick, D. J., Moddrelle, D., Yoder, J., Gauvin, D. V., et al. (2013). Influence of surgically implantable telemetry solutions on in-life and post-mortem toxicology endpoints. *Journal of Pharmacological and Toxicological Methods*, *67*, 148–161.
Bowes, J., Brown, A. J., Hamon, J., Jarolimek, W., Sridhar, A., Waldron, G., et al. (2012). Reducing safety-related drug attrition: The use of in vitro pharmacological profiling. *National Review of Drug Discovery*, *11*, 909–922.
Chui, R. W., & Vargas, H. M. (2009). A comparison of three software platforms for automated ECG analysis. *Journal of Pharmacological and Toxicological Methods*, *60*(1), 28–38.
Guo, L., Dong, Z., & Guthrie, H. (2009). Validation of a guinea pig Langendorff heart model for assessing potential cardiovascular liability of drug candidates. *Journal of Pharmacological and Toxicological Methods*, *60*, 130–151.
Kano, M., Toyoshi, T., Iwasaki, S., Kato, M., Shimizu, M., & Ota, T. (2005). QT PRODACT: Usability of miniature pigs in safety pharmacology studies: Assessment for drug-induced QT interval prolongation. *Journal of Pharmacological Sciences*, *99*(5), 501–511.
Koboziev, I., Karlsson, F., Zhang, S., & Grisham, M. B. (2011). Pharmacological intervention studies using mouse models of the inflammatory bowel diseases: Translating preclinical data into new drug therapies. *Inflammatory Bowel Diseases*, *17*(5), 1229–1245.
Lawrence, C. L., Pollard, C. E., Hammond, T. G., & Valentin, J. P. (2005). Nonclinical proarrhythmia models: Predicting Torsades de Pointes. *Journal of Pharmacological and Toxicological Methods*, *52*, 46–59.
Lee, N., Authier, S., Pugsley, M. K., & Curtis, M. J. (2010). The continuing evolution of torsades de pointes liability testing methods: Is there an end in sight? *Toxicology and Applied Pharmacology*, *243*(2), 146–153.
Lindgren, S., Bass, A. S., Briscoe, R., Bruse, K., Friedrichs, G. S., Kallman, M. J., et al. (2008). Benchmarking safety pharmacology regulatory packages and best practice. *Journal of Pharmacology and Toxicological Methods*, *58*, 99–109.
Luft, J., & Bode, G. (2002). Integration of safety pharmacology endpoints into toxicology studies. *Fundamental and Clinical Pharmacology*, *16*(2), 91–103.
Markert, M., Stubhan, M., Mayer, K., Trautmann, T., Klumpp, A., Schuler-Metz, A., et al. (2009). Validation of the normal, freely moving Göttingen minipig for pharmacological safety testing. *Journal of Pharmacological and Toxicological Methods*, *60*, 79–87.
Miyazaki, H., Watanabe, H., Kitayama, T., Nishida, M., Nishi, Y., Sekiya, K., et al. (2005). QT PRODACT: Sensitivity and specificity of the canine telemetry assay for detecting drug-induced QT interval prolongation. *Journal of Pharmacological Sciences*, *99*(5), 523–529.
Mullard, A. (2013). 2012 FDA drug approvals. *Nature Reviews Drug Discovery*, *12*(2), 87–90.
Olson, H., Betton, G., Robinson, D., Thomas, K., Monro, A., Kolaja, G., et al. (2000). Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regulatory Toxicology and Pharmacology*, *32*, 56–67.
Omata, T., Kasai, C., Hashimoto, M., Hombo, T., & Yamamoto, K. (2005). QT PRODACT: Comparison of non-clinical studies for drug-induced delay in ventricular repolarization and their role in safety evaluation in humans. *Journal of Pharmacological Sciences*, *99*(5), 531–541.

Pugsley, M. K. (2004). Safety pharmacology matures into a unique pharmacological discipline. *Journal of Pharmacological and Toxicological Methods*, *49*, 137–139.

Pugsley, M. K., Authier, S., & Curtis, M. J. (2008a). Principles of safety pharmacology. *British Journal of Pharmacology*, *154*, 1382–1399.

Pugsley, M. K., Gallacher, D. J., Towart, R., Authier, S., & Curtis, M. J. (2008b). Methods in safety pharmacology in focus. *Journal of Pharmacological and Toxicological Methods*, *58*, 69–71.

Pugsley, M. K., Towart, R., Authier, S., Gallacher, D., & Curtis, M. J. (2010). Non-clinical models: Validation, study design and statistical consideration in safety pharmacology. *Journal of Pharmacological and Toxicological Methods*, *62*, 1–3.

Redfern, W. S., Ewart, L. C., Lainee, P., Pinches, M., Robinson, S., & Valentin, J. -P. (2013). Functional assessments in repeat-dose toxicity studies: The art of the possible. *Toxicology Research*, http://dx.doi.org/10.1039/C3TX20093K.

Sasaki, H., Shimizu, N., Suganami, H., & Yamamoto, K. (2005). QT PRODACT: Inter-facility variability in electrocardiographic and hemodynamic parameters in conscious dogs and monkeys. *Journal of Pharmacological Sciences*, *99*(5), 513–522.

Seok, J., Warren, H. S., Cuenca, A. G., Mindrinos, M. N., Baker, H. V., Xu, W., et al. (2013). Inflammation and host response to injury, large scale collaborative research program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(9), 3507–3512.

Shiotani, M., Harada, T., Abe, J., Hamada, Y., & Horii, I. (2007). Methodological validation of an existing telemetry system for QT evaluation in conscious guinea pigs. *Journal of Pharmacological and Toxicological Methods*, *55*, 27–34.

Taboureau, O., & Jørgensen, F. S. (2011). In silico predictions of hERG channel blockers in drug discovery: From ligand-based and target-based approaches to systems chemical biology. *Combinatorial Chemistry & High Throughput Screening*, *14*(5), 375–387.

Turner, M. (2009). Straight talk with… Mervyn Turner. Interview by Prashant Nair. *Nature Medicine*, *15*(1), 8–9.

Valentin, J. -P., Bass, A. S., Atrakchi, A., Olejniczak, K., & Kannosuke, F. (2005). Challenges and lessons learned since implementation of the safety pharmacology guidance ICH S7A. *Journal of Pharmacological and Toxicological Methods*, *52*, 22–29.

Valentin, J. P., & Hammond, T. (2008). Safety and secondary pharmacology: Successes, threats, challenges and opportunities. *Journal of Pharmacological and Toxicological Methods*, *58*, 77–87.

Vormberge, T., Hoffmann, M., & Himmel, H. (2006). Safety pharmacology assessment of drug-induced QT-prolongation in dogs with reduced repolarization reserve. *Journal of Pharmacological and Toxicological Methods*, *54*, 130–140.