Original article
Safety pharmacology investigations in toxicology studies: An industry survey
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A B S T R A C T
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 employ-
ees. Results: A majority (68.2%) reported having experience in designing, performing or interpreting
SP endpoints in toxicology studies 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 stud-
ies was to generate additional data to allow for determination of an integrated risk assessment thereby test-
ing 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 con-
tributes 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/in-
stead 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.

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1. Introduction
Non-clinical drug safety testing encompasses use of a broad range of
assays. Recently, application of in silico modeling was suggested to com-
plement 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 actu-
ally 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, over-
arching 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 gen-
eration 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 investigates the potential undesirable pharma-
codynamic effects of a substance on physiological functions in relation-
ship 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 behav-
ioral) endpoints in validated animal models (Lindgren et al., 2008;
Valentin, Bass, Atrakchi, Olejniczak, & Kanno-Sukue, 2005). Thus, single
dose SP studies despite being dissimilar to repeat dose toxicology stud-
ies (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 de-
veloped 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 poten-
tially 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 ap-
proach 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 prac-
tices relative to the inclusion of SP study endpoints in toxicology
studies and also to ascertain from participants on their thoughts re-
garding the advantages/disadvantages and acceptability of this com-
bination 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 ex-
pertise (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 geograph-
icical 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; con-
tact research organizations) in the global drug development community.
Consequently, the results from the survey reflect practices and percep-
tions of individuals working predominantly in larger institutions. It was
interesting to note that a majority of study participants (67.2%) had expe-
rience 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 experi-
ence with the inclusion of regulatory SP study endpoints into toxicol-
yogy studies for biologics (59.7%) than with new chemical entities
(44.8%). This is in accord with the ICH S6(R1) guideline for the Pre-
clinical 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 al-
ways 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 respon-
dents 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
group, rat canine, non-human primates (NHP) and mini-pigs as choices) — responding scientists selected canines as the most fre-
quently used species (Fig. 2). This is likely in keeping with both the
ICH S7A SP guidance and also the M3(R2) toxicity guidance de-
scribing the nonclinical safety studies for the conduct of human clin-
ic 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 (func-
tional observation battery or POB) in the rat was the most frequent
addition in studies with NCE, followed by an ECG evaluation in re-
strained animals (cane 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 respon-
dents (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 interpre-
tation 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
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

<table>
<thead>
<tr>
<th>Study day(s) SP endpoints are measured in toxicology studies.</th>
<th>Answer options</th>
<th>Response percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>On what study day(s) do you measure safety pharmacology endpoints in your toxicology study (Day 1 = first day of dosing)?</td>
<td>Baseline</td>
<td>73.6%</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>69.8%</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Day 2 to avoid interferences from study activities on Day 1</td>
<td>39.6%</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Last week of dosing</td>
<td>61.3%</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>After the last dosing</td>
<td>39.6%</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>During week 1 for biological agents</td>
<td>30.7%</td>
<td>65</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>The need to stagger the study start in order to measure SP endpoints on the appropriate day.</th>
<th>Answer options</th>
<th>Response percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you needed to stagger the study start in order to measure safety pharmacology endpoints on the appropriate day?</td>
<td>Never</td>
<td>26.1%</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Occasionally</td>
<td>59.6%</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Routinely</td>
<td>14.2%</td>
<td>31</td>
</tr>
</tbody>
</table>

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).
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 57A and/or 57B 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., 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

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

<table>
<thead>
<tr>
<th>Answer options</th>
<th>This methodology was considered acceptable by the agency</th>
<th>This methodology was NOT considered acceptable by the agency</th>
<th>The agency suggested modification(s) to the design</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG in restrained animals</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>ECG implanted telemetry</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>ECG jacketed animals</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Arterial pressure with indirect measurement (cuff)</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Arterial pressure with implanted catheter e.g. ear artery</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Arterial pressure with implanted telemetry device</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Functional observation battery</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Respiratory measurement</td>
<td>21</td>
<td>0</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Renal assessment</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>GI assessment</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Answer options</th>
<th>My organization has experience with the following therapeutic areas</th>
<th>Methodology accepted</th>
<th>Methodology NOT accepted</th>
<th>Modifications to methodology required</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>46</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>29</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>GI</td>
<td>16</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>CV</td>
<td>29</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>CNS</td>
<td>32</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Anti-bacterial/anti-viral</td>
<td>22</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>24</td>
</tr>
</tbody>
</table>

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).
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 studies was considered important to ensure the quality of the data obtained.
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.

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### Table 5

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

<table>
<thead>
<tr>
<th>Answer options</th>
<th>Very important advantage</th>
<th>Important advantage</th>
<th>Modest advantage</th>
<th>Not an advantage</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased sensitivity due to increased number of treated animals and assessment after repeat dosing</td>
<td>43</td>
<td>73</td>
<td>35</td>
<td>19</td>
<td>170</td>
</tr>
<tr>
<td>Overall reduction in number of animals used (3Rs)</td>
<td>57</td>
<td>68</td>
<td>40</td>
<td>16</td>
<td>181</td>
</tr>
<tr>
<td>Added value interpretation due to combined experimental endpoints in same animals</td>
<td>52</td>
<td>71</td>
<td>41</td>
<td>14</td>
<td>178</td>
</tr>
<tr>
<td>Practice acceptable to regulatory agencies</td>
<td>42</td>
<td>53</td>
<td>56</td>
<td>17</td>
<td>168</td>
</tr>
<tr>
<td>Cost savings on overall program development</td>
<td>43</td>
<td>40</td>
<td>69</td>
<td>23</td>
<td>174</td>
</tr>
<tr>
<td>Allows better risk mitigation by enabling more diverse evaluation panels for core battery systems</td>
<td>29</td>
<td>61</td>
<td>57</td>
<td>24</td>
<td>169</td>
</tr>
</tbody>
</table>

### Table 6

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

<table>
<thead>
<tr>
<th>Answer options</th>
<th>Very important disadvantage</th>
<th>Important disadvantage</th>
<th>Modest disadvantage</th>
<th>Not a disadvantage</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferences on functional safety pharmacology endpoints by toxicology related activities in the room are unavoidable</td>
<td>41</td>
<td>55</td>
<td>52</td>
<td>26</td>
<td>174</td>
</tr>
<tr>
<td>Safety pharmacology investigations in toxicology studies could have significant interferences on toxicology endpoints and parameters.</td>
<td>13</td>
<td>35</td>
<td>67</td>
<td>59</td>
<td>173</td>
</tr>
<tr>
<td>Assignment of safety pharmacology expert technical staff to conduct investigations in toxicology studies is problematic</td>
<td>15</td>
<td>27</td>
<td>62</td>
<td>68</td>
<td>172</td>
</tr>
<tr>
<td>Sensitivity of safety pharmacology in toxicology is insufficient to provide an acceptable assessment in most programs</td>
<td>31</td>
<td>47</td>
<td>46</td>
<td>47</td>
<td>171</td>
</tr>
<tr>
<td>Safety pharmacology in toxicology represents a risk during regulatory submission as it is not an industry standard</td>
<td>15</td>
<td>25</td>
<td>72</td>
<td>58</td>
<td>169</td>
</tr>
</tbody>
</table>
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 to 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 phylogenetic 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 toxicity 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 toxicity 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, Fruscio, & Troncy, 2007; Authier et al., 2011; Baird et al., 2013; Chui & Vargas, 2005; Gao, Dong, & Guthrie, 2009; Kano et al., 2005; Lawrence, Pollard, Hammond, & Valentin, 2005; Markert et al., 2005; Miyazaki et al., 2005; Omata, Kasai, Hashimoto, Hombo, & Yamamoto, 2005; Sasaki, Shimizu, Suganami, & Yamamoto, 2005; Shiotsui, 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 toxicity study environment 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 toxicity 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, toxicity 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


