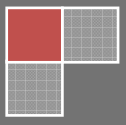
2012

3Rs Benchmarking Survey: Strengths, Opportunities and Next Steps

IQ 3Rs Leadership Group

A 69-question survey was conducted in 2012 to perform a high level assessment of how a number of our IQ member companies are adopting and advancing the 3Rs of Replacement, Reduction and Refinement above and beyond the minimum regulatory requirements.

3Rs Leadership Group
IQ
1/1/2012



Introduction and Scope

The International Consortium on Innovation and Quality (IQ) was created in 2010. As a technically focused organization of pharmaceutical and biotechnology companies, IQ's mission is to advance science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products worldwide. In January 2012, the 3Rs Leadership Group (3Rs LG) was formed with prior approval by the IQ BOD. The mission of the 3Rs LG is to promote sharing and integration of high quality scientific practices to advance the replacement, reduction, and refinement of animals used in the discovery and development of new medicines, vaccines, medical devices and health care products for humans and animals.

With this mission in mind, one of the first initiatives of the 3Rs LG was to create a Benchmarking Working Group (WG) to develop a 3Rs survey. Several of the 3Rs LG company representatives had participated in the 2009-2010 European Federation of Pharmaceutical Industries and Associations' Research Animal Welfare (EFPIA-RAW) group's 3Rs survey and affirmed that this was a worthwhile activity. The 3Rs benchmarking survey was created with input from the Benchmarking WG members and the 3Rs LG members, which represented a total of twenty biopharmaceutical companies at that time. The WG members reviewed the EFPIA survey and used some of the same questions but included other questions to broaden the focus of the survey. The primary goals of the survey were to gather data to assess a variety of current 3Rs practices, to help demonstrate the industry's overall commitment to the 3Rs, to attempt to identify areas of consistency in the 3Rs, to identify opportunities to advance the 3Rs, and to use this information to guide some of the future 3Rs LG strategies. The scope of the survey focused on four main categories of 3Rs questions, including: 1) Management of 3Rs, including the ethical review processes; 2) Technical applications of 3Rs; 3) Scientific applications of the 3Rs; and 4) Promotion and/or communications about the 3Rs.

Fifteen of the twenty 3Rs LG member companies participated in the survey, for a 75% response rate. This report provides an overview of each of the survey questions and a brief summary of what we learned from our member companies based on the survey results. Overall,

It is important to remember that each of the 3Rs LG member companies fully adheres to all applicable animal care and use regulations with regards to consideration of the 3Rs. The focus of the survey was to assess how companies are meeting those regulations and what they are doing to promote and adopt the 3Rs above and beyond the minimum regulations.

the survey data affirmed that the biopharmaceutical industry is highly committed to advancing and adopting the 3Rs for both ethical and scientific reasons and is making progress by promoting a variety of 3Rs initiatives. Nevertheless, the survey results also showed that there are opportunities where our companies should continue to consider new alternatives to

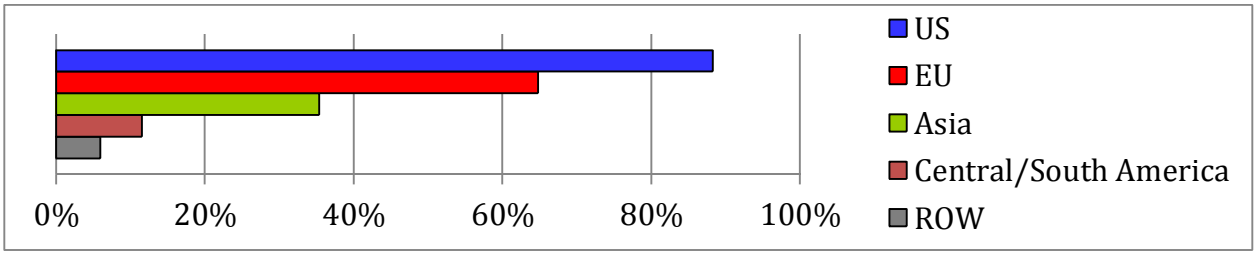
advance some general good practices that promote welfare and the 3Rs. We can do this by working together to share our 3Rs successes and when possible, align our practices for more consistent 3Rs implementation. This report is not meant to suggest that there is one best way for companies to proceed in promoting or adopting the 3Rs since many of these decisions depend on the type of research program being managed and the professional judgment of those involved. There are many different ways to adopt and promote the 3Rs. In fact, one of the strengths of the 3Rs LG is that it allows our member companies' 3Rs experts to share practices in a precompetitive way to enhance learning and promote discussions with the aim of advancing the 3Rs across the industry. This report should serve as a useful tool to help member companies learn what peer companies are doing and should also help to promote more consistent 3Rs practices across member companies, when applicable.

Survey Responses

A brief summary of how the 3Rs LG interpreted the data from the sixty-nine questions and what we believe are some key take home messages from the survey are provided below.

1. **Please specify what regions(s) you will be responding for?**

   Fifteen of twenty companies completed the survey. Of the twenty 3Rs LG member companies represented at the time of the survey, there is a great diversity in the size of the companies, with the smallest having approximately fifteen hundred employees and the largest having more than one hundred thousand employees. A majority of these companies are global biopharmaceutical companies although some conduct all of their animal studies at contract laboratories. Fourteen companies provided one "global" response but one company submitted three different survey responses with site-specific input from their various regions. Thus, there was a maximum of seventeen responses to any question, although many times some respondents skipped a question, presumably because the question was not applicable to their company's program or perhaps the person(s) completing the survey didn't think they could provide an accurate response to a particular question.



2. **Do you have a global animal welfare policy across all animal sites, or do you allow difference techniques and practices at each site?**

   86% of companies with more than one vivarium do have a global animal welfare policy or animal welfare standards that apply across all sites. One of the two companies that did not have a global policy in place was committed to creating one soon. Importantly, a majority of our companies still

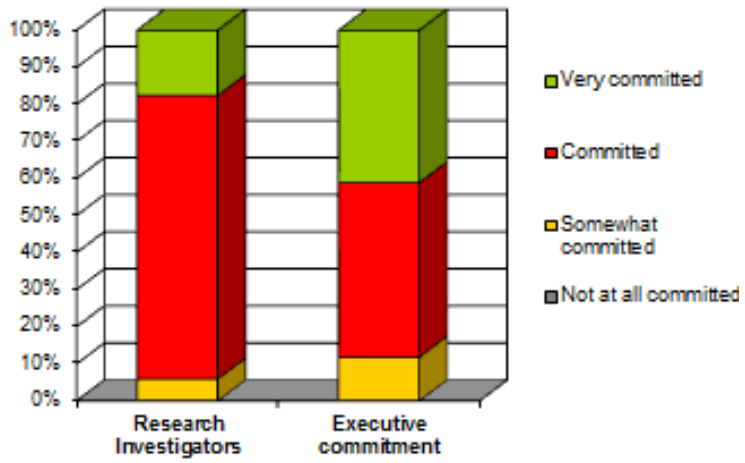
allow flexibility in animal care and use techniques at different sites based on regional differences but ensure the practices meet a common threshold for animal welfare standards.

3. **How would you rate your research investigators commitment to the 3Rs/animal welfare activities in your programs?**

   76% of respondents rated their research investigators as being "committed" to the 3Rs with an additional 18% rating their investigators as "very committed". Thus, 94% of the companies ranked their investigators as being committed to very committed. One respondent ranked their investigators as being "somewhat committed". Several comments indicated that implementation of the 3Rs by the research scientists sometimes has to be encouraged by the IACUC or a veterinarian since there can be resistance to changing practices. However, it was also noted that the culture is slowly changing over time as the investigators embraced the philosophy that implementation of the 3Rs is part of their responsibility to conduct ethical science.

4. **How would you rate executive commitment to 3Rs/animal welfare activities in your programs?**

   Fifteen respondents rated executive commitment to the 3Rs as "committed" to "very committed". Overall, 88% of the executives received a "committed" to "very committed" rating as compared to the researchers, who received a 94% ranking for these two categories. Notably, 41% of respondents considered their executives to be "very committed" as compared to the 18% that placed their investigators in the "very committed" category. Several comments indicated that Executives showed support for the animal welfare award program in particular. Two respondents rated their executives' commitment to the 3Rs as "somewhat committed."



5. **Do you have executive level leadership or support of your 3Rs program/network?**

   76% of respondents indicated that they do have executive level leadership or support for their 3Rs program. This leadership varied from support for creation of a full-time 3Rs position, to support for the awards program, to having an awareness of the animal welfare program and providing their support for the overall program.

6. **If you have executive support, how would you rate the overall influence of this executive role on your company's ability to adopt/promote the 3Rs?**

   Executive support was ranked as either having a "significant influence" or being "highly influential" by 60% of respondents. The remainder rated their executives as having "some influence." Several comments reflected that having top down support ensures easier implementation of 3Rs initatives. At one company, there appeared to be more support from executives in Europe as opposed to the rest of the world.

7. **Please rank the reasons your company believes the 3Rs are important (with 1 being the most important reason and 4 being the least):**

   59% of respondents ranked ethics as the top reason that companies believe the 3Rs are important, while 24% ranked science improvements as the main reason. The other two reasons, including "it's a regulatory mandate: and "it reassures the public we are looking for alternatives", each received the same number of votes, tying them at 8.5% each as the third reason why companies think the 3Rs are important. One company included a comment that the 3Rs are also important because these initiatives motivate employees.

8. **Do you have coordinated 3Rs activities within your organization? (e.g., Alternatives Committee, Enrichment Committee, 3Rs journal club, Global Animal Welfare Committee, Process to share advances in 3Rs)**

   53% answered that they do have coordinated 3Rs activities within their organizations. Almost as many respondents (47%), indicated that this is not the case at their institutions.

9. **Does your company create goals for specific 3Rs objectives/projects on an annual basis?**

   Five of seventeen respondents indicated that they currently have 3Rs goals for their company, while the remainder stated that they do not have 3Rs goals.

10. **A good global program typically has policies and practices that ensure that the 3Rs are integrated into all of your research involving animals. Do your policies and practices ensure the 3Rs are integrated in the following areas? (Please check all that apply)**

    Two thirds of respondents indicated that they do require a literature search for alternatives to procedures causing more than momentary pain/distress for all species. Ten out of seventeen respondents (59%) actually require an alternatives search for all protocols and all species, while four (24%) require an alternatives search only for specific species. Presumably, the latter are U.S. programs with USDA-covered species, since the USDA mandates an alternatives search for protocols with the potential for more than momentary pain or distress in species covered by the Animal Welfare Act. Eight of seventeen respondents (47%) include a question about adoption of the 3Rs in their annual protocol review questionnaire.

11. **Do you have a separate/central budget for 3Rs research initiatives within your company?**

12% of companies indicated that they do have a separate 3Rs budget, 88% do not. Several comments indicated that despite not having a separate 3Rs budget, they can still request spending to support the 3Rs as needed.

12. **If no, do you believe there would be a benefit in having a separate/central budget for 3Rs research initiatives within your company?**

    About half the respondents thought that having a separate budget for the 3Rs would be beneficial, while the remainder did not consider a separate budget to be an added benefit. Several comments indicated that perhaps a separate 3Rs budget could help them to proactively pursue 3Rs research, promote 3Rs initiatives, support a 3Rs award program or expand internal efforts to develop refinements. However, one comment stated that, "These activities seem to happen most effectively as an integrated part of existing research."

13. **What are your 3Rs priorities for the next five years?**

    All seventeen respondents provided input to this question about their 3Rs priorities. The list was quite varied but fell into the following primary categories: 1) 3Rs Technology; 2) 3Rs Leadership; 3) Statistical rigor to drive the 3Rs; 4) 3Rs Research; 5) 3Rs Recognition; 6) 3Rs in Regulatory Filings; 7) 3Rs Communication; and 8) Accreditation to Refine the Animal Care and Use Program.

14. **How would you describe a company that is a leader in terms of advancing the 3Rs?**

    Thirteen respondents provided their description of a 3Rs leader, but the responses were varied. Several terms that were listed as leadership qualities included *innovative, ethical, forward-thinking, taking the initiative, dedicated to implementation, proactive, willing to invest time and money, willing to disseminate accomplishments, transformational,* and *progressive scientifically*.

15. **What would you say are your greatest 3Rs successes?**

    Fifteen out of seventeen respondents also shared what they considered to be their greatest 3Rs successes. Examples varied widely and included: 1) creation of a full-time 3Rs position; 2) formation of a global animal welfare committee; 3) refinements in anesthesia/analgesia; 4) changes in vaccine production that in some cases eliminated animal testing completely; 5) microsampling; 6) reduced animal numbers; 7) animal welfare awards; 8) executive support for the 3Rs; 9) replacement of monkeys with mice for vaccine testing; 10) use of dried blood spot and jacketed external telemetry; 11) refinements in housing and telemetry; 12) *in silico* methods to replace dog use; 13) a global 3Rs policy; 14) preclinical organization alternatives; and 15) including a biostatistician on the IACUC membership.

16. **Do you have at least one person committed full-time to promoting 3Rs across your company (e.g. not a clinical vet or IACUC person who has other responsibility)?**

    Only two of the fifteen companies responding currently have a full-time 3Rs position. One individual commented that a full-time 3Rs person could advance a 3Rs strategy more robustly because it's their

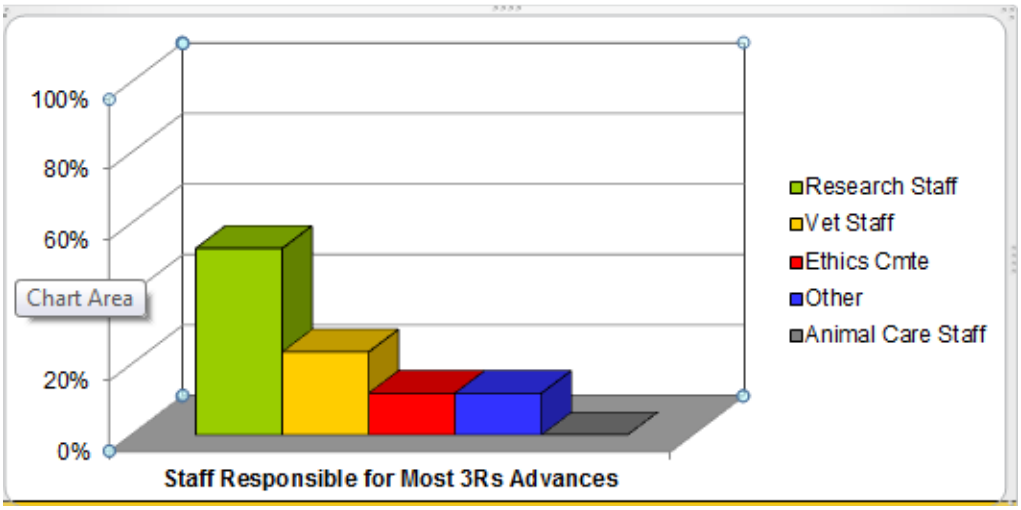
primary focus, but another respondent stated that they consider the 3Rs to be everyone's job. In the UK, a full-time Animal Care and Welfare Officer is required by law.

17. **If not, do you think having at least one person dedicated full time to promoting 3Rs might be an enhancement to your program? Why or why not?**

Thirteen respondents provided input about whether they thought a full-time 3Rs position might enhance their program. Nine respondents thought a full-time person would or could enhance their program. Two respondents did not feel that a 3Rs person would be an enhancement since the IACUC and veterinarians already had this responsibility and they didn't think this should be the responsibility of just one person. Two others were not sure if a full-time person would enhance their programs or be reasonable considering the small size of their programs.

18. **In the past, what individual/group of individuals has come up with most of the 3Rs initiatives at your company?**

53% of respondents indicated that research personnel are most likely to drive the 3Rs at their company, while at other institutions this was most likely to be the veterinary staff (23%) or the IACUC/ethics committee (12%). 12% assigned "other" as the group most likely to advance the 3Rs, and a number of the comments suggested that 3Rs initiatives most often involve a collaborative effort between the researchers, veterinary staff, animal caretakers and ethics committee members, with better science as the driver. It was also noted that a dedicated 3Rs person could be useful to help drive consistent 3Rs changes.



19. **Does your company proactively plan the development, validation, and registration of alternative test methods, or does it follow accepted standards?**

Sixteen of seventeen respondents (94%) indicated that their companies proactively develop and validate alternative test methods or adopt them readily, while one (6%) indicated that they do not do this. Several comments noted that there is a lack of consistency globally, and some parts of their company are more proactive in adopting alternatives than others. Others commented that many of

these initiatives are adopted through collaborations with organizations such as EPAA, the EU Framework program, and other consortia.

20. **Does your company provide training on the importance of animal welfare and the 3Rs for all staff working with animals?**

    All but one respondent stated that they do provide such training. Training methods were quite varied and included: 1) computer-based training courses; 2) didactic classroom training; 3) hands-on training; 4) webinars; 5) continuing education; 6) licensee training (FELASA); 7) AALAS Learning Library; 8) newsletters; and 9) local and national laboratory animal science meetings. Some companies require this type of training only once, while other programs require annual or refresher training at regular intervals.

21. **If there is disagreement between the study director and the attending veterinarian concerning whether or not a study animal requires treatment or euthanasia, who is the final authority?**

    Fourteen respondents affirmed that the Attending Veterinarian (AV) or the Animal Welfare Officer (in the EU) has the final authority for deciding whether a study animal requires treatment or euthanasia. Several comments clarified that it's typically a collaborative decision between the AV and the Study Director or IACUC, which is a very reasonable way to handle these important decisions to ensure all perspectives are considered.

22. **Does your company assess the animal welfare at CROs used by your company?**

    Sixteen respondents all answered in the affirmative that they do assess animal welfare at the CROs used by their companies. Comments clarified that there are some regional differences as well as differences between therapeutic areas and device companies but they are working to improve their oversight process.

23. **If yes, what process is used to validate and monitor the animal welfare program at CROs used by your company? If not applicable, please skip (Please check all that apply)**

    81% of respondents use veterinarians to conduct assessments of the animal welfare program at CROs. 63% responded that they will send their Quality Assurance units to perform these assessments, and 56% also use their toxicology staff. 63% of institutions conduct "virtual" audits, using a questionnaire for lower risk animal studies. Comments included mention of a risk-based approach to determine what kind of assessment is needed, as well as using a team comprised of all of the above to perform these assessments.

    63% of companies preferentially select CROs that are accredited by AAALAC or the Canadian Council on Animal Care (CCAC), and 19% only use AAALAC or CCAC accredited programs as CROs. However, one individual emphasized that we shouldn't rely too heavily on AAALAC or CCAC accreditation since they have seen non-accredited programs with higher standards than accredited ones.

24. **Are the animal care and use study protocols from the CRO reviewed by your company?**

88% of respondents indicated that they do review the CRO's IACUC protocol, while two respondents (12%) do not. Comments clarified that some companies only review protocols when the type of research poses a higher potential risk to the company. These reviews are performed by a variety of staff, including the veterinarians, study directors, project leaders, IACUC members, or scientists.

25. **If yes, does your company use a risk-based system to determine the need for CRO audit (e.g., audit only non-accredited programs conducting studies in NHPs and dogs)? Please elaborate on any regional differences.**

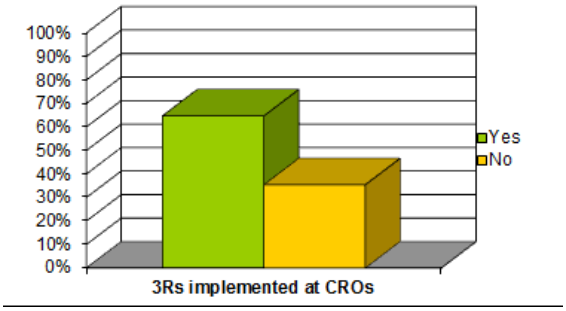
Two thirds of companies use a risk-based approach to determine if an on-site audit is necessary or if a virtual audit will suffice. The remaining third do not currently have a formal risk-based approach in place for performing these assessments.

26. **If animal welfare concerns occur at CROs, who is informed of these issues (please choose all that apply)?**

94% of respondents indicated that the Study Director is informed about animal welfare concerns at CROs. The Sponsor Animal Welfare Officer (41%), the Sponsor Attending Veterinarian (35%), and the Sponsor IACUC or ethics committee (24%) are also kept informed. Comments clarified that there are a variety of ways that their company would respond to an animal welfare concern at a CRO, including a site assessment, teleconference, Corrective and Preventative Action (CAPA) report, follow up on resolutions, collaboration to improve welfare, as well as stopping the study or dropping the CRO from their approved list if deemed appropriate.

27. **Are your 3Rs practices ever implemented with external collaborators/providers (e.g. if a blood collection technique is banned at your company, do you apply that ban for CRO animal research)?**

65% of respondents indicated that they do implement the 3Rs at CROs, while this is not done consistently by the remainder. Comments clarified that consistent housing for NHPs is a good example of regional differences and that global application of the 3Rs is not yet consistent at CROs.



28. **What is your experience with the receptivity of the regulatory authorities and chances of approval of alternative test methods?**

A majority of respondents indicated that they were unsure of how regulatory authorities would respond to alternative test methods. Both the FDA and EMA received somewhat similar scores with regard to being "responsive" to "very responsive" in terms of approving alternative test methods. Much less was known about the response of regulatory authorities in Japan, China and other countries.

29. **Has your company completed a regulatory filing that replaces, reduces, or refines animal testing with an alternative in the last 5 years (e.g. 6 month transgenic mouse carcinogenicity study)?**

59% of respondents affirmed that they had completed a regulatory filing that replaced, reduced, or refined animal testing with an alternative in the last five years, while the remaining 41% have not. Five respondents stated that they have used the transgenic mouse as an alternative model for toxicity testing.

30. **Does your animal care and use protocol include questions about good statistical design and data analysis as a way to help justify animal use?**

88% of respondents indicated that their protocol form includes questions about the use of statistical design and data analysis to justify animal use.

31. **Do your investigators have access to a statistician to provide study design and data analysis support?**

82% of respondents indicated that investigators do have access to a statistician. Of those companies with access to a statistician, this involvement varies from 'encouraged' to 'required'. One company indicated that they employ a Good Statistical Practice policy to help drive a consistent approach to reviewing the use of statistics on all animal studies.

32. **Does your company's approach to the 3Rs differ according to species?**

76% of respondents indicated that their company's approach to the 3Rs was consistent across species. Two companies commented that some species (e.g., primates) were approached differently than rodents when conducting literature searches for alternatives and from a replacement standpoint.

33. **Do you have specific 3Rs criteria to address the following (Please check all that apply)?**

88% of respondents indicated that they consistently apply 3Rs criteria across all species. One company responded that studies that may involve pain or distress, or large numbers of animals, have specific 3Rs criteria applied. This is accomplished through a combination of IACUC activities, Corporate Animal Welfare Committee input, and Alternatives Committee efforts.

34. **Describe what forms of enrichment including social housing are provided for the following animals on GLP regulated toxicology studies:**

Examples provided included:

- Mice and Rats – sticks, wood blocks, certified chew objects, Nylabones, nesting material, resting platform, igloo, tunnel, maze, tunnels, houses, solid flooring inserts (if on wire), social or group housing, when possible
- Rabbits – various manipulanda (dumbbell, jingle ball, hanging bell, hanging washers, sticks / blocks), fruit or vegetables, hay cubes, resting platforms, hiding areas, raised platforms and multilevel housing, music, social or group housing, when possible
- Dogs – certified toys, Nylabones, Kong toys, hand-fed treats, raised platforms or resting boards, outside runs (Europe), continuous floor with bedding, social housing, human interaction and handling through dog socialization programs, frequent exercise routines, music
- Mini-pigs / Pigs – various toys, social housing, scratching apparatus, food treats and processed hay
- NHPs – foraging boards, hanging toys (mirrors, wire balls, Kong toys, Nylabones, cano-nuts, rattles, etc.), bedding on cage floor for foraging, exposure to movies, bubble machine, exercise in gang housing, play cages, resting platform (stainless-steel perch), rope, positive reinforcement training, hand-fed popcorn, puzzle feeder, artificial grass, pools, foraging program, outdoor runs, positive reinforcement training, certified enrichment treats
- Specific mention was made of the use of indoor / outdoor pen systems and solid substrate floors with bedding in Europe.

35. **Describe what forms of enrichment including social housing are provided for the following non-GLP animals:**

There appeared to be little difference between enrichment for GLP and non-GLP studies although certified treats are not required for non-GLP enrichment as they are for GLP studies. See previous question.

36. **Does your company mandate solid bottom caging for all rodents?**

58% of respondents indicated that solid bottom caging was mandatory. Comments suggested that some may have interpreted mandatory to mean "in all circumstances" while others considered this mandatory "unless scientifically justified". These comments made interpretation of the responses difficult, but it appears that a majority of companies require solid bottom caging unless otherwise scientifically justified.

37. **Please describe how your company applies humane endpoints.**

From the Eighth edition of the *Guide for the Care and Use of Laboratory Animals,* "The humane endpoint is the point at which pain or distress in an experimental animal is prevented, terminated or relieved. 94% of respondents indicated that they require humane endpoints to be described in the animal care and use protocol. 88% involve the veterinary staff when there are questions about the use of humane endpoints, and 82% indicated that all studies expected to cause more than moderate to severe pain or distress are monitored by both the researchers and the veterinary staff.

65% of respondents indicated that special training is provided to the staff involved in determining humane endpoints in challenging models, and 59% use a scoring sheet with select models to improve objective decision-making.

38. **Has your company banned any techniques because of animal welfare concerns (e.g. toe clipping, retro-orbital blood collection)?**

    75% of respondents indicated that their company has banned select techniques due to welfare concerns or because there were better alternatives available. Toe clipping, retro-orbital bleeding, and foot pad injections were cited as examples.

39. **Does your company conduct systematic reviews of (a rigorous review, synthesis and meta-analysis of all relevant internal and external data) to refine, reduce and replace animal testing?**

    75% of respondents indicated that their company does not conduct systematic rigorous reviews of internal and external data in their efforts to implement the 3Rs. Comments indicated that although systematic reviews may be a more strategic process, current 3Rs reviews are more often focused on specific activities or procedures. These reviews may be conducted at various levels, including reviews by investigators, statisticians, or working groups. Metrics are being utilized in some instances to track and analyze usage, trends, and species distribution for communication to management.

40. **Have you reduced the number of dose groups or the number of animals per group used for routine IND enabling studies?**

    71% of respondents indicated that they have reduced the number of dose groups or animals per group for these studies. This has been accomplished by combining scientific endpoints on relevant studies where possible, using computer-based risk assessments and implementing reductions based on statistical analysis. One company recommended challenging the classic study design by engaging the FDA for approval of alternative approaches.

    Additionally noted was the NC3Rs Workshop Report: "*Challenging the regulatory requirement for acute toxicity studies in the development of new medicines: A workshop report (2007)*". This initiative illustrates the benefits that can be achieved in terms of implementing the 3Rs by a coordinated approach and sharing data to reach a common position based on evidence and science.

41. **If positive reinforcement is used to train animals to be more cooperative, please describe:**

    Respondents indicated that types of positive reinforcement may include food rewards, human interaction, and training/conditioning programs in all species including rodents. Although positive reinforcement is increasingly being used to refine research practices, reduce stress and create a "willing-worker" paradigm, without specifically defining "positive reinforcement", responses to this question may not accurately reflect a facility's use of actual positive reinforcement training.

42. **Has dried blood spot, dried plasma spot, or microsampling been adopted by your company to reduce the need for animal studies? (e.g. satellite TK rodents, PK studies)**

    81% of respondents reported that the use of these microsampling techniques has been adopted to some extent at their company. Comments indicated that in most cases the technology is being applied to limited early studies (e.g., mouse PK) or is under evaluation for use in other species or study types. There was optimism that this technology has the potential to positively contribute to the 3Rs and requires further investigation.

43. **Where, outside of Europe, does your company plan to adopt European cage sizes, per the new EU Directive, for your animal programs?**

    Only five companies responded to this question. Of those that responded, 80% indicated that they have adopted EU cage standards in China and 60% indicated adoption in the United States.

44. **Will the adoption of European cage sizes be implemented: internally, externally at CROs or both?**

    Again, there was a low response rate of 53% to this question. In general, respondents indicated that European cage sizes will be implemented at their facilities in Europe or, in some instances, at CROs outside of Europe performing studies for European-based companies.

45. **Are animals acclimated to dosing procedures prior to the start of studies?**

    24% of respondents indicated that acclimation to dosing procedures occurs for all species while 59% of respondents indicated that acclimation only occurs for study specific reasons (e.g., administration of a bitter compound). Comments indicted that the stress of acclimation procedures should be weighed against the stress and duration of the anticipated study procedure (e.g., single dose studies).

46. **Are animals acclimated to more than momentary restraint procedures prior to start of studies?**

    Respondents indicated that most species are acclimated to more than momentary restraint procedures prior to the start of studies at least 75% of the time or greater. Minipigs only received a 50% acclimation rate but that may indicate that fewer companies are using minipigs routinely.

47. **Do you have any protocols that withhold analgesics in animals undergoing a survival surgical procedure? (Check all that apply)**

    More than half of all organizations (60%) require at least one administration of analgesia for all survival surgeries. Some institutions (40%) do allow withholding of analgesia, but only in rodent studies and based on scientific evidence that analgesia would interfere with the studies.

48. **Are there any animal models that might benefit from enhanced pain relief and for which your company has conducted or is conducting animal welfare studies to better address unmet pain relief?**

    Nearly a third of companies are conducting studies to address enhanced pain relief for animals on studies where there is unmet pain relief. Other companies use scientific publications, experience with the model, alternative endpoints, and surrogate markers as ways to address unrelieved pain.

49. **Does your company have a method to assess or characterize the predictivity of efficacy models (e.g. a formal validation process, a company-wide annual review process)?**

    Only 35% of the responding companies have a method to characterize the predictivity of efficacy models. One company belongs to a cross-pharma collaboration known as the Animal Models Framework for evaluation of the utility of animal models. Other companies are engaged in scientific review processes to critique the efficacy of animal models.

50. **Does your program have a way to capture *in vitro* screens that are used prior to conducting animal studies (e.g., included in animal care and use protocol as a question, *in vitro* screens are highlighted in a 3Rs database)?**

    44% responded that their companies have ways to capture and use the outcomes of *in vitro* screens predictively prior to conducting animal studies. Some companies review the *in vitro* data as part of the ethical review process while others use internal processes such as meta-analysis to correlate the *in vitro* data for *in vivo* outcomes.

51. **What studies do you require before putting a compound into non-human primates? Please elaborate on any regional differences.**

    Companies had varying responses to this question. Responses included: scientific justification; test article characterization; *in vitro* screens; rodent studies (including pK); and dose escalation studies. One company requires de-selection of the dog and minipig.

52. **Are your employees actively encouraged to participate in scientific consortia that are investigating opportunities to promote the 3Rs (e.g. EPAA, ILSI/HESI, NC3Rs)?**

    A majority of our companies (82%) actively do encourage participation in scientific consortia to promote the 3Rs. A few respondents acknowledged that they have not taken advantage of these opportunities as they should.

53. **Do you have any measures or Key Performance Indicators (KPIs) that demonstrate the impact of policy and practice on your company's 3Rs effort? If so, please provide examples.**

    Thirteen responses were received and 54% of these indicated that they do have some way to measure the 3Rs using KPIs, such as qualitative performance on USDA inspections, AAALAC site visits, 3Rs awards, and publications on the 3Rs.

54. **If you identified new approaches with 3Rs impact, what process and dissemination tools would you use to ensure broader implementation within your company?**

    A majority of companies reported using staff training (94%), development of animal use guidelines (82%), and use of the animal use protocol form (82%) to encourage and drive new 3Rs approaches. Other creative approaches include distribution of a newsletter highlighting 3Rs advances; promotion of 3Rs advances at departmental meetings; workshops with thought leaders in academia; and public 'in-reach' for employees. It was generally agreed that creativity in promoting the 3Rs internally can help to change the corporate culture, and this is an opportunity for the future

55. **Would your company support a proactive industry strategy to collectively communicate its achievements in the 3Rs?**

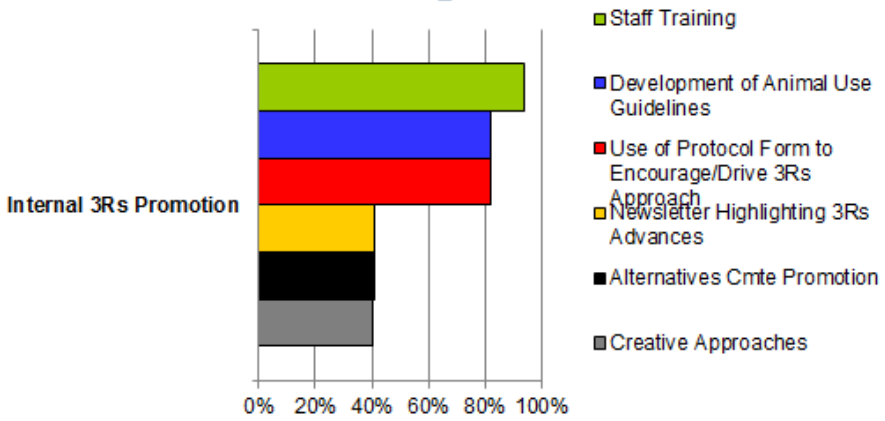
    100% of companies expressed support for developing a proactive industry strategy to communicate 3Rs achievements, though some caveats included a need for confidentiality and internal review of submitted data. While everyone thinks this is a good idea, it is still unclear what would be the best mechanism to do this, and this is an important area of opportunity for the 3Rs LG and Working Groups.

56. **How does your company address external pressure (e.g., pressure from media, shareholders, employee concerns, etc.) regarding the use of animals in testing and research and your company's implementation of the 3Rs?**

A majority of companies have adopted proactive outreach strategies as best practices. Some of these include the use of their public website to share 3Rs advances (76%), employee outreach activities at local schools (71%), and support for external organizations that promote biomedical research (71%). Members have also strengthened their employee education programs on the 3Rs and have responded strongly to shareholder resolutions submitted by animal rights organizations questioning the use of alternatives.

57. **Do you do anything unique to promote 3Rs internally that has not already been described in the earlier survey questions? Please elaborate on any regional differences.**

A few companies have been very active in this area, but most have thus far focused on 3Rs award programs and the internal communication efforts noted above.



58. **Irrespective of awards programs, how do you promote 3Rs externally?**

Members share 3Rs advances at local (31%), national (60%) and international meetings (31%) and publish their findings in scientific journals (50%). In addition to publication of their own achievements and advances as indicated below, many companies also provide financial support to 3Rs organizations in the U.S. (60%) and beyond (53%), including ACLAM Foundation, CAAT, EPAA, NC3Rs, and UFAW.

59. **Are your company's 3Rs advances reported externally on an annual basis?**

A majority (62%) of responding companies utilize their Corporate Responsibility Reports to promote their 3Rs efforts externally. Many also publish on their achievements and advances as indicated in response to Q60.

60. **Do you share/publish your 3Rs advances in scientific journals and publications?**

Members share 3Rs advances at local (31%), national (60%) and international meetings (31%) and publish their findings in scientific journals (50%). Clearly, this leaves room for improvement, and exploring ways to promote increased publication and presentation of 3Rs advances is another important area of opportunity for the 3Rs LG and Working Groups.

61. **Have you had to repeat a rodent study due to infectious disease issues that caused additional pathology or otherwise confounded your data (e.g., *Helicobacter* liver lesions, MPV effects on immune system)?**

    Only one of the sixteen respondents indicated that they have had to repeat a study due to confounding infectious disease issues.

62. **If yes, did the confounding data occur at a CRO or an internally conducted study?**

    The response to this question was somewhat confusing as two companies provided feedback although only one indicated in Q61 that they've had to repeat a study due to confounding disease issues. For both respondents, this situation occurred internally, not at a CRO.

63. **Please provide more information to clarify if sentinels are routinely required as part of your rodent CRO studies and if you feel their use helps to ensure good science and animal welfare.**

    Although the use of sentinels for rodent studies conducted externally is not yet standard practice, a third of responding companies do require sentinels for studies conducted at CROs and four additional companies recommend this as best practice. Five companies do not currently require the use of sentinels for rodent CRO studies.

64. **Please provide more information to clarify if sentinels are routinely required for some or all of your internally conducted studies?**

    In contrast, 80% of responding companies do require sentinels for internally conducted rodent studies. However, one third of those responding that they do require sentinels indicated that they require them only for longer term studies (e.g., over 3 weeks). Three companies responded that they do not routinely require the use of sentinels for their internal studies but it depends on the study duration. One company thinks we should reduce sentinel use.

65. **Is your company requiring or encouraging all animal sites across your company to seek and maintain AAALAC accreditation?**

    Fourteen of fifteen responding companies do require AAALAC or equivalent standards for all of their company-owned animal programs. AAALAC places a great emphasis on implementation of the 3Rs as an integral part of the program of animal care and use.

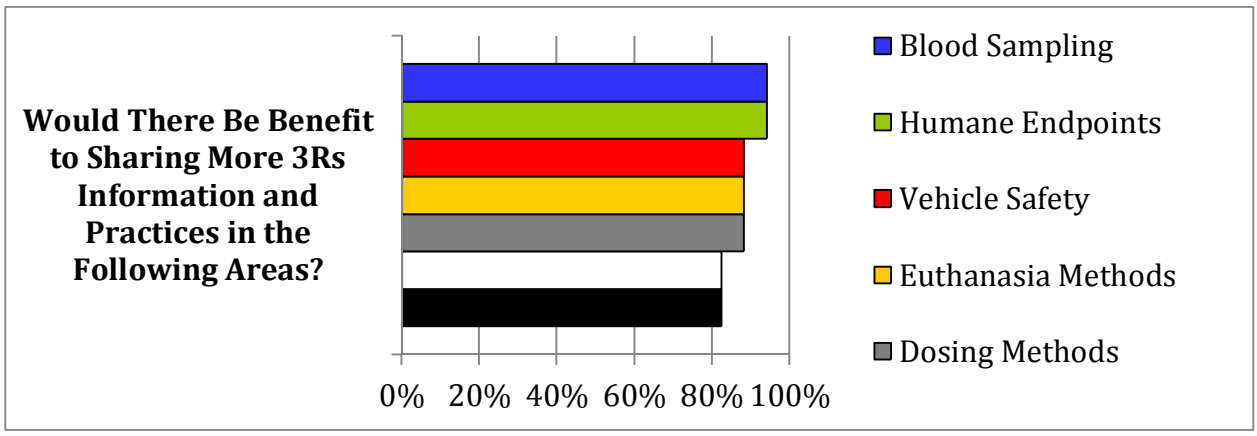
66. **Would there be benefit to sharing more information and practices that may impact the 3Rs outside of your company?**

    All respondents felt that there would be great benefit from sharing 3Rs information. We have much to learn from each other, and substantial internal knowledge to be shared. We need to break barriers to share pre-competitive information and expand the reach of effective practices.

67. **Would sharing practices in any of the following areas be useful?**

    A strong majority of respondents (82 – 94%) agreed that sharing practices for blood sampling, dosing, establishing humane endpoints, and euthanasia would be useful. They also supported sharing of information on vehicle safety, adverse effects and commonly used animal disease models. Establishing

an effective mechanism to collect and distribute this information among member companies should be an important short-term goal for the 3Rs LG.



68. **Are there any final comments/suggestions you would like to make about your company's 3Rs program or about what the IQ 3Rs Leadership Group should be focusing on in the next few years?**

    Several areas of focus for the future were strongly supported by the respondents. These have been discussed above and are detailed in the concluding comments.

69. **How could this survey be improved in the future?**

    We received a lot of good feedback on how the survey could be improved. Several respondents felt the survey was much too long and most felt that in future years it should be shorter and more focused. A few technical improvements were also suggested.

Areas of Consistency

- **All of the companies responding to this survey have 3Rs priorities and are highly committed to advancing the 3Rs as a part of good science now and into the future.**
- **A team approach has been shown to be very useful in driving the 3Rs as it allows for many different perspectives to be brought together to identify the best path forward in driving 3Rs changes. Teamwork helps to overcome obstacles that might exist if 3Rs initiatives are promoted by one group without buy-in from all of the people that will be impacted by the change.**
- **Many of our member companies are involved in consortia that advance the 3Rs by working collectively to develop and validate alternative methods and approaches to drug discovery and development. The 3Rs LG is committed to further advancing alternatives by developing new 3Rs initiatives and collaborating with other 3Rs leaders, the regulatory agencies and consortia.**

- **Most participating companies provide training on animal welfare and the 3Rs and agree that refresher training is an effective practice to ensure that these important topics remain a top priority for all individuals working with laboratory animals.**
- **Having 100% of the respondents affirm that the AV or AWO has the final authority for animal welfare decisions for regulated studies shows clear progress in an area of animal welfare oversight that was somewhat contentious only fifteen years ago. Again, a teamwork approach is suggested as an optimal way to consider all study and welfare issues, but if a rare disagreement arises, then the Attending Veterinarian does have the legal authority provided by the USDA regulations to make a decision about animal disposition.**
- **CRO audits to ensure acceptable animal care and use standards are an effective way to advance animal welfare across the industry since many of our biopharmaceutical animal studies are conducted at these CROs. There is no one best way to conduct these assessments, but veterinary input and/or participation is important. As budgets become more constrained, a risk–based approach can help to prioritize CRO audits and ensure those studies or facilities posing the greatest risk will receive top priority.**
- **The industry has a strong commitment to statistical rigor as a 3Rs method to ensure scientifically justified animal use and to avoid using either too many animals (waste) or too few (inadequate sample size for decision making). Having statisticians provide expert reviews of animal study design and data analysis plans is considered a best practice to ensure that animal use is statistically justified.**
- **A majority of our member companies are consistently applying 3Rs considerations for all species. Having 3Rs criteria to ensure alternatives are considered for all animal use is the expectation by AAALAC, the PHS Policy and the EU Directive. But while consistent application of the 3Rs across all species is considered optimal, it should also be noted that replacement of a higher species with a less sentient species, although not considered a full replacement, can still be considered a refinement in study design.**
- **Member companies have increasingly adopted social housing and enrichment opportunities for the many species they work with. We encourage programs to carefully consider the possible impact of the various enrichment devices on animal well-being as well as on study data. Detailed reporting of environmental and behavioral enrichment in the methods of scientific papers can help to ensure that the potential impact of these enrichment options on scientific outcomes are carefully considered.**
- **The 3Rs LG would also highlight the progress of a majority of our member companies in adopting solid bottom caging with bedding as the primary type of housing for rodents. Especially for longer term housing (> 1 year), the use of solid bottom cages over wire-mesh flooring, or at the very least a solid insert over a wire-mesh floor, is strongly encouraged as a refinement method to reduce or avoid the development of foot lesions which are known to cause pain and distress.**
- **A majority of our member companies are using a variety of mechanisms to ensure that humane endpoints are adopted consistently in animal studies. Veterinary involvement in decision making regarding application of humane endpoints is strongly encouraged, as is the use of training and pain/distress scoring sheets to ensure more consistent application of these endpoints as refinements to animal care.**

- **Three quarters of our member companies have banned certain controversial techniques such as toe clipping and retro-orbital blood collection due to welfare concerns. As new knowledge is gained about pain and distress caused by various techniques, companies must strive to stay current with the scientific literature to ensure that the most humane methods are adopted.**
- **Member companies have implemented reductions in dose groups or numbers of animals per group via a variety of creative study designs or the use of new technology. We encourage member companies to continue to seek ways to adopt reductions in animal use when the integrity of the scientific data is maintained.**
- **With 59% of respondents affirming their use of alternative methods in a regulatory filing, there is clear evidence that the industry is actively adopting the 3Rs for the development of drug and device products. This is significant progress, and as we work more closely in this and other 3Rs consortia, other companies may feel more confident in adopting the 3Rs for future drug development paradigms.**

Opportunities

- **Member companies should consider creating company-wide goals and coordinated initiatives as a way to strategically implement and document 3Rs advances. Although not required, a 3Rs budget could be another area of opportunity for companies to consider as a means to develop a more robust 3Rs culture/program.**
- **Companies should consider becoming more aligned in their adoption of an alternatives search as a good approach to ensuring that 3Rs advances are not missed. Additionally, in the U.S. and globally, adding a question about whether a scientist has adopted one or more of the 3Rs to an annual protocol review process could help to ensure timely capture of 3Rs advances, rather than waiting for protocol renewals.**
- **Creating a full-time 3Rs position may provide some benefit to larger, more complex animal care and use programs. Because their full focus can be on driving implementation of the 3Rs, this individual may help to ensure a bit more consistency in the adoption of alternatives across a global company.**
- **Member companies should look for opportunities to improve communication of animal welfare concerns at CROs not only to the Sponsor Study Directors but also to the Sponsor Attending Veterinarians/Animal Welfare Officers. Enhanced communication about animal welfare concerns ensures that a variety of perspectives are considered to improve future animal welfare outcomes and hopefully reduce the risk of future or ongoing animal welfare issues for both the Sponsor Company and the CRO.**
- **While some progress has been made in the implementation of the 3Rs at CROs, there is still opportunity for us to be even more consistent in applying good practices across all of our animal studies conducted at CROs globally.**
- **Increased dialogue with regulatory agencies to discuss the 3Rs, theirs concerns, and how we can address their questions about new methods would be a good way to enhance our mutual understanding of the best way to promote and advance the 3Rs in a responsible way.**

- **Member companies should consider the potential benefit of conducting systematic reviews of pertinent scientific literature to help identify opportunities for adoption of the 3Rs. Systematic reviews, including meta-analysis, are increasingly used in clinical research but could also serve as a useful tool in evaluating animal models used in both pre-clinical and drug discovery research.**
- **Some companies have begun to utilize a variety of measures to quantify progress against 3Rs implementation goals. The 3Rs LG would like to encourage and support member companies in developing key performance indicators that are applicable to their specific programs in order to track implementation of the 3Rs in a meaningful and measurable way.**
- **Many of our member companies actively participate in 3Rs consortia as a means of sharing precompetitive information to advance alternatives, animal welfare and good science. We need to continue to seek new ways to promote increased publication and presentation of science-based 3Rs advances by individual companies and consortia in the future.**

Summary and Conclusions

Of the twenty member companies participating in the 3Rs LG, fifteen submitted responses to the survey, providing some good insights about the scope and depth of 3Rs programs and initiatives across a select representation of the biopharmaceutical industry. A great deal of progress has been made in recent years regarding corporate engagement in animal welfare, with the majority of companies indicating that they do have a global animal welfare policy or animal welfare standards that apply across their organization. There is also a high level of institutional commitment to advancing the 3Rs at the leadership level as well as among the scientists, driven not solely by a 'regulatory mandate' but because these changes are perceived as ethically and scientifically important. This top-to-bottom support will be critical to sustain in order to further embed the 3Rs into our corporate and industry culture.

Many fine examples of 3Rs successes across the industry were shared by our colleagues, and there have been great advances in enrichment and housing practices for all species, on all types of studies, including GLP toxicology studies. We have reduced, refined or eliminated many practices with a negative impact on animal welfare, such as retro-orbital blood collection, toe clipping and footpad injections. And as an industry, we are actively engaged in a variety of innovative 3Rs initiatives and consortia, working collectively to develop and validate alternative methods and approaches to drug discovery and development.

We have also been very successful in expanding our circle of influence regarding animal welfare and the 3Rs to include our CRO partners. Animal welfare audits of CROs and vendors are now more or less standard practice and in most cases include review of the study protocols. Many institutions have instituted a risk-based assessment process, and this should be encouraged as a good practice to conserve limited resources by prioritizing CRO audits and ensuring those that pose the greatest risk receive top priority. These efforts have resulted in significant improvements in housing, enrichment, humane endpoints, and sentinel programs

at external facilities that conduct work on our behalf, and it is to be hoped that companies will continue to use their influence to enhance research animal welfare around the globe.

Despite the progress that has been made, however, there are still many areas of opportunity. At the level of the individual companies, finding a means to coordinate 3Rs activities across the company may be a good investment for the future. This could include establishing 3Rs goals for the company and tracking progress against these goals as a way to demonstrate on-going commitment to advancing animal welfare. While 3Rs advances are clearly happening as part of the on-going research process, allocating a dedicated budget for 3Rs initiatives could be beneficial in supporting new research activities that support the 3Rs or in cascading the impact of new, refined techniques across research lines. A few companies have also found that establishing 3Rs committees or designating a full-time 3Rs person have been helpful measures in driving forward 3Rs initiatives and priorities identified by the organization.

Another area of opportunity is communication. For example, refresher training on animal welfare and the 3Rs is a good practice to ensure that these important topics remain a top priority for all individuals working with laboratory animals. Better communication about animal welfare concerns, both internal and those arising at CROs, could help to prevent future occurrences and reduce the risk of on-going animal welfare issues for both the sponsor companies and CROs. Finally, creativity in promoting the 3Rs internally can help to change the corporate culture, and this is an important opportunity for the future.

We also need to do a better job of communicating our 3Rs successes to the public and sharing them with one another. All of our member companies expressed support for developing a proactive industry strategy to communicate 3Rs achievements. We have much to learn from each other, and substantial internal knowledge to be shared. We need to break barriers to share precompetitive information and expand the reach of effective practices, and this is an important area of opportunity for the 3Rs LG and Working Groups.

When it comes to further advancing the development, validation and acceptance of new alternatives, the 3Rs LG could also play an important role in identifying new 3Rs initiatives and facilitating collaboration with other 3Rs leaders and the regulatory agencies. Increased dialogue with the regulatory agencies to discuss the 3Rs and proposed new methods will enhance our mutual understanding of the best way to promote and advance the 3Rs in a responsible way.

The 3Rs LG could also help in developing viable Key Performance Indicators (KPIs) to help measure progress on the 3Rs. While few companies are currently using these, consistent use of 3Rs KPIs across the industry could help to demonstrate our active commitment to ethical science and is an area of opportunity for the future.

It is evident that all of the companies responding to this survey have established 3Rs priorities and are highly committed to advancing the 3Rs in the coming years. This will require a close collaboration between the researchers, veterinarians, animal care staff, IACUCs and ethics committee members, with better science as the driver. However, as we deal with the realities of decreasing budgets and increasing regulatory pressures, it will fall to the IACUCs,

veterinary professionals and scientists to keep corporate leadership engaged and to ensure that the 3Rs remain a priority for their institutions. Similarly, the 3Rs LG must continue to support 3Rs leadership across our member companies and the industry by advancing and coordinating 3Rs initiatives that can have wide-ranging impact to advance replacements, reductions and refinements as a part of good science.

Several areas of focus for the future were strongly supported by the respondents. First, we need stronger leadership in the 3Rs. It is essential for us to talk more openly about animal research and assure the "public" that our industry is upholding high standards of animal welfare and adopting the 3Rs whenever possible. We need to increase our advocacy for the 3Rs, and the IQ 3Rs LG should lead efforts to sponsor and support alternative methods. This is particularly true when it comes to contracted work or work conducted externally. The IQ 3Rs LG should work to harmonize standards and encourage the development of 3Rs requirements for all animal studies. We also need to broaden our implementation of the 3Rs, moving beyond enrichment to applying the 3Rs in all scientific areas – better animal welfare and refined techniques contribute to better science. Finally, it was noted that support from upper management is key to advancing the 3Rs across the pharmaceutical industry, and the 3Rs LG should play a key role in driving implementation of validated outcomes and change.