National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

2004-2014

Working with the pharmaceutical industry

Pioneering Better Science

A review of the NC3Rs collaboration with the pharmaceutical industry

Foreword

It is ten years since our partnership with the pharmaceutical industry began. During this time we have focused on a wide range of 3Rs programmes. These have had a significant impact on animal use by influencing company practice and regulatory requirements, and have provided the opportunity to improve efficiency and decision-making across the drug discovery and development pipeline. We have tackled some of the biggest challenges facing the industry and some of the most sensitive issues in animal research. Collaboration has been essential.

We have worked with more than 40 pharmaceutical and biotechnology companies and regulatory agencies from the UK, elsewhere in Europe and the USA fostering a cross-company approach to the 3Rs. We have established ourselves as a trusted partner for data sharing with companies providing us with extensive nonclinical and clinical data sets from historic compounds and those currently in development. By working with companies to interrogate and analyse this data we have been able to rationalise the requirement for *in vivo* studies and deliver 3Rs impacts. Importantly, through our collaborations we have been able to build evidence-bases that could not be achieved by any one company alone.

We have also championed scientific and technological innovations through our CRACK IT programme which was designed to specifically address industry challenges involving the use of animals. The success of CRACK IT is dependent on collaboration, not only between the NC3Rs and the pharmaceutical industry but also with other industries and the academic and small and medium-sized enterprise (SME) sectors. Launched in 2011, CRACK IT has already demonstrated the importance of open innovation for the 3Rs and the potential – scientific and economic – for the UK to be a world leader in this area. It is this potential that has led to a new collaboration between the NC3Rs, the Technology Strategy Board (TSB) and other leading UK funding agencies[1] to support business-led feasibility studies on non-animal technologies.

Our objective is to continue to build on the partnerships we have established with companies and regulators. This will include broadening our outreach to organisations in countries, such as India and South Korea, where we have previously not worked; maximising the 3Rs opportunities in drug development that are emerging from technological advances in microfluidic and systems pharmacology platforms for example; and ensuring the effective commercialisation and global marketing of products and services developed through CRACK IT.
All exciting prospects for the next ten years of the NC3Rs.

Kathryn Chapman PhD, Industry Lead
Vicky Robinson PhD, Chief Executive
June 2014

[1] Including the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council and the Defence Science and Technology Laboratory

Introduction

> “The NC3Rs has taken a science-driven and collaborative approach in challenging the way that we do things which has been highly effective and appreciated by the industry.”
>
> Dr Paul Brooker,
> Huntingdon Life Sciences

In recent years the pharmaceutical industry has faced significant challenges which have led to a re-thinking of its business model.

This has resulted in investments shifting to new geographical locations, particularly emerging markets; a greater emphasis on external collaboration and outsourcing; and changes in therapeutic priorities. At the heart of this has been the difficulty of identifying new targets, and selecting candidates to be developed into marketable drugs that are better than existing treatments. Increasingly, companies and regulators have looked for new ways of developing efficacious and safe medicines and inevitably this has led to a focus on the utility of animal models of disease, efficacy and toxicity, and concerns about the translation of information from *in vivo* studies.

Animal studies are currently an integral part of the drug discovery and development programme. Changing this paradigm – including company practices and regulatory requirements – will ultimately be dependent on a new approach which challenges the status quo, fosters collaboration and delivers scientific and technological innovations. These three principles are at the core of the work the NC3Rs has led in partnership with major pharmaceutical, biotechnology and contract research organisations, and the Association of the British Pharmaceutical Industry. This review summarises the partnership, focusing on collaboration through data sharing and CRACK IT.

A list of pharmaceutical and biotechnology companies and contract research organisations who have participated in our industry programmes is in the Annexes.

Data sharing

> “The MHRA have used data from NC3Rs programmes to support changes in regulatory guidelines.”

Dr David Jones,
Medicines and Healthcare Products Regulatory Agency (MHRA)

The collation and analysis of data can allow new 3Rs opportunities to be identified based on existing knowledge and practice.

We have led a cross-company approach to pre-competitive data sharing primarily focused on toxicology studies carried out for regulatory purposes. We have acted as an ‘honest broker’, facilitating the sharing and analysis of data on hundreds of compounds and studies across therapeutic areas from oncology to metabolic diseases. Through this work we have highlighted how animal use can be replaced, reduced and refined without compromising the drug development process, regulatory requirements or human safety.

Here we provide six examples of our data sharing and analysis programmes by test, therapeutic type, study design, procedure, scientific discipline and animal species. An associated bibliography is provided in the Annexes.

By test

In 2009 the requirement for conventional single dose acute toxicity testing prior to first-in-human studies was removed from the international pharmaceutical guidelines, ICH M3. This was a landmark change as historically this was the only test in pharmaceutical development with death of the animals as an endpoint. The impact on animal use on clinical trial applications has been significant as shown in Table 1 (information provided by the MHRA).

Table 1: The impact of regulatory change:

The proportion of clinical trial applications for drugs going into humans for the first time in the UK which contain the results from conventional single dose acute toxicity tests.

The saving in animals is significant with up to 100 rodents used per drug for these tests.

2007	2011	2012	2013
86%	58%	20%	16%
(66/78)	(76/132)	(27/134)	(15/93)

The regulatory change was in response to a data sharing initiative led by the NC3Rs and AstraZeneca and involving 17 other companies from Europe and the USA. This demonstrated that the single dose acute toxicity test was of little scientific value in terms of identifying major organ toxicities and setting dose levels for subsequent studies, and that information could be provided from other studies already carried out as part of the drug development process, such as the maximum tolerated dose (MTD).

The remaining driver for single dose acute toxicity tests, to support the management of overdose in Phase 3 trials and for registration, was removed following a survey of international poison centres and discussions with regulators which showed that the studies were not used by clinicians or regulators for the assessment of pharmaceutical overdose.

The initiative has gone on to provide evidence to refine MTD studies focusing on body weight loss. Body weight loss is often used as a surrogate measure of animal welfare and as an objective clinical endpoint to decide when to terminate studies.

Based on an analysis of 151 compounds from 13 companies we have published recommendations for maximum body weight loss limits of 10% in the rat and dog and 6% in non-human primates, lower limits than current practice for MTD studies as shown in Table 2.

Publications arising from our work on single dose acute toxicity tests are listed in the Annexes.

Table 2: Improving animal welfare: refining maximum % body weight loss in MTD studies

	Rat	Dog	Non-human primate
Typical	>20	>16	>10
Refined	10	10	6

By therapeutic type

Since the late 1990's the number of monoclonal antibodies (mAbs) entering the clinic has increased substantially as companies exploit the potential benefits to patients offered by these new biotherapeutics. The nonclinical testing of mAbs, however, poses some challenges because their high degree of target specificity can mean that there is either no relevant species to use or that the non-human primate is the only option.

Most adverse effects observed with mAbs are exaggerated pharmacology rather than off-target toxicity. In order to provide safety data for internal and regulatory decisions, companies have focused on screening mAbs for potency in the cynomolgus monkey. This ensures that there is a clear nonclinical testing strategy but drives up the number of non-human primates used, particularly for chronic and reproductive toxicology.

Over the last eight years we have worked with the international pharmaceutical and biotechnology industry to embed the 3Rs in the development of mAbs, influencing the addendum to the ICH S6 guidelines on the nonclinical safety evaluation of biotechnology-derived pharmaceuticals. We initially focused on opportunities to reduce the use of non-human primates by facilitating cross-company data sharing on group sizes, and also the number of doses, recovery animals and studies carried out. Our analysis of over 100 compounds from 15 companies has provided the scientific rationale to halve the number of non-human primates used in a typical mAb development programme from 144 to 64 as shown in Tables 3a and 3b.

Table 3a: Number of non-human primates used in a typical mAb safety evaluation programme

Dose group	Low	Medium	High	Control
Number of animals	4♂ + 4♀	4♂ + 4♀	4♂ + 4♀	4♂ + 4♀
Number of recovery animals	2♂ + 2♀	2♂ + 2♀	2♂ + 2♀	2♂ + 2♀
Total for one study				**48**
Total per programme (three studies)				**144**

Table 3b: A new paradigm for the safety evaluation of mAbs that reduces the number of non-human primates used without compromising the drug development programme

Dose group	Low	Medium	High	Control
Number of animals	3♂ + 3♀	3♂ + 3♀	3♂ + 3♀	3♂ + 3♀
Number of recovery animals			2♂ + 2♀	2♂ + 2♀
Total for one study				**32**
Total per programme (two studies)				**64**

This is based on: using group sizes of three males and three females, rather than four of each sex; including fewer recovery animals; dropping the medium dose group; and reducing the number of studies from three to two with a short-term study to support first-in-human trials and a six month study to support registration.

The importance of establishing data-driven recommendations on non-human primate numbers has been highlighted by recent approvals of biosimilars, that is, generic versions of currently used mAbs. Testing requirements for approval of biosimilars differ widely from one country to another with some requiring extensive animal testing. Many biosimilars are manufactured in countries outside the reach of the ICH. Working with the MHRA and 13 companies we are now examining the need for *in vivo* studies when the biosimilar and innovator product are indistinguishable by a variety of *in vitro* test methods.

With the recent shift in industry to selecting mAbs with potency in rodents, we have also started to focus on maximising the information derived from the rat or mouse to further minimise the use of non-human primates and to avoid the risk of a two species approach becoming common practice. This was launched with a joint symposium with Charles River Laboratories in Carlsbad, USA, in 2013, which highlighted the use of rodent studies in mAb development and the requirement for improved bioanalysis and microsampling technologies to reduce the number of animals used.

Our mAbs programme with industry was launched in 2006 with a workshop on the feasibility of developing mAbs without the use of animals. This goal remains a significant challenge. In June 2014 we will be re-visiting this with a workshop in Washington, USA, to set out a ten year vision with companies, regulators and technology providers focusing on the use of emerging technologies, such as stem cell biology and microfluidics, to better predict adverse effects arising from exaggerated pharmacology in humans. We have already invested £500k in this area through our CRACK IT Challenges funding competition, working with scientists at Huntingdon Life Sciences and the University of Southampton to develop predictive *in vitro* systems for assessing the risk of antibody-induced cytokine release ('cytokine storms') in humans, which would usually be investigated in animal studies.

Publications arising from our work on the development of mAbs are listed in the Annexes.

By procedure

Toxicokinetic analysis identifies the level of drug exposure which elicits an adverse event in animals. Most short and long-term toxicity studies include 'main study animals' which are used to determine potential adverse effects, plus 'satellite animals' for toxicokinetics. Direct biological comparison of exposure and adverse events in the same animal is limited by the volume of blood required for analysis – typically around 200µl per time point. For small molecules, bioanalytical methods exist that allow drugs to be measured in blood samples of less than 50µl per time point. This provides the opportunity to take microsamples of blood from the main study group without the need for satellite animals, giving scientific as well as 3Rs benefits. Removing the need for specific groups of rodents for the sole purpose of toxicokinetics represents the single biggest opportunity to reduce the use of animals in regulatory toxicology studies – providing up to a 55% reduction for some studies as shown in Table 4.

There is still some way to go, however, in delivering this reduction. Many companies are concerned about the potential impact of blood sampling on toxicological and pathological endpoints in the main study animals. To address this we are leading an international group, including 27 companies and regulators, to extend the use of microsampling so that adverse effects and exposure levels can be assessed in the same animal without compromising the study or animal welfare. We are acting as an honest broker for data sharing, with the evidence that we are collating supporting the re-opening of the ICH guidelines on toxicokinetics.

Publications arising from our work on microsampling are listed in the Annexes.

Table 4: The potential level of reduction from the use of microsampling

Comparison of conventional and microsampling study designs using rats and mice. The number of male and female main study animals and satellite animals are shown per dose group and typical numbers assume three dose groups plus control. The reduction in animal use ranges from 23% to 55% depending on the number of satellite animals used (which differs between companies and studies).

Study Type	Conventional design with satellite animals	Microsampling design	Animal reduction
Dose Range Finding Rat	3 ♂ + 3 ♀ /group, plus 3 ♂ + 3 ♀ /group for TK sampling Typical numbers = 48	3 ♂ + 3 ♀ /group Typical numbers = 24	**50%**
One Month GLP Toxicity Study Rat	10 ♂ + 10 ♀ /group, plus 3 ♂ + 3 ♀ /group for TK sampling Typical numbers = 104	10 ♂ + 10 ♀ /group Typical numbers = 80	**23%**
Three Month GLP Toxicity Study Mouse	10 ♂ + 10 ♀ /group, plus 6 ♂ + 6 ♀ /group for TK sampling at beginning and end of study Typical numbers = 176	10 ♂ +10 ♀ /group Typical numbers = 80	**55%**

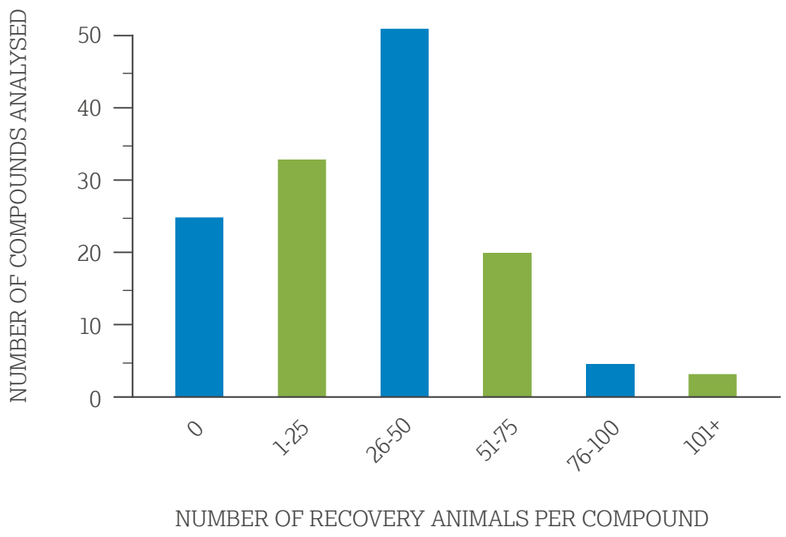
GLP – Good laboratory practice | TK – Toxicokinetics

By study design

Recovery animals are included in many toxicology studies to determine whether animals can recover from any adverse effects caused by the compound being tested. Rodents, dogs and non-human primates are used. In an initiative led by the NC3Rs and the MHRA, and involving 32 organisations (including companies and regulators), we have examined whether recovery animals are required on all studies and all dose groups and how reducing this use might impact on internal and regulatory decision making.

Our analysis has shown that there is variation in industry practice, for example with the number of recovery animals used per compound to support first-in-human clinical trials ranging from 0 to over 100 as shown in Figure 1. The most common rationale for the inclusion of recovery animals is 'default' company practice or perceived regulatory expectation. By sharing data on 259 studies for 137 compounds (including 53 biologicals and 78 small molecules) we have identified that the use of recovery animals could be reduced by up to 66%, saving thousands of animals globally each year. Based on this we have developed recommendations that move away from a default approach to the inclusion of recovery animals and instead encourage science-based case-by-case consideration.

Figure 1: Variation in the number of recovery animals included per compound in regulatory toxicology studies to support first-in-human trials.



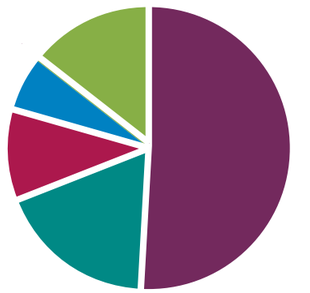
By scientific discipline

Safety pharmacology consists of a core battery of tests on vital organ systems that are carried out prior to first-in-human studies to identify adverse properties relevant to human safety. The main test battery focuses on cardiovascular and respiratory functions and the central nervous system, and involves *in vitro* and *in vivo* studies, including rodents, dogs or non-human primates.

We are coordinating two complementary programmes, which aim to evaluate how well animal studies predict adverse events in the clinic and whether the use of human tissue could replace some studies. The latter is in partnership with the MHRA.

Working with seven companies we have analysed nonclinical and clinical data on respiratory and central nervous system endpoints for 111 and 141 compounds respectively. For respiratory endpoints, the analysis has shown that nonclinical measurements from rodent plethysmography do not predict specific effects seen in the clinic in Phase 1. A similar picture is emerging for central nervous system endpoints comparing the Irwin test, or functional observational battery, with clinical symptoms. The analysis suggests that some safety pharmacology studies have limited value. We are now evaluating whether they have more utility when conducted to support late stage clinical trials or registration, and whether studies can be amended to give greater face validity.

Drivers for human tissue use in safety pharmacology



Summary of responses from 27 organisations

By animal species

Working primarily with Pfizer we have provided an evidence base for avoiding the use of the dog and non-human primate in the pharmacokinetic (PK) analysis of renally and hepatically cleared compounds, and the non-human primate for abuse potential.

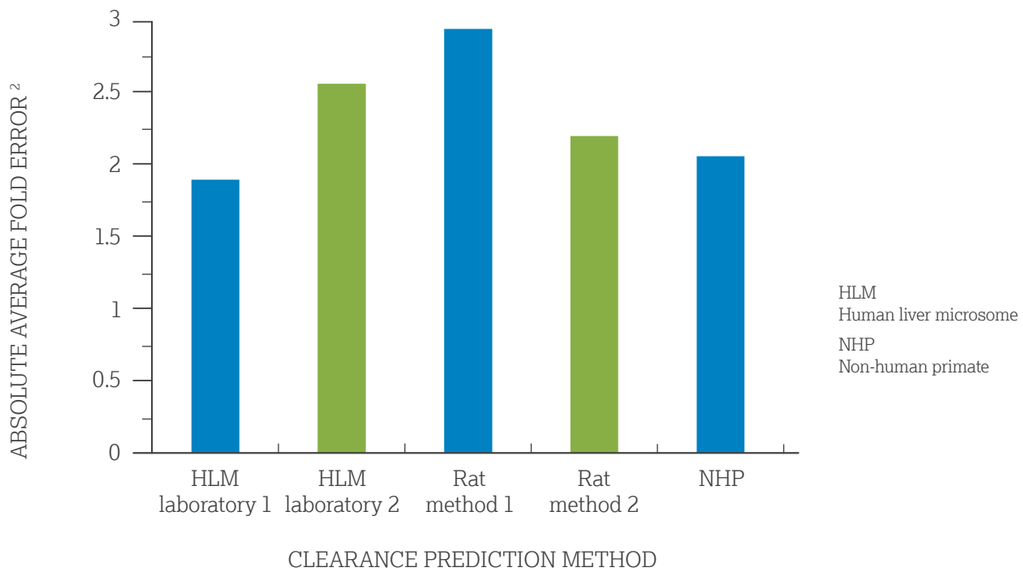
Pharmacokinetics in candidate selection

Prediction of human PK is a critical part of candidate selection and the identification of compounds which have appropriate exposure levels in man. Frequently, human PK in early drug discovery is predicted using allometric scaling from a number of different species. Up to 27 animals are used per candidate, including rats, dogs and non-human primates. By analysing data on the clearance of 74 compounds we have shown that human liver microsomes can be used to predict PK for compounds cleared by hepatic cytochrome P450 enzymes (as shown in Figure 2) as accurately as the non-human primate, and that the rat alone can be used for renally cleared compounds (data not shown). The human liver microsome data has been confirmed by Huntingdon Life Sciences in a study commissioned by the NC3Rs. This work has provided the basis for a predictive framework which allows compounds with the most desirable PK properties to be selected using *in vitro* methods alone, or *in vitro* methods combined with a single species study in the rat.

Publications arising from our work are listed in the Annexes.

Figure 2: Comparison of human liver microsomes and rat and non-human primate scaling methods for predicting human clearance for compounds metabolised by hepatic cytochrome P450 enzymes.

Note the human liver microsome studies were conducted in two different laboratories for reproducibility purposes; two different methods were used for rat single species scaling (based on published data); and the non-human primate data is based on the hepatic blood flow method (using published data).



[2] This method of calculation values both underprediction and overprediction in the same manner. A perfect prediction would exhibit a value of 1; a 2-fold error (i.e 50% below or 100% above) would exhibit a value of 2.

Abuse potential

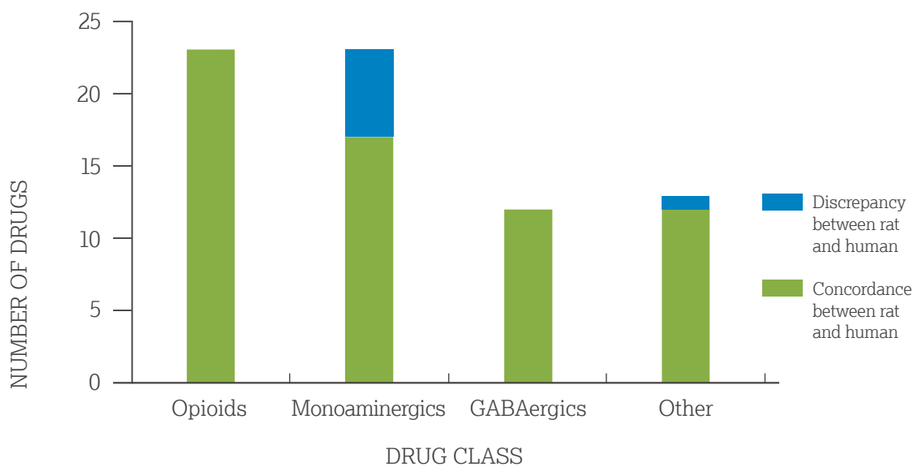
Studies of abuse potential for drugs targeting the central nervous system have historically used the non-human primate as the 'gold standard model'. Although this often involves naïve animals, many studies use substitution paradigms where animals are trained to self-administer known substances of abuse, such as cocaine, which are then removed to determine whether the animal self-administers the test drug.

Practice varies among companies with some using the rat and others the non-human primate. We have built a case to use the rat, supporting a change in ICH M3 to accept rodent instead of non-human primate data. We have analysed more than 500 papers reporting data on 71 drugs that were assessed in the rat self-administration model and the clinic. We found that overall there was 90% (64/71) concordance between the rat and human for a range of drug classes as shown in Figure 3. For the drugs where non-human primate data were also available there was no statistical difference between the rat and the non-human primate at predicting human abuse liability and scheduling status. We have also generated data for certain classes of substances, such as opioids, which shows that the rat has the same self-administration dose response as the non-human primate.

We are currently looking at specific aspects of study design to identify recommendations for refinement to the rodent studies. In collaboration with the CAMARADES[3] group we are carrying out a systematic review and meta-analysis of opioid self-administration studies in the rat to investigate the impact of variables, such as feeding restrictions, restraint, the type of training animals receive and the amount of time they are exposed to a drug. Understanding how these variables influence the response will enable us to formulate recommendations to improve the welfare of the animals used.

Publications arising from our work on abuse potential are listed in the Annexes.

Figure 3: Number of drugs analysed for which rat self-administration studies show concordance with at least one clinical indicator of abuse liability.



[3] Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies

CRACK IT

> “Through CRACK IT, the NC3Rs has brought together industry, academia and third party technology providers to deliver innovative solutions for big 3Rs questions.”

Dr Malcolm Skingle CBE,
GlaxoSmithKline

Industry is increasingly seeking solutions from the academic and SME sectors to the problem of predicting clinical efficacy and safety from nonclinical studies. We have responded to this by launching CRACK IT Challenges and CRACK IT Solutions, which link large pharmaceutical, chemical and consumer products companies, academia and the SME sector.

Here we provide a summary of the key features of CRACK IT Challenges and CRACK IT Solutions. Figure 4 provides a schematic of the CRACK IT innovation pipeline.

CRACK IT: The philosophy

The Challenges

CRACK IT Challenges is a novel competition that funds collaborations between industry, academics and SMEs to solve business challenges involving animals. There are benefits for all participants; industry gets access to scientific and technological innovation emerging from the science base and an end product which meets their needs; academics have a pathway for exploiting their research; and SMEs are provided with a ready-made market.

The Solutions

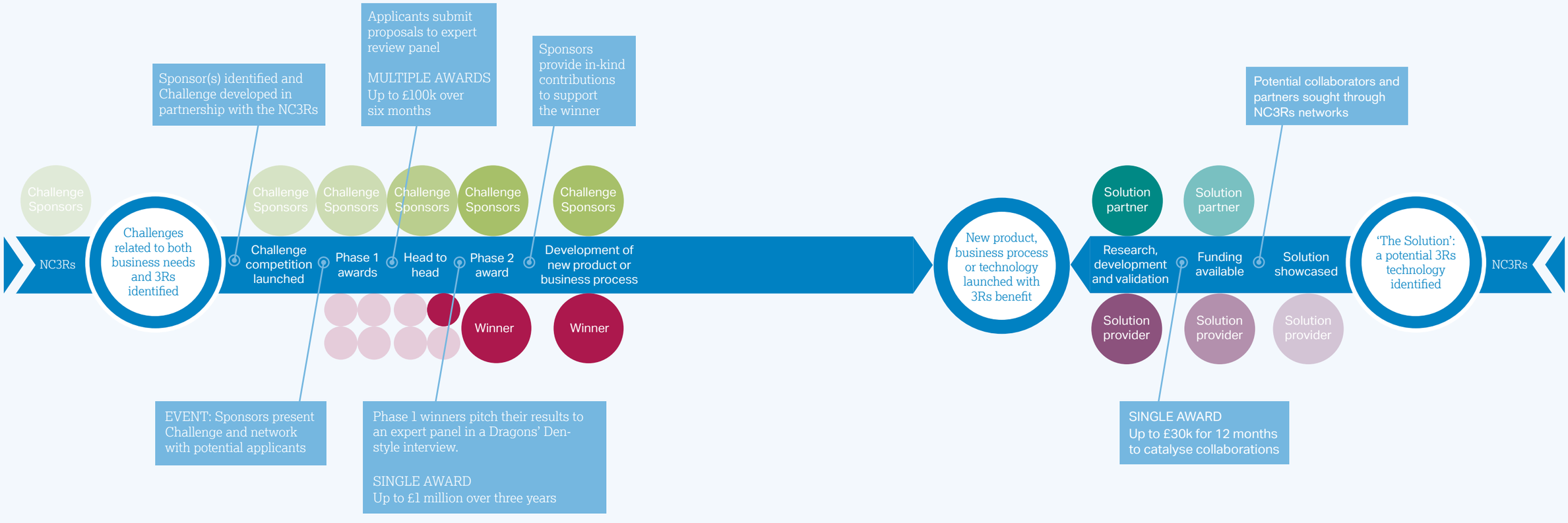
CRACK IT Solutions is a technology partnering hub designed to accelerate the translation of technologies, referred to as ‘Solutions’, out of the science base and into application to maximise the scientific, commercial and 3Rs benefits. The aim is to assist Solution providers in identifying new partners and customers to validate and adopt their technology.

Figure 4: Innovation pipeline CRACK IT Challenges and Solutions

Challenge Sponsor(s) - with unmet business need

Predominantly from the pharmaceutical, chemical or consumer products sectors

Solution partners - potential end user



Challenge applicants - innovators

From the SME or academic sectors

Solution provider - technology developer

From the SME or academic sectors

CRACK IT Challenges: Open innovation competition to tackle industries' big challenges

The Challenges

We award contracts for funding to solve specific scientific or business 'Challenges'. The Challenges are identified by the NC3Rs in partnership with companies. To date there have been 15 Challenges, as shown in Table 5. Of these, 12 are directly relevant to pharmaceutical development. These cover a range of major issues, which if solved could help to identify new targets and drugs, or reduce attrition rates through improved efficacy or safety. The Challenges encompass the major organ systems and key therapeutic areas and require scientists from different disciplines – biology, chemistry, engineering, computer science and mathematics – to work together to solve them.

The sponsors

Sponsors define the Challenge, working with the NC3Rs to set out the business case and 3Rs benefits of solving it. The sponsors are ultimately an end user of any new product developed through the competition so they have a key role in outlining the properties of the ideal solution so that it can be readily adopted into their business practices, for example, the need for inclusion of specific cell types or endpoints, miniaturisation, or the required level of throughput. To date there have been 15 sponsors, seven from the pharmaceutical sector.

Sponsors are required to provide funding and/or in-kind contributions to help solve the Challenge. In-kind contributions can include access to data, compounds, equipment, tissue samples or expertise.

The funders

The main funder of the competition is the NC3Rs. We have also been able to secure additional funding for specific Challenges from the TSB, the Medical Research Council, the Department for Environment, Food and Rural Affairs and Alzheimer's Research UK. A total of £8.3 million has been committed for the competition to date.

The process

The Challenges are published by the NC3Rs including the background to the problem to be solved, key deliverables and 3Rs benefits, and pitched to the wider scientific community for solving. Applicants are required to submit an application detailing how they would solve the Challenge, the expertise they provide and how they would work with the sponsors, including the use of the in-kind contributions. This is Phase 1. Applications are evaluated by an expert Review Panel, which includes the sponsors and funders, and up to four awards are made per Challenge for proof-of-concept studies of £100k over six months. These are subsequently assessed in Phase 2 by a Dragons' Den-style Panel with each Challenge winner being awarded up to £1 million over three years.

We use the TSB's Small Business Research Initiative to run the competition.

The innovators

The Challenges are complex, requiring multi-disciplinary teams for solving, plus the ability to commercialise the end product. Teams which involve academic and SME partners are essential to delivery. To date we have awarded contracts to 33 teams, involving a total of 65 organisations, 35% of which are SMEs. New intellectual property is retained by the lead contractor and/or collaborator in each team, with sponsors obtaining early access to new technologies emerging from the CRACK IT Challenge.

The teams work closely with the NC3Rs and the sponsors in Phase 1 and 2 with quarterly project management meetings and payments linked to specific deliverables. The first products developed through CRACK IT Challenges will be launched in 2014.

> "Winning the Rodent Big Brother Challenge has provided new and exciting opportunities for our company. The monitoring system that we have developed for assessing the behaviour and welfare of rats used in safety pharmacology and toxicity studies has the potential to have a global impact. We estimate that there are circa 2.5 million rat procedures per annum in our target users. With a 5% market penetration we estimate $60 million of sales."
>
> David Craig, Chief Executive Officer, Actual Analytics

CRACK IT Solutions: Showcasing 3Rs technologies

The Solutions

We have showcased 16 Solutions (eight from SMEs and eight from academics) across a range of applications, including enabling technology platforms, stem cell approaches for toxicity testing and non-mammalian models for basic and applied research.

To date, 14 of the Solutions providers have identified new contacts and potential collaborators through the scheme.

The process

The Solutions, including the technology and its potential uses, are developed into a pitch by the NC3Rs and the Solution provider, and are subsequently promoted through our networks. A funding scheme to support new collaborations between Solution providers and potential end users has been established. Five awards of £30k over 12 months have been awarded. In addition £112k of external funding has been secured from end-users and Solution providers.

> “One of the issues as an academic is that although you’ve got an idea, you don’t always have the contacts in industry to make use of it.
>
> The great thing about CRACK IT Solutions is that the NC3Rs team helped me to put together a pitch to make sure that industry would be interested in what I had to say, they used their extensive contacts to help me link to people, but once they’d set up that link they stepped back and let me talk to them directly so that I kept complete ownership of the idea.”

Alex Easton, Neuroscientist, Durham University – Solution provider

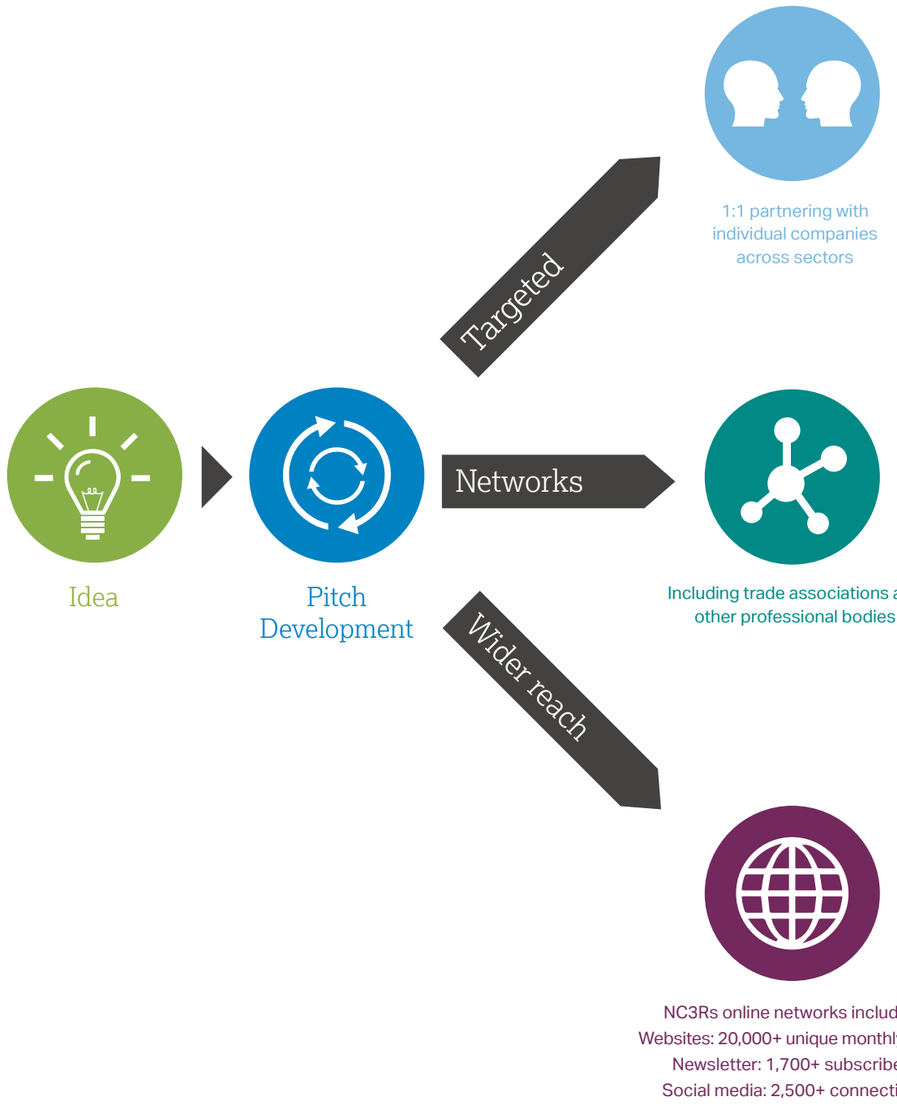


Table 5: Summary of CRACK IT Challenges 2011 to 2013

	Theme	Sponsors	Challenge	End product	'R'
2011	Wireless recording of electrophysiology in rodent psychiatric disease models	Eli Lilly	Recording of brain activity and behavioural outcomes in freely moving animals	Prototype for a wireless 16-32 channel recording system and associated software	Refinement allowing home cage analysis without tethering
	Rodent Big Brother	AstraZeneca	Improved assessment of animals on toxicology studies by better monitoring	An automated non-surgical system for measuring activity and body temperature in standard caging	Refinement through non-invasive home cage monitoring of rats in social groups
	Cytokine release	Huntingdon Life Sciences	Better prediction of cytokine storm for antibody-based therapeutics	Human cell-based models to detect cytokine release	Replacing the use of non-human primates
	In vitro to *in vivo* extrapolation for systemic toxicity	AstraZeneca, Syngenta, Unilever	Improved understanding of the relevance of toxicity concentration response data from human *in vitro* systems to predictions of safety following relevant *in vivo* human exposure	A model to predict the *in vivo* concentration effect and dose response in humans for a chosen toxicity pathway	Avoiding the use of animals for chemical risk assessment
	Bipolar affective disorder	Eli Lilly, Janssen	Improved screening of potential drugs for bipolar affective disorder	A validated *in vitro* screen based on induced pluripotent stem cell (iPS) cells from patients	Reducing the use of rodents for novel drug screening
2012	Rodent Little Brother	MRC Harwell	Improved phenotyping of genetically modified mice	An automated, non-surgical system to measure mouse activity, behaviour and interaction in the home cage	Refinement through home cage monitoring of mice in social groups
	Biodistribution of macromolecules	GlaxoSmithKline	Advanced imaging for determining the biodistribution properties of macromolecules *in vivo*	New imaging probes for macromolecules plus a streamlined imaging platform for non-invasive 3D assessment of biodistribution combined with efficacy readouts	Reduction in the number of animals used for biodistribution purposes by allowing longitudinal monitoring
	Source of human dorsal root ganglia for target identification and pharmacology	Grünenthal, Pfizer Neusentis	Improved drug discovery for chronic pain	Commercial supply of viable human dorsal root ganglia	Replacement of the use of rodents, dogs and non-human primates as a source of dorsal root ganglia

Table 5: Continued

	Theme	Sponsors	Challenge	End product	'R'
2012	Prediction of human developmental and reproductive toxicity through non-mammalian assays	Shell, Syngenta	Development of non-mammalian assays that can provide an indication of developmental and reproductive toxicity potential to mammals, including man	A stable, medium-throughput test system providing early indication of developmental toxicity	Reduction and replacement of the use of rodents and rabbits in developmental toxicity testing
	Refinement of techniques for intravitreal (IVT) injection to avoid side effects in rabbits	GlaxoSmithKline	The design, development and validation of a device to facilitate and standardise IVT drug delivery to rabbits	An IVT injection device specific to the rabbit eye	Refinement through minimising the risk of adverse effects associated with IVT injection
2013	Tau protein pathology associated with Alzheimer's disease	Alzheimer's Research UK, Eli Lilly, Janssen	Development of an *in vitro* assay for tau protein aggregation, seeding, pathology, transmission and toxicity, leading to improved identification of mechanisms and drug targets that are relevant to humans	A human cell-based assay to predict the efficacy and unexpected pharmacological effects of new chemical entities and biologics targeting tau in Alzheimer's disease	Reduction in the number of transgenic mice used to investigate tau pathology
	Use of induced pluripotent stem (iPS) cell-derived cardiomyocytes in cardiovascular research	GlaxoSmithKline	Improved assessment of drug-induced cardiac contractility liabilities	An iPS cell cardiomyocyte platform which is robust and reflects the 3D architecture of cardiac tissue with mature cell phenotypes	Reduction and replacement of animals used to study cardiovascular safety liabilities
	Toxicity resulting from inhaled therapies for chronic inflammatory diseases of the airways	GlaxoSmithKline Huntingdon Life Sciences, Pfizer,	Enabling the longitudinal and non-invasive assessment of inflammation and foamy macrophage (FM) toxicity in the same animal through a series of dose-escalation stages	Tools to assess FM modulation and inflammation in a longitudinal manner in rodent lungs	Reduction in the number of animals used through longitudinal evaluation of the same animal
	Drug-induced nephrotoxicity	GlaxoSmithKline, Pfizer, Roche	Development of an *in vitro*, human-based model to more accurately measure the toxic effects of preclinical drugs	A multi-compartmental, microfluidic tissue assay that models the renal tubular injury observed in nephrotoxicity	Reduction in the number of rodents used in nephrotoxicity studies
	Virtual Infectious Disease Research	NC3Rs	The use of virtual information and tools to enhance disease modelling and new target development	A virtual platform that models infection and the host response to pathogen assault in an individual animal	Reduction in the number of animals used in efficacy studies for new antibiotics or vaccines

Annexes

Our partners

Companies engaged in NC3Rs programmes

AbbVie
Amgen
AstraZeneca
Bayer HealthCare
BIOCAD
Biocon
Biogen Idec
Boehringer-Ingelheim
Bristol-Myers Squibb
Charles River Laboratories
Chugai
Covance
Eli Lilly
Genentech
Genzyme
Gilead
GlaxoSmithKline
Grünenthal
Harvest Moon Pharma
Huntingdon Life Sciences
Janssen
Medimmune
Merck
Novartis
Novo Nordisk
PAREXEL International Corp
Pfizer
Pfizer Neusentis
Roche
Sanofi
Sequani
UCB
Vertex
Wickham Laboratories
WIL Research

Summary of NC3Rs publications

By test

Chapman, K., and Robinson, S (2007)
Challenging the Regulatory Requirement for Acute Toxicity Studies in the Development of New Medicines: Workshop Report. NC3Rs, London.

Robinson, S., J. L. Delongeas, *et al.* (2008)
A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. *Regulatory Toxicology and Pharmacology* **50**(3): 345-352.

Robinson, S., and Chapman, K (2009)
Are acute toxicity studies required to support overdose for new medicines? *Regulatory Toxicology and Pharmacology* **55**(1): 110.

Chapman, K., S. Creton, *et al.* (2010)
The value of acute toxicity studies to support the clinical management of overdose and poisoning: a cross-discipline consensus. *Regulatory Toxicology and Pharmacology* **58**(3): 354-359.

Chapman K., F. Sewell, *et al.* (2010)
A Global Pharmaceutical Company Initiative: An Evidence-Based Approach to Define the Upper Limit of Body Weight Loss in Short Term Toxicity Studies. *Regulatory Toxicology and Pharmacology* **67**(1): 27-38.

By therapeutic type

Workshop report: NC3Rs/ABPI (2006)
Opportunities for reducing the use of non-human primates in the development of monoclonal antibodies a workshop report. London: NC3Rs/ABPI.

Chapman, K., N. Pullen, *et al.* (2007)
Preclinical safety testing of monoclonal antibodies: the significance of species relevance. *Nature Reviews Drug Discovery* **6**(2): 120-126.

Chapman, K., N. Pullen, *et al.* (2009)
Preclinical development of monoclonal antibodies: considerations for the use of non-human primates. *MAbs* **1**(5): 505-516.

Chapman, K. L., N. Pullen, *et al.* (2010)
The future of non-human primate use in mAb development. *Drug Discovery Today* **15**(5-6): 235-242.

Buckley, L. A., K. Chapman, *et al.* (2011)
Considerations regarding non-human primate use in safety assessment of biopharmaceuticals. *International Journal of Toxicology* **30**(5): 583-590.

Chapman, K. L., L. Andrews, *et al.* (2012)
The design of chronic toxicology studies of monoclonal antibodies: implications for the reduction in use of non-human primates. *Regulatory Toxicology and Pharmacology* **62**(2):347-54.

By procedure

Chapman, K., S. Chivers, *et al.* (2014)
Overcoming the barriers to the uptake of nonclinical microsampling in regulatory safety studies. *Drug Discovery Today* (epub ahead of print).

By animal species

Lave, T., K. Chapman, *et al.* (2009)
Human clearance prediction: shifting the paradigm. *Expert Opinion on Drug Metabolism & Toxicology* **5**(9): 1039-1048.

Beaumont, K., I. Gardner, *et al.* (2011)
Towards an integrated human clearance prediction strategy that minimizes animal use. *Journal of Pharmaceutical Sciences* **100**:1167–1783.

O'Connor, E. C., K. Chapman, *et al.* (2011)
The predictive validity of the rat self-administration model for abuse liability. *Neuroscience & Biobehavioral Reviews* **35**(3): 912-938.

Other relevant publications

Robinson, S., K. Chapman *et al.* (2009)
Guidance on dose level selection for regulatory general toxicology studies for pharmaceuticals. NC3Rs/LASA, London.

Holmes, A. M., S. Creton, *et al*. (2010)
Working in partnership to advance the 3Rs in toxicity testing. *Toxicology* **267**(1-3): 14-19.

Sparrow, S. S., S. Robinson, *et al.* (2011)
Opportunities to minimise animal use in pharmaceutical regulatory general toxicology: a cross-company review. *Regulatory Toxicology and Pharmacology* **61**(2): 222-229.

Chapman K., H. Holzgrefe, *et al.* (2013)
Pharmaceutical toxicology: Designing studies to reduce animal use, while maximizing human translation. *Regulatory Toxicology and Pharmacology* **66(**1): 88-103.

NC3Rs funders

The NC3Rs is primarily funded by the Department for Business, Innovation and Skills via the Medical Research Council and the Biotechnology and Biological Sciences Research Council. It also receives core funding from the Home Office. Funding for specific posts and programmes is provided by a range of organisations from the public, private and charitable sectors.

Since 2005, the NC3Rs has received funding from the Association of the British Pharmaceutical Industry[4] to help support its industry programmes. The Wellcome Trust has also provided funding for the delivery of the CRACK IT Challenges programme since 2011. Additional funding for specific Challenges has been secured from the TSB, the Medical Research Council, the Department for Environment, Food and Rural Affairs and Alzheimer's Research UK.

[4] In accordance with the Association of the British Pharmaceutical Industry's (ABPI) Code of Practice regulating the pharmaceutical industry, the following companies have provided funding to the NC3Rs as part of the ABPI-NC3Rs collaboration: ABPI, AstraZeneca plc., Covance Laboratories Ltd., GlaxoSmithKline plc., Huntingdon Life Sciences Ltd., Eli-Lily and Company Ltd., Pfizer Ltd., and Novartis Ltd.

NC3Rs
Gibbs Building
215 Euston Road
London NW1 2BE

T +44 (0)20 7611 2233
F +44 (0)20 7611 2260
enquiries@nc3rs.org.uk
twitter: @nc3rs

www.nc3rs.org.uk
www.crackit.org.uk

The material used in this publication is derived from sustainable and renewable sources. The Paper is FSC® and ISO14001 accredited. All inks used are vegetable based and all pulp is Elemental Chlorine free (ECF)