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The future of non-human primate use in mAb development

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It has been predicted that the use of non-human primates (NHPs) is going to increase considerably in the development of monoclonal antibodies (mAbs). Opportunities exist to focus on a rigorous, science-based approach to drug development, however, which will minimize this increase. In this article, the authors review current and future NHP use in mAb development based on surveys, experience and expert opinion and propose a framework that will minimize future NHP use and continue to support science and innovation.

Introduction

The revision of European Union legislation governing the use of animals in research has recently returned the controversial topic of research using non-human primates (NHPs) to the fore, triggering an intense debate on whether the use of NHPs should be restricted to research into life-threatening or debilitating diseases only. This – in combination with other regulatory changes, such as the amendment of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S6 guidelines covering the safety evaluation of biotechnology-derived pharmaceuticals – provides a timely stimulus to examine the relevance and justification of NHP research. Various expert bodies (e.g. SCHER in 2009 [1] and Weatherall in 2006 [2]) have previously attempted to do this, but too often, the focus has been on endorsing the use of primates by collecting evidence on the scientific discoveries emerging from their use. The fact that NHP research has led and will continue to lead to new discoveries cannot be disputed, but the questions that must be addressed in the present scientific and ethical climate are 'For what purposes are NHPs used?' and 'Can these be met in other ways?'

Frequently, the debate on the utility of NHP use is not well informed, and this perpetuates the polarization of viewpoints. On one side, calls for abolition are upheld on the unrealistic grounds that alternatives already exist, and on the other side, the position is equally entrenched; continued NHP use is often justified on the basis of their close relatedness to man and their assumed additional value, over and above other species and methods, for studying human diseases and assessing the safety of potential therapeutics. The current debate lacks an agreed vision and a robust coordinated framework to minimize NHP use that continues to support science and innovation. This can only be achieved with sustained engagement of the scientific and regulatory communities, as well as an environment that enables rational discussion, openness and a willingness to change.

The greatest use of NHPs occurs in the safety assessment of new medicines (approximately 90% [3]). In recent years, the number of animals used has started to rise [3,4], primarily driven by the increase in the development of biopharmaceuticals – most notably monoclonal antibodies (mAbs), for which the NHP is often deemed to be the only relevant species for preclinical safety testing [5–10]. A relevant species is one in which comparative pharmacological activity to human (in terms of both potency and mechanism of action) can be demonstrated, tissue expression patterns are comparable to human and immune response does not limit exposure. Consequently, the species of choice for safety assessment and toxicity studies is often the Old World monkey, usually the cynomolgus macaque. Although pharmacological activity that is restricted to primates might mean that NHP use is unavoidable, there is also a trend for more NHP data to be generated for new mAbs to support market authorization. This

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might be caused by regulators requesting more NHP data or by internal decisions within companies in anticipation of regulatory requests, or simply because of an assumption that more NHP data will lead to quicker drug development. A scientific approach, in which functional potency, target modulation and downstream effector function are determined, is essential to assessing whether the NHP is relevant to assess safety. The case-by-case approach used in the development of mAbs is threatened with substitution by a standardized, 'tick-box' pathway, which does not necessarily provide the safest approach to mAb development and underexploits the unique properties of mAbs to minimize NHP use during preclinical testing.

Against this background, the UK's National Centre for the Replacement, Reduction and Refinement of Animals in Research (NC3Rs),* working with the pharmaceutical industry, has started to develop a framework for minimizing NHP use in mAb development [9]. At the heart of this is an examination of whether the requirement for NHP studies to predict the performance of mAbs in man can be reduced through the use of alternative strategies or methods without compromising human safety. The NC3Rs has taken a unique approach to facilitating data sharing across the industry and engaging regulators, with the primary objectives of minimizing NHP use, supporting scientific and economic benefits, and addressing societal concerns about the use of NHPs. This article will explore how the development of mAbs has changed over recent years, outlining the areas predicted to generate an increased use of NHPs and the opportunities for minimizing this. Knowledge gaps and priorities for future investigation will also be addressed.

The changing environment of mAb development and its impact on NHP use

The scientific and regulatory environment in which mAbs are being developed is evolving rapidly. There are currently 22 approved mAbs, and the number in late-phase clinical trials continues to rise [11]. Approximately a third of the molecules in the drug pipeline are biopharmaceuticals, and if this trend continues, there will be more biopharmaceuticals than new chemical entities (NCEs) in development within three years. The majority of these products are mAbs or recombinant proteins. Whereas clinical recombinant proteins (excluding the interferons) usually have pharmacological activity in a range of species, mAbs are frequently only potent in the NHP.

The shift in focus of big pharma towards biotechnology products in the past few years has been demonstrated by the increase in R&D expenditure in this area [12] and in the number of notable acquisitions (e.g. Astra Zeneca/MedImmune, Amgen/Abgenix, Johnson and Johnson/Centocor, and Roche/Genentech). The quest for new biotechnology products to supplement the weak pharmaceutical pipeline has also provided opportunities for smaller companies, many of which are spin-offs from academic institutions, to compete or collaborate with big pharma. Some smaller companies use innovative approaches that minimize NHP use. Lack of experience and expediency, however, has meant that many conduct comprehensive packages of NHP studies, not necessarily based on scientific merit but because they assume that a potential partner or the regulators will require these data.

To increase the efficacy of mAbs and reduce immune response to treatment, development has shifted away from murine antibodies to chimeric, humanized and fully human mAbs. Rapid growth in the number of human mAbs with high species specificity has affected the choice of animals for preclinical safety and toxicity studies, precluding the use of the clinical molecule in species other than the Old World monkey. Many companies now screen for cross-reactivity with the cynomolgus monkey early in development and are reluctant to develop mAbs without pharmacological activity in the NHP because of perceived difficulties in designing a regulatory toxicology package. We reported previously that some companies screened their novel mAbs for potency with rodents and in some cases made decisions based on rodent data alone [9]. Our data show approximately 80% of mAbs currently in development have potency/cross-reactivity in the NHP and human only. The draft ICHS6 addendum states that the use of one species is justified in longer term studies when the biological activity of the biopharmaceutical is well understood and recommends consideration of the rodent instead of the NHP where pharmacologically relevant.

The therapeutic focus of mAb development has also widened. Many of the early mAbs were for cancer indications and, therefore, limited safety assessment was conducted; however, there has been an expansion of mAbs into chronic disease areas, for life-debilitating rather than life-threatening conditions. For example, for oncology, the benefit of clinical trials in humans can outweigh the toxicological uncertainty, and fewer preclinical studies are often necessary before human trials. This is often not the case for chronic disease areas such as rheumatoid arthritis, where more complex and larger NHP studies (e.g. reproductive toxicity studies) might be required to give greater assurances of safety and tolerability given the changed risk/benefit ratio for patient populations (e.g. women of child-bearing potential, pediatric).

Future increases in NHP use for mAb development

As the number of mAbs in the drug pipeline expands, there is a concomitant increase in NHP use driven by factors such as species specificity, a shift in clinical priorities and scientific developments in mAb design. Related to these, there are other changes that are anticipated to further increase NHP use over the next few years (Box 1). The most notable of these are developmental and

BOX 1

Predicted increase in the use of NHPs

- Rapidly increasing size of mAb portfolio.
- Increase in fully human mAbs where NHPs are the only relevant species.
- Developmental and reproductive toxicology studies.
- Larger studies for changes in manufacturing or administration routes.
- Juvenile toxicity studies.
- Number of recovery animals.

* The NC3Rs is an independent, scientific organization set up by the UK Government to find innovative solutions to minimize animal use and improve animal welfare in research. More information can be found at www.nc3rs.org.uk.

reproductive toxicology studies and toxicity studies to support changes in manufacturing or administration routes.

Historically, studies to identify toxic effects on development and reproduction for NCEs have been carried out in rats or rabbits. These studies are designed specifically to assess the effect of a drug on fertility and early embryonic development, organogenesis during embryo-fetal development, and pre- and post-natal development. Study protocols, readouts and historical databases are well established for reproductive toxicology assessment in rats and rabbits. Because of the species specificity of mAbs and differences in the placental transport of IgGs between rodent and primate species including man [13–15], however, there is a trend towards conducting reproductive toxicology studies in the NHP. For a comparison of preclinical developmental and reproductive toxicology studies for currently approved mAbs, see Ref. [13]. A decade ago, the technical difficulties of carrying out reproductive toxicology studies in NHPs precluded their widespread use. In some cases, there were no reproductive toxicology studies carried out (for example, rituximab and erbitux [16,17]) or, on occasion, studies using a homologous protein in the rodent (for example, efalizumab and infliximab [18–21]) were accepted by regulators. However, some of the challenges associated with carrying out reproductive toxicology studies in Old World monkeys, such as high spontaneous abortion rate and long gestation, now no longer inhibit these studies, and the background database is growing. Consequently, it is predicted that there will be an increase in the requirement for NHP reproductive toxicity studies to take account of new therapeutic areas and in areas where historically the risk/benefit ratio has been considered low (e.g. oncology and transplantation). These studies might also be conducted with much larger group sizes, owing to the shift from hazard identification towards risk assessment [13]. Whether these larger and more comprehensive studies will actually contribute to improved human safety is not clear and, indeed, the significance of species differences in placental transfer in extrapolating preclinical data in animals to humans is hotly debated.

The use of NHPs is also expected to increase for the study of toxicological effects caused by changes in manufacturing (e.g. site, scale, process, cell line or formulation) or development of biosimilars that necessitate comparability or equivalence testing. For example, if the cell line used to produce the mAb is changed or there is a change in glycosylation patterns, whole new regulatory packages might be triggered either in anticipation of or in response to regulatory requests. Although the number of NHPs used for this purpose is increasing, important questions remain as to whether the data are providing additional information on human safety. Further investigation is necessary into which manufacturing changes, if any, are likely to produce effects in humans and which require *in vivo* toxicity studies.

A further issue is the expansion of therapeutic modalities targeting identical mechanisms. For instance, in the therapeutic neutralization of TNFα, there are – in addition to the five approved and marketed mAbs and fragments (Remicade, Humira, Cimzia, Enbrel and Simponi) – more than ten anti-TNFα agents and scaffolds in development. Although extensive safety information and the consequences of TNFα neutralization are known, full toxicology packages in NHPs, including reproductive toxicology, are still being requested. For classes of molecules where strong supporting evidence shows the target mechanism of action is the same, consideration should be given to limited or no NHP studies because the value of additional NHP safety data to human safety is questionable.

There is also a general increase predicted in the number of NHPs used in toxicology studies for individual mAbs. This is due to a combination of factors, such as the requirement for more animals to increase the statistical power of studies, the use of recovery animals to investigate delayed toxicity at all doses studied and more chronic toxicology studies. The TGN1412 incident [22–24] seems to have set the standard for a conservative approach to mAb development. What TGN1412 clearly demonstrates, however, is that a tick-box approach to predicting human safety is deeply flawed and that an intelligent, science-based approach is needed that questions each assumption about the relevance of the animal species used for development and the types of studies that are needed. The toxicity studies in NHPs gave a false prediction of safety for TGN1412 because of important functional differences in T-cell activation between humans and NHPs. Retrospective studies of immobilized TGN1412 showed measurement of cytokine release and cell proliferation in human peripheral blood mononuclear cells could have better predicted the human response [23]. TGN1412 challenges the assumption that because NHPs are closer to man, they are always the most appropriate species for mAb development.

Although increases in NHP use in some areas might be inevitable because of advances in science, acceptance of a general upward trend without further critique or analysis is a dangerous gamble, as many in industry recognize. Action to prevent future unnecessary increase is crucial for several reasons. Aside from the ethical perspective, with greater societal concern over research using NHPs than other species such as rodents, the requirement for more and larger studies points towards a more conservative environment for mAb development. This will have an impact from a business perspective, not least because larger NHP studies of longer duration have considerable financial implications. Reliance on the NHP and the assumption that the NHP is always the most predictive model of man will preclude the use of science-based, innovative approaches, potentially missing valuable information. The NC3Rs/industry collaboration was set up to gather information to predict where the major increases in NHP use are likely to be, whether these provide added scientific value to the mAb development package and human safety, and how the impact on NHP use could be minimized.

Opportunities to minimize NHP use

Informed by the sharing of key information (e.g. NHP study design and availability of homologous proteins) on more than 100 unique mAbs in a range of therapeutic areas, experts involved in the NC3Rs/industry collaboration have already prioritized areas where there are opportunities for NHP use to be minimized (Table 1). These are based on the unique nature of mAbs compared with small-molecule drugs: high specificity, low off-target toxicity, immunogenicity, reduced placental transfer in early development, intravenous route of administration minimizing the risk of misuse by volunteers and patients, and low doses often showing full saturation of the target. A number of these priorities are currently being addressed by the NC3Rs and complementary work by other groups within the

TABLE 1

Opportunities to minimize primate use[a]

Timeframe for opportunity	Opportunity	What needs to be done?
Chronic toxicology studies		
ST	Combining studies where possible (e.g. safety pharmacology studies into toxicology studies)	Translation into individual company practice. Some companies already combine studies.
ST	Reducing the length of studies (e.g. studies longer than six months are not necessary)	Compilation of data between pharma/biotech and regulators to support recommendations. Translation into individual company practice.
ST	Reuse of recovery animals (e.g. for small-molecule drugs)	Translation into individual company practice. Some companies already reuse recovery animals.
MT	Fewer animals used per dose group (e.g. three per sex per group)	Some companies use more than three per sex per group because of real or perceived regulatory requirements. To address regulatory precedent, compilation of data between pharma/biotech and regulators to confirm evidence for optimal sample sizing. Is more information on human safety gained from studies with larger group sizes?
MT	Fewer recovery animals (e.g. only on high-dose groups)	Confirm there are no existing examples of delayed toxicity for mAbs. Are recovery animals necessary?[b]
MT	Fewer studies (e.g. one-month study for FIM trials, one further study for marketing)	Do additional studies provide more information? Data collection and analysis of whether conclusions are the same without the additional studies.[b]
LT	Fewer dose groups after initial studies (e.g. low and high only on studies longer than one month)	What additional value does the mid-dose group provide? Data collection and analysis to assess the added value of the mid-dose group.
LT	Sharing or using historical control data	Compilation of control data between pharma/biotech – development of a 'Control' database, especially with respect to reproductive toxicology studies.
Reproductive toxicology studies		
ST	If primate studies are the only option, carry out a combined study (e.g. where embryo/fetal and pre/postnatal segments are studied together)	Translation into individual company practice. Some companies already combine studies.[b]
ST	Fertility endpoints can be included in chronic toxicology studies	Translation into individual company practice. Some companies already collect fertility data from chronic toxicology studies.[b]
ST	If studies are necessary, delay until phase III	Agreement between industry and regulators on appropriate risk mitigation strategies for clinical trials. See also Ref. [13].
ST	Not necessarily doing any studies, depending on indication, historical information, and so on (Fig. 1)	Translation into individual company practice. Case-by-case approach.
MT	Use of homologous proteins and genetically altered mice	Does reproductive toxicology data from rodents correlate with NHP and human exposure data? Data collection and analysis to assess where rodents are appropriate even when the NHP is relevant.[b]
MT	Fewer dose groups (e.g. one high-dose group only)	What additional value does the mid-dose group provide? Data collection and analysis to assess the added value of the mid-dose group.[b]
Bridging studies – manufacturing and administration changes		
LT	Manufacturing (e.g. not necessarily carrying out any *in vivo* studies unless drug substance has changed significantly)	Do manufacturing changes of mAbs present risk to human safety? Data collection and analysis to assess under which circumstances *in vivo* studies are required?
LT	Administration route (e.g. SC to IV)	Are there situations where toxicity profile differs between routes? Does this have implications for human safety? Data collection and analysis to identify where sizeable bridging studies might not be necessary.

Abbreviations: FIM, first-in-man; ST, short term; MT, medium term; LT, long term.

[a] See also Ref. [25].

[b] Topic being considered as part of ICHS6 addendum.

industry. The priorities have been divided into achievable short-term and more aspirational medium- and long-term initiatives. For detailed comparisons of case studies and specific examples of development pathways, including where alternative approaches to NHPs have been used, see Refs. [8,13,25,26].

The areas where NHP use could be minimized in the short term are generally in chronic toxicology studies, including developmental and reproductive toxicology. They fall into three categories: changes in the design of individual studies to reduce the number of NHPs used; altering the timing of studies so that fewer mAbs are tested owing to candidate selection; and reducing the number of studies carried out, even where the NHP is the only relevant species in terms of potency as outlined in Table 1.

There is evidence that long-term studies of nine or 12 months only provide additional information on safety in exceptional circumstances [27]. A typical mAb development pathway could comprise a one-month toxicology study to support first-in-man clinical trials and one further study of six months to support registration and marketing only [25]. Currently, there is often at least one additional study carried out. This might be due to expediency to fulfil short-term goals, such as a three-month study to progress to phase II more quickly, or due to real or predicted regulatory requests for longer studies of nine or 12 months. Further data are necessary to support the wider uptake and regulatory acceptance of reducing the number of chronic toxicology studies.

Opportunities also include minimized study designs that combine embryo/fetal and pre/postnatal segments of reproductive toxicology where it is necessary to understand the potential risk to the developing fetus [28]. In cases in which the NHP has been shown to be the only relevant species, this minimized approach has been shown to be appropriate for assessing developmental defects (P. Jarvis, abstract, European Teratology Society Meeting, 2000). Examination of whether studies are absolutely necessary (for example, based on intended patient population or dosing regime; Fig. 1), the presence of a robust risk mitigation strategy,

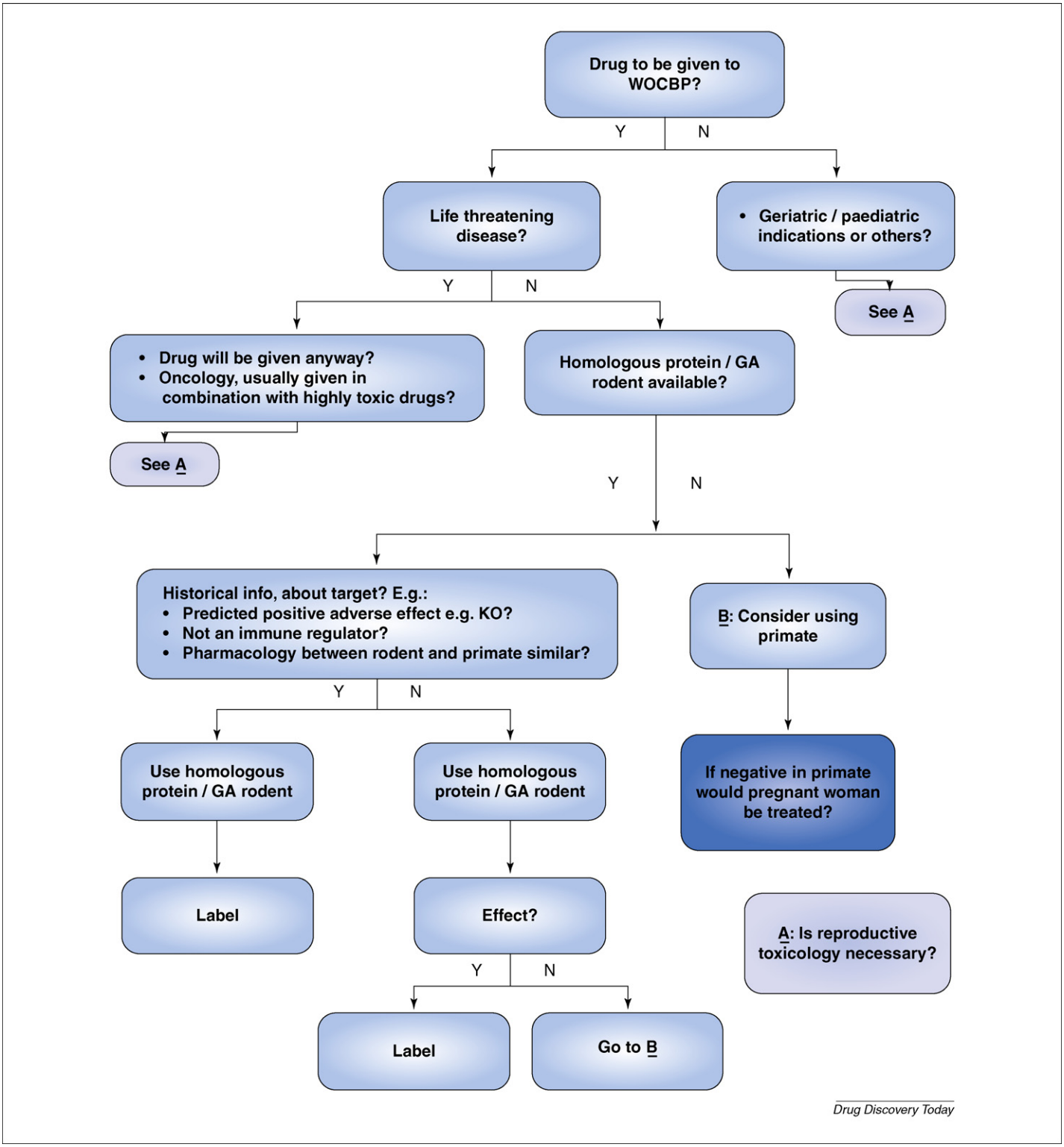

FIGURE 1

Flow diagram illustrating general principles that inform decisions around NHP use for reproductive toxicology. Abbreviations: GA, genetically altered; WOCBP, women of child-bearing potential; KO, knock-out.

and delaying reproductive studies until later in drug development when more data and assurance that the drug will provide clinical benefit are available also provide key opportunities to minimize NHP use.

Other medium- and long-term priorities have been identified, where as yet there has been little or no supporting data collection but further investigation might provide important opportunities to minimize NHP use (Table 1). For example, mAbs often show 100% saturation of the target receptor even at the lowest dose selected for toxicity testing (no-observed-adverse-effect level). In these cases, the need for both a low- and a mid-dose group is questionable. Remaining questions relate to whether the therapeutic index would be limited by fewer dose exposure levels and whether this could be avoided by judicious selection of the high-dose level. To address these questions, data from mAbs should be reviewed retrospectively, to assess whether different conclusions on human safety would have been made in the absence of the low- or mid-dose group. This should be carried out either within companies or as a collaborative project, to increase the scale and scope of the study. Based on the evidence gathered, reducing the number of dose groups – initially in reproductive toxicology studies where there is precedence for more flexibility – could be the first step towards chronic toxicology studies with two dose groups for mAbs with appropriate pharmacological profiles. This, and the other priorities defined in Table 1, could be achieved in practice by building on existing examples of collaborative, pre-competitive practice such as the NC3Rs/industry partnership.

That mAbs are often only active in NHPs drives the increase in the use of NHPs and can limit the development and use of other approaches. Currently, one of the most controversial areas in mAb development is the use of homologous proteins and genetically altered (GA) mice to minimize the use of NHPs, even when the mAb shows pharmacological activity in the NHP. The value of NHP developmental and reproductive toxicology studies and the use of alternative models is a particularly active area of discussion [13,14,26]. If the purpose of undertaking reproductive toxicology studies is to provide information to women becoming pregnant while on therapy, then NHP studies are underpowered and have limitations that homologous proteins and GA rodents could go some way towards addressing. Well-characterized GA mice, where the endogenous gene has been replaced with the human, enable the clinical molecule to be tested (for example, keliximab [29]), whereas homologous proteins might be more likely to activate effector function and downstream pathways. For both models, differences in placental transfer between rodents and primates mean that rodents might be more useful in assessing reproductive risk to humans than predicting effects on fetal development. However, further analysis is needed to determine whether the use of a homologous protein or a humanized, knock-in GA rodent with the clinical candidate could have provided the same or additional safety data for a particular target than that acquired from an NHP developmental and reproductive toxicology study. This should include investigation of the circumstances in which there is good correlation and whether this can be applied to identify cases when homologous proteins or GA rodents could be used to predict an adverse effect, even when the NHP is a relevant species.

A framework to translate opportunities to minimize NHP use into reality

The development and licensing of efficacious and safe medicines is undoubtedly the primary goal of pharmaceutical and biotechnology companies, as well as regulatory bodies. Within this shared vision, however, most companies and regulatory bodies also have a commitment to support the most ethical science and where possible to implement measures that replace or reduce the use of animals. Therefore, there is common ground on which to build a framework to minimize NHP use, the most sensitive and contentious of all animal testing issues.

For any framework to be successful there must be (i) international collaboration between companies and regulators and agreed priority areas, (ii) identification of specific issues to be addressed within the priority areas, (iii) a willingness to share (non-commercial) data and to challenge the *status quo*, (iv) analysis and publication of findings, (v) dissemination of the results to regulators and colleagues, and (vi) translation of findings into changes in practice to reduce NHP use (Fig. 2). The most challenging aspect of this framework is the translation of the outcomes of the data analyses into genuine, quantifiable reductions in NHP use.

So how far are we in delivering this framework and making tangible progress in minimizing the use of NHPs in the development of mAbs? There are several groups active in this area, including NC3Rs, BioSafe (a subcommittee of the Biotechnology Industry Organisation), Biopharmaceutical Technical Group (a subcommittee of the Pharmaceutical Research and Manufacturers of America) and ICHS6 expert working group. Through data sharing and analysis, these groups have provided a basis for the reduction of NHP use and improved efficiency of mAb development. The impending addendum of the ICHS6 guidelines provides an opportunity to put this into practice. Nevertheless, there is increasing pressure to use more NHPs and the addendum of the ICHS6 is just the beginning. There is a need for much greater coordination and collaboration in the search for ways of reducing NHP use without compromising human safety. Increasingly, industry will be expected to not only guarantee the safety of their products but also, concurrently, to meet society's concerns about animal use. Corporate policies on animal use will not stand up to scrutiny without action and real commitment, and both industry and regulators need to be actively engaged.

The priorities identified in this paper are at various stages of exploration and are by no means exclusive, but what is clear is that there needs to be wider participation from industry and regulators if real progress is to be made. Companies of all sizes need to be willing to share non-confidential data on study design and development strategies, including the use of alternative approaches such as homologous proteins. As the body of clinical information for mAbs increases, the reverse translation of clinical findings to minimize NHP use and improve predictivity of preclinical studies for humans will also be increasingly powerful. Efficient processes need to be in place to reduce the burden of providing information; organizations, such as the NC3Rs, providing an honest broker role can facilitate this greatly. Global collaboration between companies, regulators and trade associations is essential, not only in terms of expanding and analysing the data set and identifying priorities but also in terms of the dissemination and uptake of strategies and approaches that could lead to a reduction in NHP use.

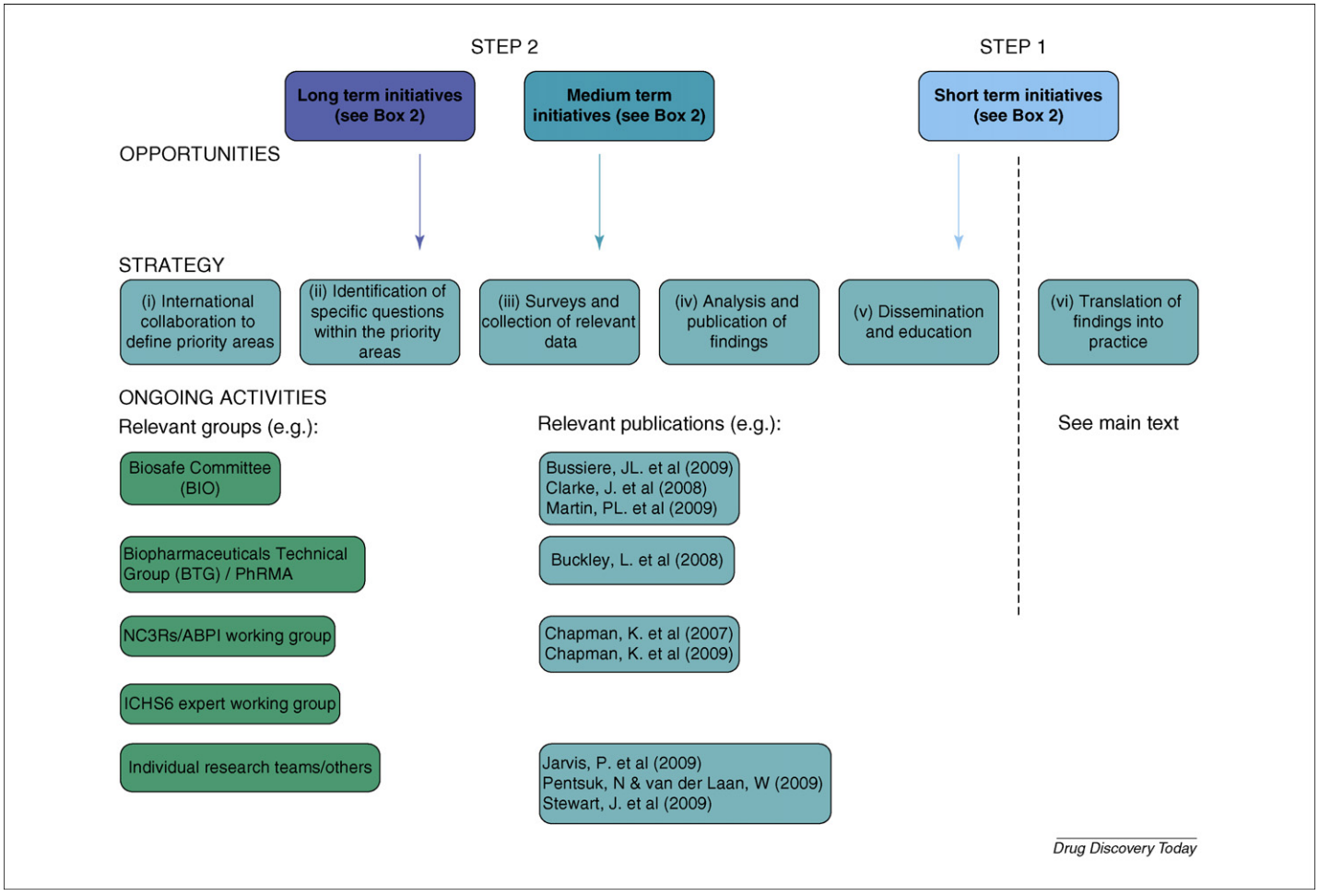

FIGURE 2

Overview of a framework to minimize NHP use. This figure illustrates working groups and expert committees currently active in identifying opportunities to improve the preclinical development of mAbs, many of which have implications for minimizing NHP use. Initiatives are evidence-based, follow the general strategy shown and are at various stages of exploration, as illustrated by the blue arrows. Relevant publications by each of these groups are highlighted.

Taking part alone is not sufficient, and achieving this will require bold steps from industry and regulators and, most importantly, leadership and buy-in from the very top. Industry must be prepared to take minimized regulatory packages to the regulators on the basis of scientifically justified arguments and the regulators must give clear, consistent guidance on whether these packages are acceptable. Previous experience has shown that once one company has made a change in their drug development strategy to reduce animal use, others are willing to change, even in the absence of overt regulatory approval [30]. Early engagement with the regulators is vital, however, because their vast experience with a wide range of mAbs can help shape priorities and define opportunities and, ultimately, their support for innovation in this area will facilitate a reduction in NHP use.

Concluding remarks

The use of NHPs has played and will continue to play an important part in assessing the risks posed by mAbs. There are many current and emerging pressures that are driving the use of NHPs, and these could be offset with new strategies and approaches to study design and regulatory packages. Decisions that companies and regulatory bodies make now have the capacity to make a real difference. The use of more NHPs does not necessarily equate to safer medicines or an expedient path to the clinic, as demonstrated by TGN1412. The companies working with organizations like the NC3Rs and Biosafe are leading the efforts to support effective and efficient mAb development while minimizing NHP use, and the ICHS6 addendum is perfectly timed to take account of this. Now is the time for concerted action from industry and regulators to maintain the momentum and further explore the short-, medium- and long-term priorities identified.

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References

1 Scientific Committee on Health and Environmental Risks SCHER (2009) The need for non-human primates in biomedical research, production and testing of products and devices (http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_110.pdf)

2 Weatherall, D. *et al.* (2006) The use of non-human primates in research (http://www.acmedsci.ac.uk/images/project/nhpdownl.pdf)
3 UK Home Office (2008) Statistics of scientific procedures on living animals, Great Britain (http://www.homeoffice.gov.uk/rds/pdfs09/spanimals08.pdf)
4 United States Department of Agriculture Animal and Plant Health Inspection Service (2007) Animal care annual report of activities (http://www.aphis.usda.gov/publications/animal_welfare/content/printable_version/2007_AC_Report.pdf), p. 13
5 Tabrizi, M.A. and Roskos, L.K. (2007) Preclinical and clinical safety of monoclonal antibodies. *Drug Discov. Today* 12, 540–547
6 Tabrizi, M.A. *et al.* (2009) Translational strategies for development of monoclonal antibodies from discovery to the clinic. *Drug Discov. Today* 14, 358–372
7 Lynch, C.M. and Grewal, I.S. (2008) Preclinical safety evaluation of monoclonal antibodies. *Handb. Exp. Pharmacol.* 181, 19–44
8 Buckley, L.A. *et al.* (2008) Nonclinical aspects of biopharmaceutical development: discussion of case studies at a PhRMA-FDA workshop. *Int. J. Toxicol.* 27, 303–312
9 Chapman, K. *et al.* (2007) Preclinical safety testing of monoclonal antibodies: the significance of species relevance. *Nat. Rev. Drug Discov.* 6, 120–126
10 Schneider, C.K. (2008) Monoclonal antibodies – regulatory challenges. *Curr. Pharm. Biotechnol.* 9, 431–438
11 Reichert, J.M. (2008) Monoclonal antibodies as innovative therapies. *Curr. Pharm. Biotechnol.* 9, 423–430
12 Malik, N.N. (2009) Biotech acquisitions by big pharma: why and what is next. *Drug Discov. Today* 14, 818–821
13 Martin, P.L. *et al.* (2009) Considerations in assessing the developmental and reproductive toxicity potential of biopharmaceuticals. *Birth Defects Res. B: Dev. Reprod. Toxicol.* 86, 176–203
14 Pentsuk, N. and van der Laan, J.W. (2009) An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth Defects Res.* 86, 328–344
15 Simister, N.E. (2003) Placental transport of immunoglobulin G. *Vaccine* 21, 3365–3369
16 European Medicines Agency (EMEA) European public assessment report for MabThera (http://www.emea.europa.eu/humandocs/Humans/EPAR/mabthera/mabthera.htm)
17 European Medicines Agency (EMEA) European public assessment report for Erbitux (http://www.emea.europa.eu/humandocs/Humans/EPAR/erbitux/erbitux.htm)
18 Clarke, J. *et al.* (2004) Evaluation of a surrogate antibody for preclinical safety testing of an anti-CD11a monoclonal antibody. *Regul. Toxicol. Pharmacol.* 40, 219–226
19 European Medicines Agency (EMEA) European public assessment report for Raptiva (http://www.emea.europa.eu/humandocs/Humans/EPAR/raptiva/raptiva.htm)
20 Treacy, G. (2000) Using an analogous monoclonal antibody to evaluate the reproductive and chronic toxicity potential for a humanised anti-TNFα monoclonal antibody. *Hum. Exp. Toxicol.* 19, 226–228
21 European Medicines Agency (EMEA) European public assessment report for Remicade (http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm)
22 Suntharalingam, G.M. *et al.* (2006) Cytokine storm in phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N. Engl. J. Med.* 355, 1018–1028
23 Duff report. NIBSC Special Cytokine Study and Follow up study, pp. 56–67 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117)
24 Horvath, C.J. and Milton, M.N. (2009) The TeGenero incident and the Duff report conclusions: a series of unfortunate events or an avoidable event? *Toxicol. Pathol.* 37, 372–383
25 Chapman, K. *et al.* (2009) Preclinical development of monoclonal antibodies: considerations for the use of non-human primates. *mAbs* 1, 505–517
26 Bussiere, J.L. *et al.* (2009) Alternative strategies for toxicity testing of species-specific biopharmaceuticals. *Int. J. Toxicol.* 28, 230–253
27 Clarke, J. *et al.* (2008) Duration of chronic toxicity studies for biotechnology-derived pharmaceuticals: is 6 months still appropriate? *Regul. Toxicol. Pharmacol.* 50, 2–22
28 Stewart, J. (2009) Developmental toxicity testing of monoclonal antibodies: an enhanced pre- and postnatal study design option. *Reprod. Toxicol.* 28, 220–225
29 Bugelski, P.J. *et al.* (2000) Preclinical development of keliximab, a primatized anti-CD4 monoclonal antibody, in human CD4 transgenic mice: characterization of the model and safety studies. *Hum. Exp. Toxicol.* 19, 230–243
30 Robinson, S. *et al.* (2007) European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. *Regul. Toxicol. Pharmacol.* 50, 345–352