Responsible research

Society depends on us to conduct effective, ethical and thorough research in the development of medicines and treatments that save and improve lives. Patients who take our medicines have a right to safety. In order to meet those expectations, we set ourselves high standards of ethical practice across all aspects of our research activity worldwide, from clinical trials to our research with animals.

We believe society expects us to take every safety precaution and responsible decision that is required of us by regulators, as well as those that are ethically sound. We also work to ensure that we are aware of any risks to patient safety such as side effects or cases of product counterfeiting, which is a serious global problem that, if left unchecked, can cause severe health problems for its victims.

2015 highlights

$17.3 million

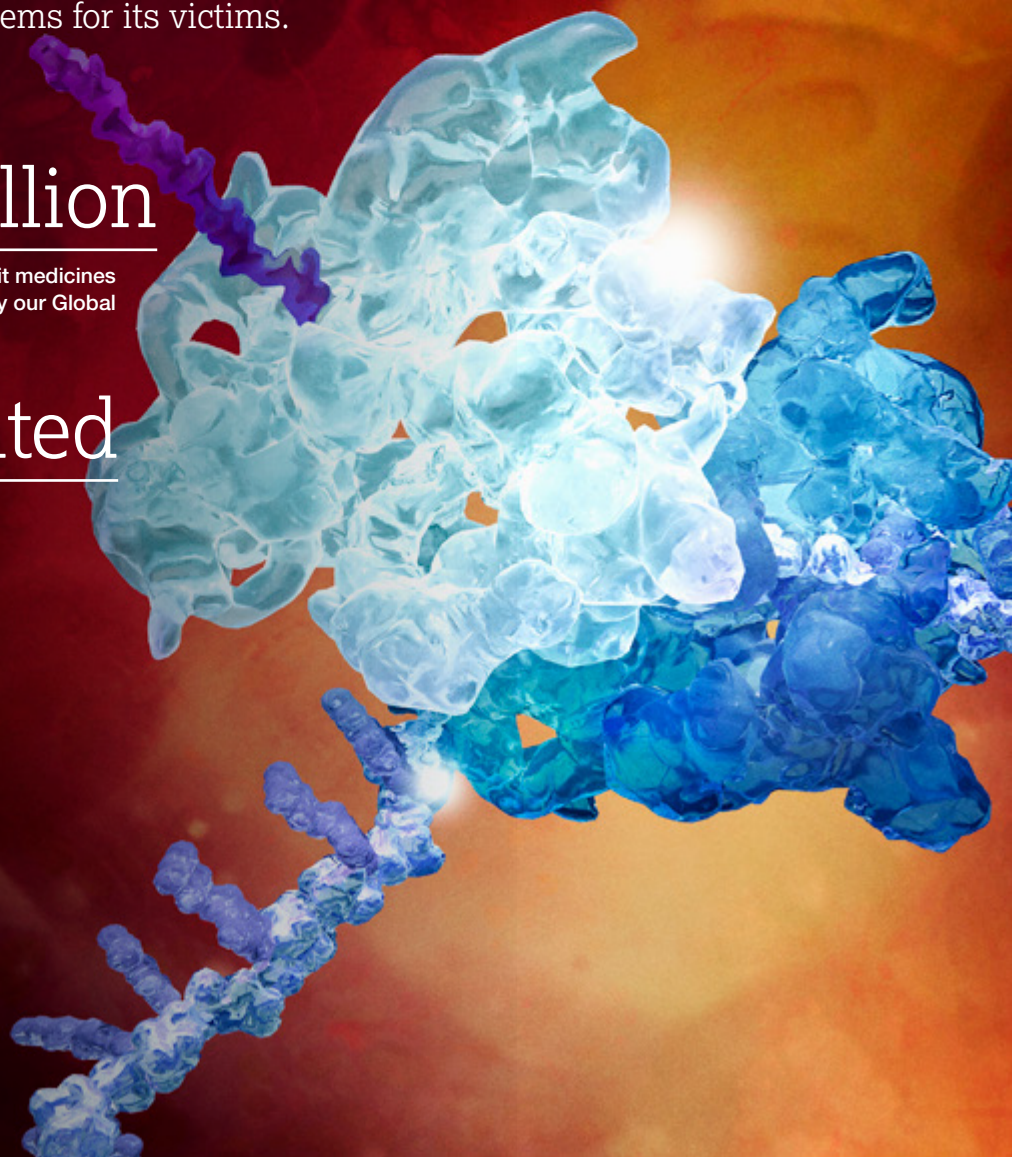
worth of AstraZeneca counterfeit medicines seized through operations led by our Global Security team

Contributed

to the first Concordat on Openness on Animal Research Annual Report

Created

a dedicated Clinical Trial Transparency team



Our approach

We want to be recognised for our high-quality science and for the impact we can make on serious disease – and to be trusted for the way in which we do that. This means setting and living up to high standards of ethical practice across all aspects of our research activity worldwide, including clinical trials and research with animals.

Our Code of Conduct requires that our research be conducted in accordance with all relevant external laws and regulations. It also requires compliance with our Bioethics Policy, which describes our commitment beyond legal compliance and defines the ethical standards, principles and behaviours governing all our research and development (R&D) activity worldwide. In addition, our Global Standard Expectations of Third Parties sets out the standards to which we hold external partners.

Our Code of Conduct also requires all AstraZeneca employees to report any possible adverse effects relating to our medicines within 24 hours through our established procedures. Our safety standards are global and apply in all countries where we operate. We audit our patient safety systems regularly to make sure our policies and standards are being implemented.

We are constantly reviewing laws, regulations and best practice to ensure we abide by the very highest standards, wherever we operate around the world.

Patient safety and product security

Developing a new medicine carries inherent risk, and ensuring patient safety is our top priority. It is our responsibility to eliminate all risk where possible, and to minimise it where it is not possible to eliminate it completely.

During the development phase, extensive and rigorous pre-clinical and clinical testing is done to establish a potential new medicine's safety and efficacy. Once we establish an acceptable benefit and risk profile, we submit comprehensive information, including clinical trial data, to the regulatory authorities responsible for approving medicines in each country or region in which we want to launch the product.

While enormously helpful in defining how patients will broadly respond to a medicine, clinical trials cannot replicate the complete range of patient circumstances that exist among larger and more diverse patient populations. Rare side effects can often be identified only after a medicine has been launched and used in far greater numbers and over longer periods of time. Information is provided from many sources, among others including reports on suspected adverse drug reactions from healthcare providers and patients, as well as from reviews of the scientific literature. Our Global Patient Safety Database is the central source of information for patient safety across our organisation and for reporting to regulatory authorities.

We develop patient risk management plans for all our medicines. These help us identify, further evaluate and reduce risks to patients and, where appropriate, we provide the plans to the regulatory authorities. We review plans regularly and update them with new safety information as our knowledge of the medicine's safety profile evolves.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. It is our responsibility to our patients, and we take it very seriously.

Patient communication

As we develop each medicine, we work with regulators to develop prescribing information that provides healthcare professionals with the information they need to promote patient safety, including indications for use, dosing recommendations, warnings and contraindications, as well as what side effects might occur.

In addition, where it is appropriate, we make information available directly to patients about our medicines and how they should be taken.

We have comprehensive and rigorous systems in place for detecting and rapidly evaluating adverse effects, including mechanisms for highlighting those that require immediate attention. We provide any new safety data to regulators, doctors, other healthcare professionals and, where appropriate, patients.

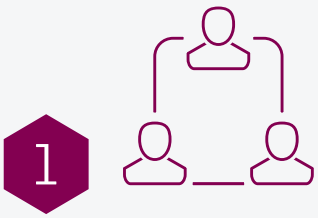
Fighting illegal trade, protecting our patients

Key for Product Security is protecting our patients from the dangers of illegally traded (including counterfeits or stolen) medicines. Counterfeits, for example, often fail to provide effective treatment and sometimes cause direct harm to patients. It is impossible to estimate on a global scale how common is the illegal trade in medicines.

Although the scale, complexity and covert nature means it is impossible to prevent illegal trade entirely, we aim to protect patients by disrupting networks and operations, and making it as difficult as possible for people to carry out these illegal activities.

We require our employees to report suspicions of possible illegal trade of medicines that come to their attention. We also find illegally traded medicines through the work of our Global Security investigators, Customs, other law enforcement agencies, regulatory authorities, healthcare professionals, patients and others. Our Global Security investigators gather the evidence needed (according to globally acceptable standards) for a prosecution and pass this to, for example, relevant local law enforcement agencies. We analyse samples that are suspicious and have a global team to coordinate our response, such as reporting cases to health authorities, alerting doctors, pharmacists or wholesalers. We rely on their cooperation and the local health authority to stop such medicines from reaching patients.

Our Global Product Security strategy focuses on three key areas:



Building strong, collaborative partnerships – to strengthen enforcement, raise awareness and provide advocacy to increase the likelihood of regulation in this area being effective and efficient

Working in enforcement – to combat illegal activity through reporting and professional investigation of suspicions

Securing our products – through the introduction of pack features and enhanced integrity of the end-to-end supply chain

Our Global Product Security strategy

The illegal trade of medicines is not a problem AstraZeneca can tackle alone. We work closely with other pharmaceutical companies through, for example, industry trade associations (IFPMA, EFPIA, PhRMA) and coalitions (EAASM (European Alliance for Access to Safe Medicines) and ASOP EU (Alliance for Safe Online Pharmacy – Europe)), to raise awareness of the threat of counterfeit medicines, for example.

One such initiative to help raise awareness among patients, healthcare professionals and regulators is the IFPMA Fight the Fakes campaign and their False Friends video.

Our Global Security investigators are responsible for the enforcement activities for AstraZeneca and work closely with law enforcement agencies, Interpol and Customs, to dismantle illegal trade operations/networks. In addition, Global Security works closely with other pharmaceutical companies through the Pharmaceutical Security Institute, a not-for-profit organisation, to identify cases of illegal trade and coordinate investigations.

As there is no global law enforcement agency or regulator, pharmaceutical companies like AstraZeneca can often act as an interface between authorities in different countries. In 2015, investigations conducted by Global Security led to the seizure of $17.3 million worth of AstraZeneca counterfeit medicines, and disrupted counterfeiting operations that had netted in excess of $100 million, leading to over 140 arrests.

What to do if you are concerned about receiving an illegally traded medicine or you have a suspicion about your medicine

AstraZeneca urges patients and healthcare professionals to be alert to the possibility of illegally traded medicines. Anyone who is concerned that their AstraZeneca medicine may not be genuine can contact their doctor (physician), pharmacist (or other healthcare professional) or health authority. You can also contact AstraZeneca through this website or in the country where you are based.

Patients can protect themselves from illegally traded medicines by obtaining their medicines only from licensed and regulated outlets, and avoiding unregulated sources on the internet. Patients should be vigilant when examining their medicines, paying attention to altered or unsealed packaging or changes in the product packaging.

Security along our supply chain

We include security features on our packs to enable us to distinguish legitimate products from counterfeits. We also work to improve security in our supply chains for our investigational and commercialised products (bespoke product security audits, collaborating with others to share best practice and supply chain integrity principles for supply chain design) to inhibit the entry of illegally traded medicines.

This includes:

- Strengthening our due diligence processes for third parties and adding product security clauses in our contracts with supply chain partners
- Training our third parties to report any suspicions and to maintain secure distribution channels
- Using seals and/or unique identification numbers (a serial number) on some packs to make it more difficult and expensive for counterfeiters to copy our packaging, and help identify packs that have been tampered with. Applying serial numbers to packs is now becoming a legislative requirement in some markets as governments recognise this as part of their anti-counterfeiting strategy.

Driving greater protection

As the illegal trade in medicines is an illegal activity and therefore hard to measure, we do not publish performance targets around our work. However, we continue to make positive progress on all three areas of our strategy.

As an industry, there has been a lot of progress in terms of raising awareness of the dangers of counterfeit medicines, including the dangers of buying medicines online, but there is more work still to be done. While the counterfeiting of any product is illegal, we need to ensure that patients recognise the potentially life-threatening risks specifically associated with counterfeit medicines.

We are also encouraging regulators to address this issue of illegal trade by enacting legislation that will better protect patient safety and by ensuring that the sentencing of those convicted of producing and distributing counterfeit medicines, for example, reflects the seriousness of the crime.

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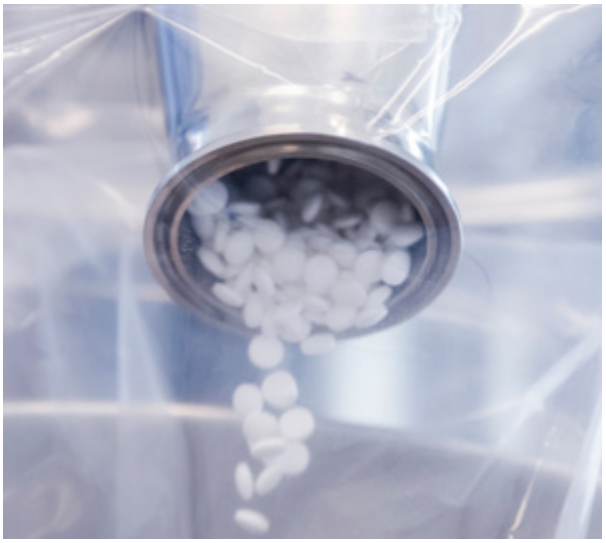


Clinical trials

We study the effects of potential new medicines in humans using clinical trials. The clinical trial phase is essential in the development of new medicines. At any one time, AstraZeneca may have hundreds of clinical trials under way in different locations around the world. We take very seriously our commitment to delivering consistently high standards of ethical practice and scientific conduct in all our trials, wherever they take place.

A potential new medicine is tested in humans only after rigorous and extensive pre-clinical research has confirmed its potential efficacy and safety. Trial medicines go through three phases of testing before they are submitted to regulatory authorities for an approval to market. All medicines have side effects that may affect some people, so the safety of any medicine needs to be assessed in terms of its benefit and risk profile.

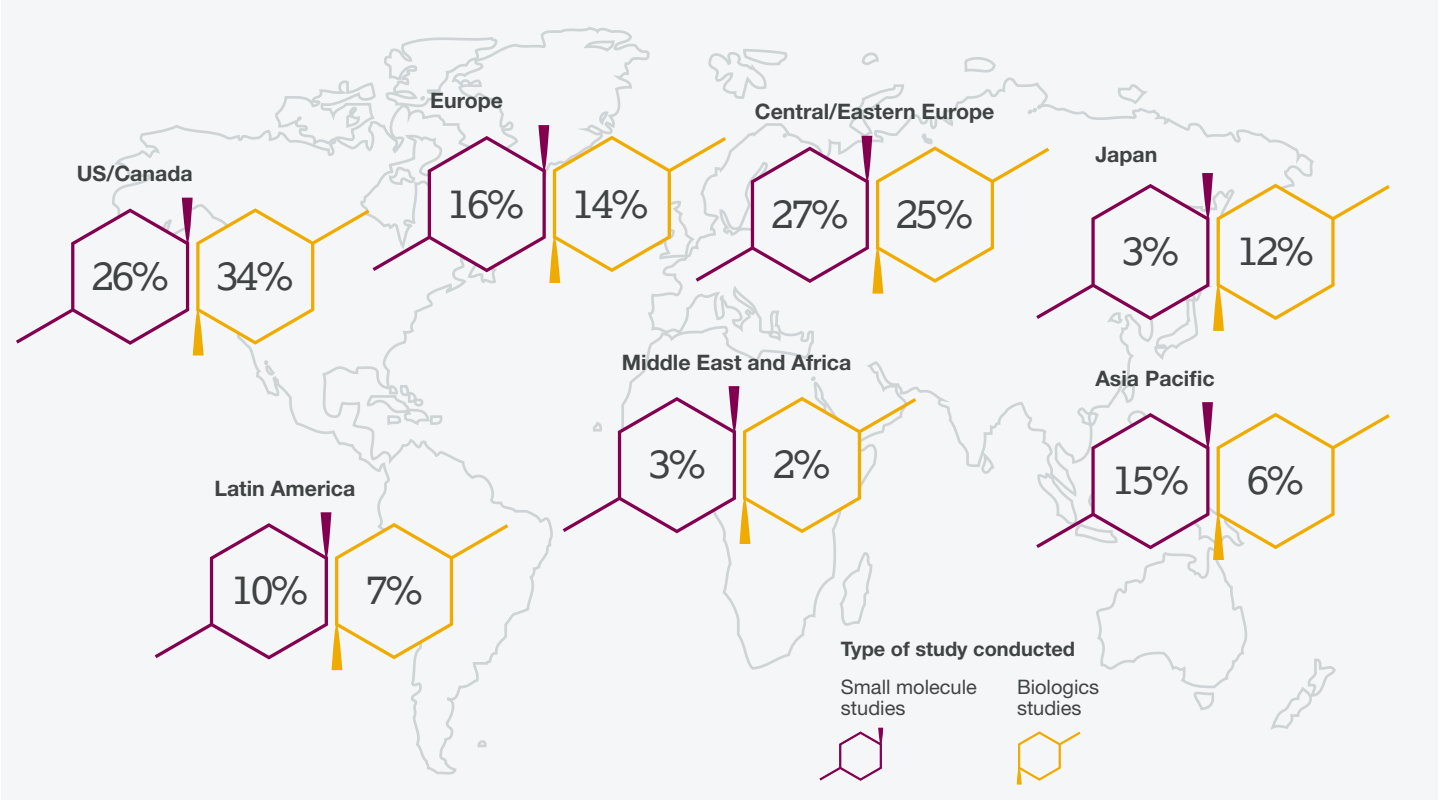
We cannot eliminate all the risks to clinical trial participants, but we aim to minimise risks as much as possible. Our top priority is to make sure that those taking part in our studies are not exposed to any unnecessary risks and that, before they give their consent, they fully understand what taking part in a trial means.

Our informed consent process ensures that patients participating in any and every trial understand the benefits and risks, the purpose of the trial and how it will be conducted. We explain that they could receive a comparator drug or placebo and that they can pull out of the trial at any time, with or without giving a reason.

To ensure patients understand all the information that is being given to them, we provide it written in a language they understand or, if literacy is an issue, we provide the information verbally. We use independent witnesses to ensure patient safety. These witnesses are responsible for confirming that a participant has received and understood all the information they need to be able to give their informed consent.

All our clinical studies are designed and finally interpreted in-house, but some are conducted by contract research organisations (CROs) on our behalf. In 2015, approximately 36% of patients in our small molecule studies and 56% of patients in our biologics studies were monitored by CROs. We require these organisations to comply with our global standards and we conduct risk-based audits to monitor compliance.

Clinical trials around the world in 2015



Implementing the highest standards

Our standards are global and apply to all AstraZeneca clinical trials, in all locations, whether they are being conducted by us or on our behalf by external CROs. If our policies differ from local regulations, we adopt whichever standard is higher.

Our Standard Operating Procedures and Policies require that all staff involved in clinical trials and all investigators are trained in ICH (the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines and local Good Clinical Practice regulations. Our standards apply to all AstraZeneca-sponsored clinical trials, in all locations, but the conduct of our trials in emerging countries is a specific focus for our compliance monitoring and assurance activities.

Clinical trial transparency

In 2015, we created a dedicated Clinical Trial Transparency team whose primary task is to ensure our compliance with clinical trial policies and governance. We have committed to allowing external parties to request patient-level data as part of our commitment to the Principles for Responsible Clinical Trial Data Sharing. Sharing more data in this way will help the industry as a whole develop new products and treatments, improve existing ones, and will save money by avoiding duplication of research.

The commitment to responsible data sharing is a voluntary, industry-wide scheme designed to improve transparency across the pharmaceutical industry.

In order to communicate better with clinical trial patients, AstraZeneca has developed a suite of 95 different patient engagements. For example, our lay-language summaries explain research findings in a way that patients and the general public can understand.

In 2016, we will be preparing to meet the Redacted Clinical Report Package of the European Medicines Agency (EMA) Publication of Clinical Data Policy. The Policy is designed to further improve transparency and access to research information. Throughout 2015, we have taken significant steps to make increasing amounts of data available to those who request it. Our challenge is to protect patients' personal information and company confidential information, while still achieving the highest levels of transparency.

Research with animals

We are committed to helping the public understand our use of animals in research and our methods for Replacing, Reducing and Refining the study of animals in research (the 3Rs). We understand that the use of animals in research is still a difficult issue for many people, but animal studies remain a critical stage in the development of new life-saving and life-improving medicines and treatments.

Our commitment to the 3Rs and high standards of animal welfare begins in the Code of Conduct, and is reflected in our global Bioethics Policy. In addition, we practise high standards of animal welfare. This year, we submitted our progress for inclusion in the first Concordat on Openness on Animal Research Annual Report.

Rapid advances in technology in recent years have led to the increasing availability and use of alternatives to animal research. But these alternatives cannot yet provide all the essential information needed about how a potential new medicine works on a disease and the living body, and what the possible side effects might be.

Animal studies continue to play a vital role in the search for new and improved medicines. All medicines we have available today have involved some animal research, and animal studies are required by regulators before they approve a new medicine to be tested in humans during clinical trials.

While we will always focus on replacing animal studies with better, more accurate models, we know that in the interim it is essential to provide the best possible care and the highest welfare standards available, while using the minimum number required to achieve the benefits.

Our Bioethics Policy states that all research involving animals must be carefully considered and justified, that the principles of the 3Rs be applied and that the welfare of the animals we use is a top priority. Our requirements apply globally across all our internal animal research, to third parties who conduct research on our behalf, and to the breeders and suppliers of animals for use in such studies.

Our consistent global standard for animal welfare is compliance with relevant external laws and regulations, and consistency with the principles of the Guide for the Care and Use of Laboratory Animals ('the Guide') – the internationally respected good-practice guideline for this area. Wherever possible we prefer to use facilities accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC International). AAALAC International accreditation serves as an independent quality mark, validating that the standards of the Guide are being met.

Openness in animal research

AstraZeneca is committed to being transparent about our use of animals in research and, as such, we became a signatory of the Concordat on Openness on Animal Research in 2014. In 2015, we compiled our first progress update for inclusion in the Concordat's Annual Report.

© Understanding Animal Research

The Concordat on Openness on Animal Research

We signed up to all four of the Concordat's commitments in 2014:

- Being clear about when, how and why we use animals in research
- Enhancing our communications with the media and the public about our research using animals
- Being proactive in providing opportunities for the public to find out about our research using animals
- Reporting annually on our progress.

We welcome and engage in open and constructive dialogue with stakeholders who have a legitimate interest in our use of animals in research. As well as supporting organisations and working groups that educate the public about the use of animals in research, we have conducted over 30 facility tours to staff and external representatives from UK universities and animal welfare organisations to showcase our unique facilities. Additionally, we offer opportunities for open Animal Welfare Ethical Review Body (AWERB) meetings, where we discuss past, present and future animal work to ensure appropriate ethical review.

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Animal welfare

The welfare of the animals we use in research is a top priority. It is the right thing to do ethically, but it is also essential for reliable research outcomes. Stress can cause different responses in different animals. Ensuring animals are fit and well, and that their behavioural needs are met reduces stress and variation, and produces better quality data from fewer animals. Read more about our collaboration with the University of Stirling on improvements in laboratory dog standards here.

To reduce stress in the animals we use, and to work to the highest standards of animal welfare, we provide mandatory training, ongoing competency assessments and continual professional development opportunities, such as certifications and ratifications for employees involved in our animal research. All AstraZeneca employees involved in research with animals work to consistent standards and in accordance with the Guide for the Care and Use of Laboratory Animals – the internationally respected good-practice guide.

All employees involved in our animal research programme undertake mandatory training, and are assessed on their technical competency before being allowed to work with animals.

We used 182,055 animals in-house and a further 33,220 animals at external CROs in 2015. The majority of the animals used are rodents and many are undergoing mild procedures, such as oral dosing, blood sampling or a simple injection under the skin.

The total number of animals we use will continue to vary because use depends on a number of factors, including the amount of pre-clinical research we are doing, the complexity of the diseases under investigation and regulatory requirements. We believe that without our active commitment to the 3Rs, our animal use would be much greater.

Our priorities are to ensure we are using the right number of animals needed to deliver a statistically reliable result, and to avoid repeating studies unnecessarily. We are also committed to ensuring the welfare of the animals we use.

Number of animals used in research	2013	2014	2015
In-house	260,930	194,162	182,055
External contract research	19,676	15,634	33,220
Total	**280,606**	**209,796**	**215,275**

Implementing and sharing the highest standards

Having a single council responsible for all aspects of animal care and welfare ensures that we have one consistent global standard for all work involving animals, and one consistent approach to animal welfare and compliance. Our Council for Science and Animal Welfare (C-SAW) is the expert decision-making group accountable for animal welfare and compliance across the AstraZeneca Group of companies. Chaired by AstraZeneca's Chief Veterinary Officer, the C-SAW is responsible for developing and implementing policies and standards, and provides the highest level of governance for animal welfare across the organisation.

The C-SAW includes representative members, who are its eyes and ears in each region, as well as experts in specific areas, such as the 3Rs, statistical practice and regulatory compliance. Through the representative members and their networks, C-SAW is able to receive feedback from stakeholders, as well as ensuring that important communications and messages reach the necessary people.

To recognise efforts to Reduce, Refine and Replace the use of animals in research, we developed the C-SAW Global 3Rs Awards. The 2015 C-SAW Awards were announced in December 2015. Entries were judged by an internal and external panel of experts in the field, including a representative from the UK's National Centre for the 3Rs (NC3Rs). The committee received 32 submissions, including several from our third-party collaborators and CROs. Once again, there were three categories, including Scientific/Technical Advancement; Laboratory Animal Management; and Collaborator of the Year.

"We are a company focused on science and innovation and committed to our value of doing the right thing. As such, we are continuously looking for ways to support the 3Rs agenda to Reduce, Refine and Replace the use of animals in research. This is a vital part of getting medicines to patients, driving scientific discovery and helping us to challenge prevailing assumptions about the best research models. Science, animal welfare and ethical practice come together in the way we undertake animal research, and the 3Rs Awards showcase our leadership in those areas."

Pascal Soriot, Chief Executive Officer

Scientific advancement winner of the 2015 C-SAW Awards

A recent focus of AstraZeneca's anti-cancer research has been on the development of Antibody Drug Conjugates (ADCs). ADCs are targeted antibodies that are connected to a very potent chemotherapeutic drug. This allows the highly potent drug to be delivered directly to the site where the tumour is.

ADCs are challenging to develop as they are highly complex in structure. One of the leading causes of failure with ADCs has been unexpected non-specific side effects. This occurs when the ADC enters healthy tissue instead of just the tumour.

Typically, ADC research requires the use of non-human primates, because these specific interactions do not occur in other species. In this case, the research team was looking to evaluate the non-specific side effects and were able to conduct an innovative study using rats to successfully do so.

Using rats instead of non-human primates is a significant refinement and a great contribution to reducing the number of these higher animals used in research.

The use of rats allowed the selection of ADC properties that result in the fewest non-specific side effects, maximising the chances of clinical success in cancer patients.

The use of animals in research is a complex topic. For more information visit:

Understanding Animal Research:
www.understandinganimalresearch.org.uk

Foundation for Biomedical Research:
www.fbresearch.org

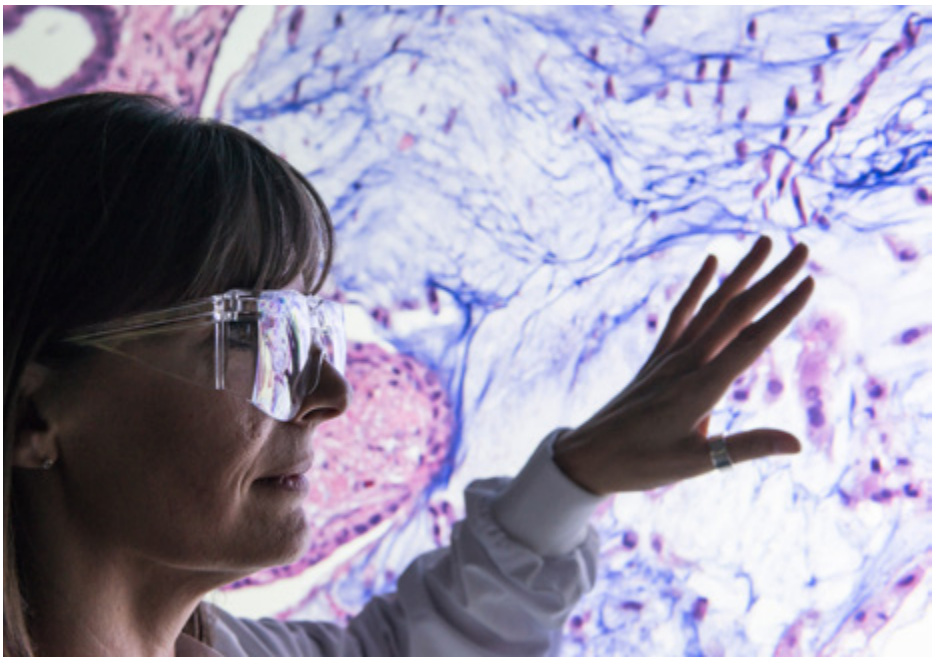
The National Centre for the Replacement, Refinement & Reduction of Animals in Research:
www.nc3rs.org.uk

Human biological samples

The use of human biological samples (HBS), such as solid tissue and biofluids, plays a vital role in developing a deeper understanding of human diseases and how they work, which helps us develop effective, new and personalised medicines. In carrying out this important area of research, we maintain policies and processes to ensure that we both comply with the law and meet regulatory concerns. This includes approval of HBS sources, which support our scientists, and third parties working on our behalf, in being compliant with the ethical principles relating to HBS in our policies and standards.

Protecting the rights of donors and their families

AstraZeneca greatly appreciates the generosity of those donating HBS for research. We place an emphasis on informed consent that protects the rights and expectations of donors and families throughout the process of acquisition, use, storage and disposal of the samples. Maintaining the anonymity of the donor is of the utmost importance, and a key part of our process includes the coding of biological samples and associated data, including genetic data, to help achieve this.



Stem cell research

Stem cell technology may offer new opportunities to develop innovative and safer medicines, and would help ensure better treatments for patients. There are two main forms of stem cell research, human-induced pluripotent stem cells, or hiPSC, which can be taken safely from adult volunteers, or human embryonic stem cells (hESC). The majority of our stem cell work uses hiPSC, which is a less ethically sensitive alternative to using human embryos. We are actively evaluating both technologies.

We use hESC when there is no alternative technology that would provide the scientific information required to increase our knowledge of a serious disease. We are interested in the potential of stem cells to differentiate into mature human cells, allowing more accurate prediction of drug metabolism and certain safety and toxicity outcomes in people.

Another area of interest for AstraZeneca where stem cells may prove valuable is for the development of more biologically relevant in vitro models for disease modelling and drug target efficacy evaluation. This would represent a significant step forward in increasing the human relevance of early drug development studies, and help us overcome current limitations that a restricted supply of normal cells presents, as well as potentially reducing animal testing.

In rare circumstances, AstraZeneca may use human foetal tissue. In these circumstances, we will conduct an internal review of the scientific validity of the research proposal. We will only give permission to use the tissue when no other scientifically reasonable alternative is available. We are committed to minimising the use of foetal tissue by exploring technological alternatives.

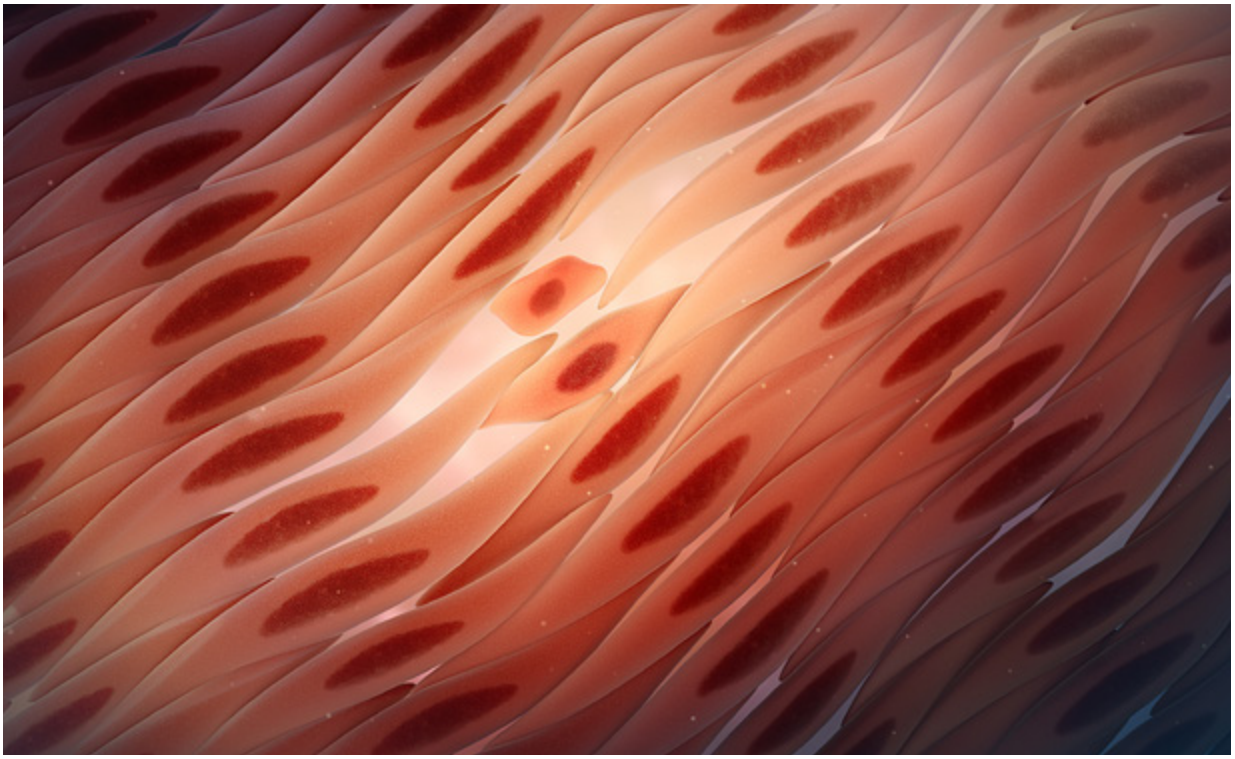
We use extremely rigorous assessments and have high quality and ethical expectations of our tissue suppliers.

AstraZeneca is not involved in any research on human reproductive cloning, for which there is a UNESCO international ban and country-level legislative bans.

The Nagoya Protocol

AstraZeneca is a signatory of the Nagoya Protocol, an international agreement to protect the benefits enjoyed by the country of origin of natural biological resources used in research.

The pharmaceutical industry sometimes uses natural biological resources (such as plant or fish extracts) that might be modified to support its R&D programmes on the path to finding a new medicine. The Nagoya Protocol is an international treaty that helps to ensure fair reward is given to the country that originally supplies the biological material. In accordance with the Protocol, users of biological resources have to record their access and use of the material and keep a record of this for 20 years ('due diligence'). They also have to set 'mutually agreed terms' – a contract that legally defines the conditions of the deal and the benefit that will be received by the country of origin if a new drug is produced. This sharing of benefit helps to ensure a more measured and transparent approach to the use of natural resources, and supports the sustainability of our planet's biological diversity.



Addressing antibiotic resistance

The increasing resistance of infectious diseases to antibiotics is a global issue on which AstraZeneca is taking a lead. We have invested in research and development in infection and are calling on our colleagues across the industry, health leaders, patients, physicians and governments around the world to come together with a multi-stakeholder approach to tackle the hurdles that prevent new antibiotics coming to the market.

We believe the fight against antibiotic resistance requires three key developments:

1. Stronger antibiotic stewardship – appropriate selection, dosing, route and duration of antimicrobial therapy, along with proper manufacturing controls and environmental management, are necessary to help address the threat posed by antibiotic resistance.

There is an urgent need for global collaboration to develop or update a locally relevant framework of stewardship practices, which delineate responsible surveillance, prescribing practices and antibiotic use to address current trends in increasing antimicrobial resistance (AMR).

2. Innovative regulatory pathways – new antimicrobial drugs are needed urgently, but the current drug pipeline is alarmingly thin, with many companies moving away from antibiotic development. Innovative regulatory approaches that balance the data needed for registration with the unmet medical need would encourage further drug development.

Positive steps have been taken by leading regulatory authorities. These new approaches to regulatory pathways will facilitate the development of new drugs to combat emerging, rare pathogens, especially those that are resistant to multiple antibiotics. It will be important to see these new ideas implemented globally.

3. Commercial models – current private/public models are not conducive to bringing antibiotics to market. The pipeline is virtually dry, especially in gram-negative bacteria; an area which particularly needs new antibiotics.

Antibiotics need to be viewed as a public good, similar to the firefighting system in place in all communities, and will require a reimbursement strategy that recognises the reality of the insurance value of antibiotics.