

Ethics and transparency

Patient safety and product security

Our approach

Bioethics

Compliance

Antimicrobial resistance

Supply chain management

Ethics and transparency

We want to be valued for the medicines we provide and trusted for the way we work. That means leading our industry in demonstrating ethical business practices and high levels of integrity in everything we do. It is why human rights, safety and health, environmental protection and business ethics are core to AstraZeneca's approach to sustainability.



Compliance

We emphasise to all our staff the importance of compliance with our AstraZeneca Values, Code of Conduct and supporting requirements. We empower our people to ask questions when they are unclear or make a report when they have a concern.

100%

of active employees trained on the Code of Conduct



Managing our supply chain

We extend our high ethical standards to our whole supply chain and regularly check and audit that our suppliers reflect our Values.

8,977

supplier assessments carried out in 2016



Product security

The illegal trade in medicines is a public health risk and our aim is to disrupt this activity by working with partners around the globe.

\$16.5 million

worth of AstraZeneca counterfeit and illegal medicines seized



Animals in science

We apply a single, consistent Global Standard for animal welfare and are committed to reducing, refining and replacing animals in our work.

100%

of staff working with animals are appropriately trained in animal care, use and welfare



Antimicrobial resistance

Although we no longer develop small molecule antimicrobials in-house, we're standing with our peers to tackle this global issue.

Signed

the Davos Declaration on Combating Antimicrobial Resistance with over 100 other companies

Our approach

We have worked hard to position ourselves as a global leader in the pharmaceutical industry. As a leader, we have a responsibility to hold ourselves to high ethical standards and to demonstrate ethical business practices. We strive for high levels of integrity in everything we do, whether it's our approach to bioethics, including the use of animals in science, the way we treat the participants in our clinical trials, our approach to human rights or the scrutiny of our supply chain to ensure our suppliers meet our high standards.



Key

- Target exceeded
- Full target achieved
- Ongoing progress
- Target not achieved, some progress

What we have achieved

Goals	Target progress	Progress highlights
All active employees to be trained on our Code of Conduct by 2016		100% of active employees trained on the Code of Conduct in 2016 Achieved a 100% score for Code of Conduct from the Dow Jones Sustainability Index
Communicate clear policies to employees by 2016		Updated our annual Code of Conduct training to provide greater clarity and simplicity for the business as well as improved accessibility via mobile devices since 2016
Ensure employees can raise concerns and that they are properly addressed by 2016		320 reports of alleged compliance breaches or other ethical concerns made through the AZethics Helpline in 2016
Meet high ethical standards across all our procurement activities and decisions worldwide by 2016		Conducted 66 high-risk supplier audits in 2016
Collate a suite of 'Culture of Care' pledges from all of our R&D sites, demonstrating our daily commitment to high standards of animal welfare by 2016		Two winners of a newly introduced 'Culture of Care' award recognising the day-to-day commitment to excellence in animal care and welfare, including one attracting the attention of the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) for further development as a project initiative
Continue to promote scientific excellence in animal care and use through a programme of global roundtable workshops by 2016		In 2016, we prepared 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

Compliance

We expect everyone at AstraZeneca to observe the highest standards of integrity and honesty, and to act with care, diligence and fairness in all they do. We are committed to delivering consistently high standards of sales and marketing practices worldwide, and we work with only those third parties who embrace high standards of ethical behaviour that are consistent with our own.

Building a culture of compliance

Our Global Compliance function exists to drive and embed a culture of ethics and integrity throughout our organisation. We require all our employees to take personal accountability for their actions and to demonstrate individual behaviour that is in line with our Values and principles. That means engaging them and supporting them to ensure they understand and follow our requirements and feel comfortable asking questions or reporting concerns.

We focus our efforts on:

- > Communicating clear policies to employees
- > Improving compliance behaviours through effective advice, training and support
- > Monitoring compliance
- > Ensuring employees and the public can raise concerns and that they are properly addressed
- > Fair and objective investigations of possible policy breaches
- > In close collaboration with Internal Audit Services, providing stakeholders with effective assurance and reporting on key issues, including risk management relating to third parties working on our behalf, as well as strengthening of compliance controls to address identified gaps.

Our Code of Conduct is at the core of our compliance programme, and compliance with the Code is mandatory for all employees. The Code has been translated into 40 languages and provides clear direction as to how our commitment to honesty and integrity is to be realised through consistent actions across all areas of the business.

Our Global Policies, as well as local and functional procedures, support the Code and provide clear guidance in key risk areas.

Every new starter receives training on the Code of Conduct. We then require all employees to complete an annual refresher

course on the Code of Conduct and ethical business practices. Our training is designed to be straightforward, to promote employee understanding.

We are committed to the highest standards of ethical conduct in all of our operations, including transparency in how we partner with physicians and medical institutions. In the US, our external transparency reporting meets the requirements of the Physician Payments Sunshine Act (Open Payments), as well as relevant state transparency laws. In Europe, AstraZeneca's reporting meets the requirements of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Disclosure Code, as well as applicable local transparency requirements.

In 2016, AstraZeneca took steps to strengthen the capabilities of our Global Compliance function, including the development of the Global Compliance Academy, a social learning platform where our Compliance professionals can interact to share learnings and best practices and build their skills through tailor-made, on-demand training.

Reporting breaches and concerns

Our Code of Conduct requires employees to report any concern they may have about a possible breach of the Code or its supporting requirements. Employees are advised to consult with their line manager or their Human Resources, Legal or Compliance functions. The Code provides additional contact channels through our Helpline, which includes the AZethics telephone lines, the AZethics website, and the Global Compliance email and postal addresses. These channels are also available to the general public for reporting concerns. Reports can be made anonymously where desired and where permitted by local law.

The AZethics website and telephone lines are managed and externally operated by an independent third party on AstraZeneca's behalf. The website is available in 38 languages, and the phone lines are operable in 96 countries, to facilitate reporting. When

an inquiry is made or a concern is raised, the details of the report are sent to AstraZeneca for appropriate follow-up and resolution.

We take all alleged compliance breaches and concerns seriously, and investigate them and report the outcome of such investigations to the Audit Committee, as appropriate. Internal investigations are undertaken by staff from our Global Compliance, Human Resources and/or Legal functions, to preserve the independent nature of the review. When necessary, external advisers are engaged to conduct and/or advise on investigations.

When allegations of misconduct by employees or third parties are confirmed after full investigation, business stakeholders take appropriate disciplinary or remediation actions, including termination of employment or termination of a third-party engagement, when necessary. They also implement the necessary enhancements within the business to help prevent future misconduct, including retraining of relevant employees and strengthening of local procedures and controls. Similarly, as part of continuing to do business with the third-party, they take the necessary steps to help prevent future misconduct, including re-emphasising our expectations of ethical behaviour to the third party's management, providing retraining to relevant third-party employees, and negotiating improved processes and controls within the third party's business.

In 2016, 320 reports of alleged compliance breaches or other ethical concerns were made through the Helpline, including reports made by any anonymous route that could be considered whistle-blowing; in 2015 there were 326 reports. The majority of cases come to our attention through management and self-reporting, which can be seen as an indication that employees are comfortable in raising their concerns with line managers, local Human Resources, Legal or Compliance, as recommended in the Code and reinforced in the 2016 Code training. We make it clear that anyone who raises a possible breach in good faith is fully supported by management and will not be subject to retaliation.

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Ethical sales and marketing

Effective sales and marketing are key to the sustainable growth of our business and to improving access to healthcare for people around the world. Accessing new markets, working with healthcare professionals and advocating for our products are all a part of that and must be done ethically. Our [Global Policy on Ethical Interactions](#) supports our Code of Conduct; as with the Code of Conduct, compliance with our Global Policies is mandatory for all employees. Our Global Policy on Ethical Interactions sets out our principles and requirements to meet our commitment to operate ethically and with integrity – including our zero tolerance for bribery and corruption. It includes guidance on appropriate product promotion to ensure we provide healthcare professionals with evidence-based, reliable information about our medicines in the best interests of patient care.

When we work with suppliers, distributors and partners on the sales and marketing of our products, we carry out appropriate risk assessments and due diligence to ensure they are reputable. We actively engage with these organisations to maintain oversight of their activities and make sure that they are operating to high standards of ethical practice that are consistent with our own.

We maintain a robust compliance programme with dedicated compliance personnel, who advise on and monitor adherence to our Code of Conduct and supporting requirements. They also support our line managers locally, seeking to ensure that their staff meet our high ethical standards.

A network of nominated signatories review our promotional materials and activities against applicable requirements. Audit professionals in Internal Audit Services also conduct compliance audits on selected marketing companies and third parties.

We identified six confirmed breaches of external sales and marketing codes or regulations in 2016 (2015: 11).

There were 1,729 instances, most of them minor, of non-compliance with our Code of Conduct, Global Policies or supporting requirements in our Commercial Regions, including instances by employees and third parties (2015: 1,749). We removed a total of 222 employees and third parties from their roles as a result of these breaches (a single breach may involve more than one person). We also formally warned 429 others and provided further guidance or coaching on our policies to 1,283 more. The most serious breaches were raised with the Audit Committee.

The US Foreign Corrupt Practices Act investigation involving AstraZeneca was resolved in 2016 following a civil settlement agreed with the Securities and Exchange Commission; the Department of Justice closed its investigation without taking action against the company.

Reports of alleged compliance breaches/ethical concerns via the Helpline

2013	149
2014	247
2015	326
2016	320

Confirmed breaches of external sales and marketing codes or regulations




2013	11
2014	6
2015	11
2016	6

Instances of non-compliance with Code of Conduct, Global Policies or supporting requirements in our Commercial Regions

2013	1,773
2014	1,847
2015	1,749
2016	1,729

Corrective actions taken in our Commercial Regions

2013	1,813	568	187
2014	1,573	454	213
2015	1,476	490	339
2016	1,283	429	222

 Guidance and coaching
 Formal warning
 Removal from role

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Preventing corruption

A key focus of our Global Ethical Interactions Policy is on anti-bribery/anti-corruption, and this Policy specifically declares AstraZeneca's zero tolerance for bribery or any other form of corruption, even if AstraZeneca loses business as a result. Our Global Ethical Interactions Policy makes clear that bribery includes giving or receiving something of value that is intended or could be seen as improper influence, and that 'something of value' can take many forms, such as: cash payments, discounts/rebates, compensation for services or reimbursement of expenses; gifts, samples or other items of value; meals, travel/accommodation or other hospitality; contributions; or even providing access to resources or information.

In 2016, the mandatory annual training on our Code of Conduct included a module dedicated to ethical business practices and featuring anti-bribery/anti-corruption principles. Also in 2016, Global Compliance developed training specific to anti-bribery/anti-corruption, using real-life scenarios to help employees put our principles into practice in their daily work. This training was made available to all employees to complement the Code of Conduct training.

The Global Compliance function works with a range of specialist functions throughout the company, including Legal and Procurement, to ensure ongoing compliance with AstraZeneca's anti-bribery/anti-corruption principles. Global Compliance also works closely with the Internal Audit Services function, and both functions separately provide quarterly reporting to the Audit Committee of AstraZeneca's Board of Directors, including assurance reporting on incidents of non-compliance relating to anti-bribery/anti-corruption. The Audit Committee also annually reviews AstraZeneca's systems and controls in place to prevent bribery and corruption.

Anti-bribery/anti-corruption auditing forms a significant part of our global monitoring and audit programmes of the commercial business. Each year, AstraZeneca uses a mixture of internal and external measures, including the Transparency International Corruption Perceptions Index, as well as market-specific risk factors, to perform its risk assessments for these programmes. These programmes cover a range of activities associated with bribery/corruption risk, including, but not limited to,

tendering, sales and distribution, engaging healthcare professionals and other third parties for services, items of value and hospitality, and contributions. Also, as part of our commitment to continuously improve our compliance programme, in 2016, AstraZeneca continued to invest in analytics techniques to review data to improve detection and correction of potential non-compliant activities. A key area of focus for this work was around anti-bribery/anti-corruption.

AstraZeneca is also an active member of alegal, an industry global working group addressing anti-bribery/anti-corruption and anti-money laundering compliance issues within the life sciences sector, including regular benchmarking and best-practices sharing. Through active participation in this and other industry associations such as the UN Global Compact, AstraZeneca keeps pace with and is firmly committed to taking the necessary internal steps to ensure alignment with current international codes and standards.

Third parties and corruption

AstraZeneca is committed to working with only those third parties who embrace high standards of ethical behaviour that are consistent with our own; we carry out this commitment by conducting appropriate risk assessments and due diligence, implementing contractual obligations with our third parties and maintaining oversight of third-party engagements. Specifically, AstraZeneca has a robust, centralised third-party risk assessment and due diligence process that is undertaken prior to engaging relevant third parties for goods or services, across local marketing companies and other business units. This process covers a wide range of risks, including, but not limited to, bribery/corruption risk.

To support the effectiveness of this process, a risk-based approach to training that is consistent with the US Foreign Corrupt Practices Act and UK Bribery Act guidance is taken. In this way, we focus on the higher-risk geographies, as well as on the higher-risk third parties and activities. In 2016, we provided anti-bribery/anti-corruption training to AstraZeneca engagement owners (who are responsible for managing third-party engagements) as well as to higher-risk third parties (such as distributors), focusing our efforts on higher-risk geographies. This training

allowed for customisation with case studies and other information specific and relevant to the particular audience, designed to make the training most impactful.

In addition, for all relevant third-party engagements, AstraZeneca provides the third party with our [Expectations of Third Parties](#), which describe our key expectations for third parties with respect to anti-bribery/anti-corruption and other relevant risks. Our Expectations of Third Parties explicitly prohibits third parties from:

- > Directly or indirectly giving, offering or promising a bribe, or authorising anyone else to do so
- > Directly or indirectly receiving, soliciting or agreeing to accept a bribe, or authorising anyone else to do so.

It explicitly states that AstraZeneca has zero tolerance for bribery or any other form of corruption and will support all refusals by third parties to engage in bribery, even if we lose business as a result.

Political donations

Neither the company nor its subsidiaries made any EU political donations or incurred any EU political expenditure in 2016. To enable the company and its subsidiaries to continue to support interest groups or lobbying organisations concerned with the review of government policy or law reform without inadvertently breaching the Companies Act 2006, we put a resolution to shareholders at our AGM, to authorise the company and its subsidiaries to:

- > Make donations to political parties or independent election candidates
- > Make donations to political organisations other than political parties
- > Incur political expenditure, up to an aggregate limit of \$250,000.

In the US, corporate political contributions are subject to both federal and state laws and regulations. In 2016, the Group's US legal entities made contributions amounting in aggregate to \$1,568,250 (2015: \$1,224,550) to national political organisations, state-level political party committees and to campaign committees of various state candidates.

We did not make any corporate donations at the federal level and all contributions were made only where allowed by US federal and state law. We publicly disclose details of our corporate US political contributions, which can be found on our [website](#).

The annual corporate contributions budget is reviewed and approved by the US Vice-President, Corporate Affairs and the President of our US business to ensure robust governance and oversight. US citizens or individuals holding valid green cards exercised decision-making over the contributions and the funds were not provided or reimbursed by any non-US legal entity. Such contributions do not constitute political donations or political expenditure for the purposes of the Companies Act 2006 and were made without any involvement of persons or entities outside the US.

Corporate tax

AstraZeneca is a global, science-led biopharmaceutical business. We are one of only a handful of companies to span the entire life cycle of a medicine from research and development to manufacturing and supply, and global commercialisation of primary care and specialty care medicines. We operate in over 100 countries and our innovative medicines are used by millions of patients worldwide.

Our business activities around the world incur a substantial amount and variety of business taxes. We pay corporate income taxes, customs duties, excise taxes, stamp duties, employment and many other business taxes in all jurisdictions where applicable. In addition, we collect and pay employee taxes and indirect taxes such as Value Added Tax (VAT). The taxes we pay and collect represent a significant contribution to the countries and societies in which we operate.

AstraZeneca aims to comply with tax laws in the countries in which it does business and is committed to transparent and constructive relationships with all relevant tax authorities.

In December 2015, the Financial Reporting Council (FRC) in the UK announced that it would conduct a review of companies' tax reporting to encourage more transparent recording of the relationship between the tax charges and accounting profit. The FRC Corporate Reporting Review Team subsequently conducted a review of the tax disclosures in our financial statements for the year ended 31 December 2015 and in 2016 confirmed that they had no substantive issues to raise. The FRC's role is not to verify the information provided but to consider compliance with reporting requirements.

The Committee took note of and was satisfied with relevant reports from the regulators that exercise routine oversight over the company's external auditors, the FRC and the Public Company Accounting Oversight Board.

The Audit Committee reviewed the company's approach to tax including governance, risk management and compliance, tax planning, dealings with tax authorities and the level of tax risk the company is prepared to accept. The full statement, which was published in November 2016, can be found at www.astrazeneca.com.

The integrated nature of our worldwide operations can produce conflicting claims from revenue authorities as to the profits to be taxed in individual countries. The majority of the jurisdictions in which we operate have double tax treaties with other foreign jurisdictions, which provide a framework for mitigating the incidence of double taxation on our revenues and capital gains. The company's worldwide operations are taxed under laws in the jurisdictions in which they operate. International standards governing the global tax environment regularly change. The Organisation for Economic Co-operation and Development (OECD) has proposed a number of changes under the Base Erosion and Profit Shifting Action Plans.

View our tax policy [here](#).

Supply chain management

Our future success depends on building and maintaining a strong and sustainable supply chain that supports our research and development of new medicines and upholds our high ethical standards. Monitoring and improving performance across the 45,000 suppliers we use around the world protects our business and, more importantly, the patients who use our medicines.

We are committed to meeting high ethical standards across all our procurement activities and decisions worldwide. We expect our third parties to meet these strict standards, as set out in our [Global Standard Expectations of Third Parties](#). Our Global Standard incorporates our Code of Conduct and key international standards such as those published by the International Labour Organization (ILO).

Every employee who sources goods and services on behalf of AstraZeneca is expected to follow responsible business processes, which are embedded into our procurement procedures. All our procurement professionals receive detailed training on responsible procurement.

We also require our suppliers to complete regular supplier assessments. At the end of 2016, 20,613 suppliers had completed compliance assessments, a 96% completion rate with the remaining 4% in progress. We maintain oversight of our supply chain and where we are spending our money.



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At AstraZeneca, we have clear company Values to guide our behaviour and the decisions we make on a daily basis, helping to ensure that we do the right thing and act with integrity in every situation.

It is critically important to us that the third parties we work with share our Values and ensure that any work on our behalf upholds our ethical standards. Only together can we maintain and enhance the trust of our customers and stakeholders and, ultimately, deliver our Purpose: to push the boundaries of science to deliver life-changing medicines.”

Pascal Soriot, CEO, AstraZeneca

In Focus: How do we ensure an ethical and transparent supply chain?

Global corporations have an extraordinary amount of power and influence, especially when it comes to buying in products and services. Big business has a responsibility to spend its money wisely and in a way that has benefits for the wider business community and the populations it serves. A transparent procurement system is critical to this.

In order to achieve our goals, complete our research and market our products, we work with suppliers and third parties all over the world. Carefully selecting which third parties we work with on the basis of their ethical standards, and providing support and training to those who want to do better, helps us ensure an ethical pipeline. It also spreads a commitment to human rights, health and safety, environmental sustainability and diversity to a wider number of businesses and organisations.

Our commitment to ethics and transparency requires us to set clear standards for those suppliers and to have strong processes in place to monitor and audit our supply chain to ensure suppliers are meeting those standards.

We start by selecting the supplier we want to work with. In some instances, we are able to select from a number of companies who carry out similar work and can choose to work with the one that best demonstrates our Values. In other instances, there might be only one company able to perform the tasks we need. On those occasions we take a collaborative approach and work with a supplier to bring that company's standards up to meet our own. Sometimes a supplier has the right intent, but without enough knowledge or experience to address risks and implement improvements. Where possible, and when a supplier shows appropriate commitment, we support them to achieve our high standards.

Our commitment to supply chain excellence goes right to the top. Each member of our Senior Executive Team (SET) is accountable for ensuring that procurement activity within their area is carried out in a manner consistent with our strategy and that the skills and resources are in place to deliver the requirements of the strategy. The Chief Procurement Officer is accountable for the governance and assurance of the Third Party Risk Management process and reports directly to a member of the SET.



We provide incentives for suppliers through a number of means from specialist training to profit-sharing of any costs saved/ revenue generated through our improvement initiatives.

AstraZeneca is a member of the Pharmaceutical Supply Chain Initiative. This not-for-profit organisation helps and supports suppliers to meet the expectations of the industry with regard to labour, health, safety, environment and management systems. The group is increasingly expanding its reach to include a range of services used across the pharmaceutical industry. We have used our experience with supplier auditing to help ensure the effectiveness of the audit approach used by the industry, contributing ideas, manpower and key documentation to ensure the success of this platform.

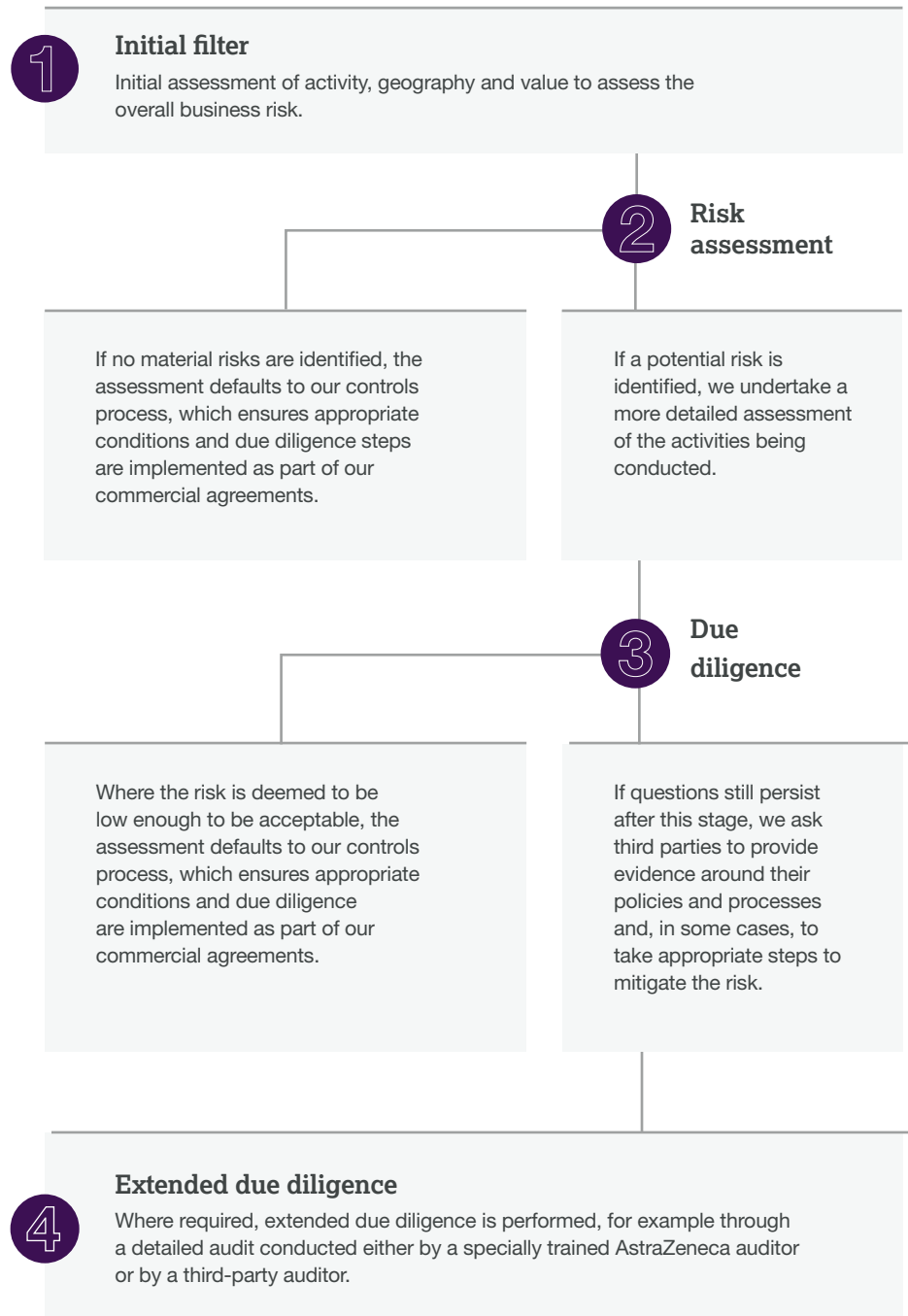
We are also members of Verisk Maplecroft, which helps organisations optimise and strengthen the risk management processes and supply chains by providing a portfolio of global risk analytics with world-leading analysis, real-time locational monitoring and innovative risk calculator technology.



Our procurement organisation works to assess and monitor risks within our global supply chain, including suppliers, downstream supply chain partners and local business development partners.

We apply a globally consistent approach to assessing risk, which allows us to focus our efforts on high-risk relationships and ensure suppliers understand and are able to meet our expectations.

Our four-stage assessment process



Monitoring standards and compliance

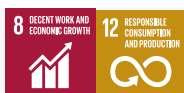
Quality audits

Year	Internal quality audits of AstraZeneca suppliers	Internal quality audits of AstraZeneca sites
2013	398	25
2014	395	24
2015	428	40
2016	461	36

In 2016, we conducted 66 extended audits on high-risk suppliers. We found 32% of suppliers met our expectations, with a further 42% implementing improvement plans to address minor instances of non-compliance. 40 potential suppliers failed to meet our

required standards and we discontinued the relationship (0.45% of total suppliers assessed, in line with external benchmarks). 1,101 assessments resulted in an action plan to help improve standards at our third parties.

Supplier assessments by region since 2014



Helping suppliers meet our ethical standards

We develop and implement ongoing supplier engagement programmes that reflect areas of specific geographical an/or supply sector risk, with a focus on any key gaps in third-party understanding. In Algeria, for example, our local organisation supported a supplier who had a number of gaps against AstraZeneca expectations. We provided subject matter expertise and shared documents to help inform and educate the supplier on the level of expectation. We also provided access to specific individuals who could coach the supplier’s management team. In particular, these related to human resource management, quality systems and anti-bribery/anti-corruption. Using this support and knowledge the supplier was able to rectify the identified gaps and raise awareness within their own organisation of responsible business practices.

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.

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.

During the development phase, we carry out extensive and rigorous preclinical and clinical testing 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.

We work with regulators to develop prescribing information that gives healthcare professionals the information they need to promote patient safety – including indications for use, dosing recommendations, warnings and contra-indications, as well as potential side effects. Where appropriate we also make information available directly to patients about our medicines and how they should be taken.

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.

For all our medicines, under development as well as on the market, we have comprehensive and rigorous systems in place for detecting and rapidly evaluating adverse effects, including mechanisms for highlighting those that require immediate attention. Each medicine has a dedicated safety team, which includes a responsible global safety physician and one or more pharmacovigilance scientists. At each affiliate, we also have at least one appropriately qualified person who is responsible for pharmacovigilance matters.

Safety information is provided from many sources, including reports on suspected adverse drug reactions from healthcare providers and patients and from review 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.

In addition, we use tools to enable signal detection and data compilation, and are investing in information technology. In compliance with regulatory requirements, all available safety information is continuously and regularly reviewed and, following stringent assessment, any new safety data is provided to regulators, doctors, other healthcare professionals and, where appropriate, patients.

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. During 2016, we implemented a system with reporting and dashboard functions to track the status of our activities to address important risks in an optimised way.

Our Patient Safety Quality System covers all products and is a part of the company's overall quality system, providing a quality environment that meets the requirements of Good Pharmacovigilance Practice and Good Regulatory Practice. A programme is in place to monitor and evaluate the performance and compliance of the quality system globally against defined quality requirements. Pharmacovigilance leadership regularly reviews summaries of these monitoring activities. The quality system is designed based on continuous improvement principles to proactively anticipate and avoid or minimise the impact of potential quality issues by taking prompt and effective measures.

Fighting the illegal trade in medicines, protecting our patients

Key for product security is protecting our patients from the dangers of illegally traded (including counterfeit and stolen) medicines. Counterfeits, for example, can fail to provide effective treatment and sometimes cause direct harm to patients. It is impossible to estimate on a global scale how common the illegal trade in medicines is, and although it is impossible to prevent entirely, our aim is to disrupt this activity.

The illegal trade in medicines is a global issue that requires global solutions. It is only through strong partnerships and good education that we can disrupt criminal activities that threaten the wellbeing of patients.

We require our employees to report suspicions of possible illegal trade of medicines that come to their attention to our global security function's mailbox. In addition to our employee reports, patients, healthcare professionals, law enforcement and regulators, for example, also report such cases to us.

We analyse suspicious samples which are sent to us and have a global team who work with local colleagues to coordinate our response. For example, we may gather evidence for a prosecution (according to globally acceptable standards) for relevant local law enforcement agencies, report appropriate cases to health authorities and we may take in-market action alerting doctors, pharmacists or wholesalers. We rely on their cooperation and the local health authority to stop such medicines from reaching patients.



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Global product security strategy

Our Global product security strategy covers three areas as follows:



The illegal trade of medicines is not a problem AstraZeneca can tackle alone. We therefore work closely with other pharmaceutical companies through industry trade associations including the International Federation of Pharmaceutical Manufacturers and Associations, the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America. We also work with not-for-profit organisations including the [Pharmaceutical Security Institute](#) and [Alliance for Safe Online Pharmacy – Europe](#), to raise awareness of the threat of counterfeit medicines.

One such initiative to help raise awareness among patients, healthcare professionals and regulators is the '[Fight the Fakes](#)' campaign.

We also conduct training, where appropriate, to raise awareness of types of illegal trade for our employees and third parties.

In addition, we work closely with other pharmaceutical companies through the Pharmaceutical Security Institute 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 2016, Global Security investigations led to 147 raids and the seizure of counterfeit and illegal AstraZeneca products worth \$16.5 million, and 59 associated arrests.

Security along our supply chain

We work to improve security in our supply chains for our investigational and commercialised products by collaborating with others to share best practice for supply chain design with the aim of inhibiting the entry of illegally traded medicines.

This includes:

- > Strengthening our 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 on some packs to make it more difficult and expensive for counterfeiters to copy our packaging, and help identify packs which have been tampered with
- > Complying with traceability legislation (application of unique codes to packs) which some countries are implementing as part of their anti-counterfeiting strategy.

Driving greater protection

The illegal trade in medicines is hard to measure. We do not publish performance targets around our work. However, we continue to make 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. 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.

Along with colleagues across the industry, we are continuing our efforts to dismantle the illegal trade in medicines and work with governments to develop legislation that will better protect patient safety and ensure that the sentencing of those convicted of producing and distributing counterfeit medicines, for example, reflects the seriousness of the crime.



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.

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Antimicrobial resistance

Supply chain management

Product quality and recalls

AstraZeneca operates a Pharmaceutical Quality System structured to meet the requirements of the internationally adopted pharmaceutical quality system, ICHQ10. This system applies throughout the life cycle of all our products, facilitating innovation, continual improvement and strengthening links between pharmaceutical development and manufacturing activities. It applies to all investigational and commercial products, large and small molecules, including Medical Devices. The Pharmaceutical Quality System is independently assessed by National Competent Authorities located in the countries where we manufacture or market products.

We comply with international standards for Good Manufacturing Practice (GMP). We are assessed by the competent authorities for the regions as well as locally.

Managing quality issues and recalls

All issues reported to AstraZeneca, which may lead to a product recall, are managed and supported by a central dedicated team. When an issue is flagged, this team convenes a meeting or meetings of the appropriate global and local (country or site) personnel. The process applies to all AstraZeneca products and all countries where AstraZeneca's products are sold.

The global procedure commits to achieve the highest possible standards around the management of product issues and recalls, and meets the criteria stipulated within the World Health Organization Guidelines. This global procedure also meets the product recall requirements of the US Food and Drug Administration (FDA), EU regulators and GMP.

In the first instance, the issues management team will work to understand the scope of the issue and the product batches and countries affected as well as the impact for patients and healthcare providers. It also assesses the relevant communications needed with regulators and customers, and establishes how returned products will be monitored to ensure a recall (if necessary) is effective.

We have Enterprise Resource Planning (ERP) systems in place to enable easy and quick identification of product batches and locations in the distribution chain in the case of a recall. These ERP systems track AstraZeneca products at batch level and readily determine supply destinations.

For onward distribution of products to hospitals, pharmacies and patients, we work with local marketing companies and preferred sales partners or distributors to identify batch and product location to ensure an effective recall. We use these networks to communicate with healthcare professionals to alert them to the issue and provide a contact phone number for customers to contact us for further information.

Our global procedure outlines the process and clear actions that must be taken identifying responsibilities for both global and local individuals. The process stipulates that actions must also follow country-specific routines and legislation for all recalls, and that simulated trace and track recalls must be performed periodically with correction of any deficiencies in the process.

We are in the process of rolling out serialisation of products; this has already been implemented in a number of countries and will be rolled out globally by 2020. This will further enhance our ability to track products within the supply chain, as well as assure the pedigree of the product delivered to the patient.

During 2016, there were no quality issues that could have led to patient impact. Consequently we have not had to trigger a single patient-level recall. We have participated in six recalls that were issued at pharmacy or distribution level. Each recall triggers a deep dive root cause investigation and preventative actions.

Recalls

Year	Number of recalls at pharmacy or wholesale level
2013	Total = 3 (All FDA Classification III)*
2014	Total = 6 (All FDA Classification III)*
2015	Total = 10 (One at FDA Classification I, one at FDA Classification II and eight at FDA Classification III)*
2016	Total = 8 (Two at FDA Classification II, six at FDA Classification III)*

*US recalls were classified by the FDA. Recalls in other territories were classified by AstraZeneca aligned to the FDA's guidance.

Inspections

We were inspected 33 times in 2016 by 18 different Health Authorities including the US FDA.

We did not receive any FDA warning letters in 2016. At the end of each inspection, the FDA provides us with a list of 'observations' or areas for improvement. During 2016 we received one FDA observation (classified as a 483), which was for a third-party site, not one of AstraZeneca's own sites.

Total FDA observations (483s)

	31	2013
	22	2014
	16	2015
1		2016

Total FDA inspections

	5	2013
	9	2014
	9	2015
3		2016

Bioethics

Bioethics are the principles, behaviours and ethical standards that govern our research and development worldwide. Our [Bioethics Policy](#) covers a number of subject areas, including the use of human biological samples (HBS), using animals in research, and the conduct of clinical trials. Where appropriate, we use internationally approved standards to achieve high ethical standards. We also constantly review our policies and procedures to ensure good practice and learning.

Our Bioethics Advisory Group (BAG) brings together subject matter experts who monitor and oversee our activities in critical areas of bioethical interest. In 2016, we reviewed how BAG operates, and implemented some changes to membership, reporting and governance to ensure it remains relevant and effective. We have aligned sponsorship of BAG with ownership of the Global Bioethics Policy, under the Chief Medical Officer. This ensures that BAG has visible senior sponsorship and authority commensurate with its objectives and obligations.

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

HBS

HBS, such as solid tissue and biofluids, are vital to developing a deeper understanding of human diseases, 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.

Protecting the rights of donors and their families

AstraZeneca greatly appreciates the generosity of those donating human biological samples for research. We place an emphasis on the principle of informed consent that protects the rights and expectations of donors and families throughout the process of acquisition, use, storage and disposal of samples. Protecting the confidentiality of a donor's identity is of utmost importance and a key part of our process includes the coding of biological samples and associated data (including genetic data). AstraZeneca takes rigorous measures to protect the data privacy of subjects, aiming to minimise the risk of their re-identification when processing the data.

The key aspects of our policies and standards extends to the approval of HBS sources and collaborations involving HBS. We use extremely rigorous assessments and have high quality and ethical expectations of our tissue suppliers. To support compliance in sourcing HBS, AstraZeneca worked with an external provider to implement a commercial centralised automated solution for simplified and compliant HBS procurement.

Stem cell research and use of human foetal tissue

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 (hiPSC), which can be taken safely from adult volunteers, and 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 accurately model for a serious human 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/toxicity outcomes in people.

Stem cells may also prove valuable 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 primary cells presents. There is also the potential to reduce the need for animal studies.

In rare circumstances, AstraZeneca may use human foetal tissue (hFT) in research to advance our understanding of serious medical disorders. In such rare cases, an internal review of the scientific validity of the research proposal will be conducted and permission to use the tissue will be granted only when no other scientifically reasonable alternative is available. To further limit and avoid future use of human foetal tissue, we use cutting-edge scientific advancements and commit to implementing industry best practices.

By the end of 2016, seven research proposals that include use of cells derived from hFT were received for consideration, but none were progressed, either for scientific or other reasons. We continue to review our processes for the supply of human foetal tissue. Currently, four projects using three different hESC lines have been approved.

HBS governance

To monitor our use of HBS, we have created the HBS governance team. This team is responsible for the governance of the collection, storage, use and disposal of HBS, hFT and hESC in R&D. It is also accountable for approving experiments using hESC and hFT as described in the HBS Standard. If there were to be an incident involving the use of HBS, the governance team is accountable for investigation and resolution.

The AstraZeneca Scientific Reference Panel sits alongside the HBS governance team and is responsible for independent internal review of proposals for use of hESC and hFT. It looks at scientific validity and ensures there are no other reasonable means available to conduct the research. In each case, it asks two key questions:

- > Will the proposed study address the experimental aims?
- > Does the proposed research require the use of hFT/hESC rather than other tissue?

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 underway 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.

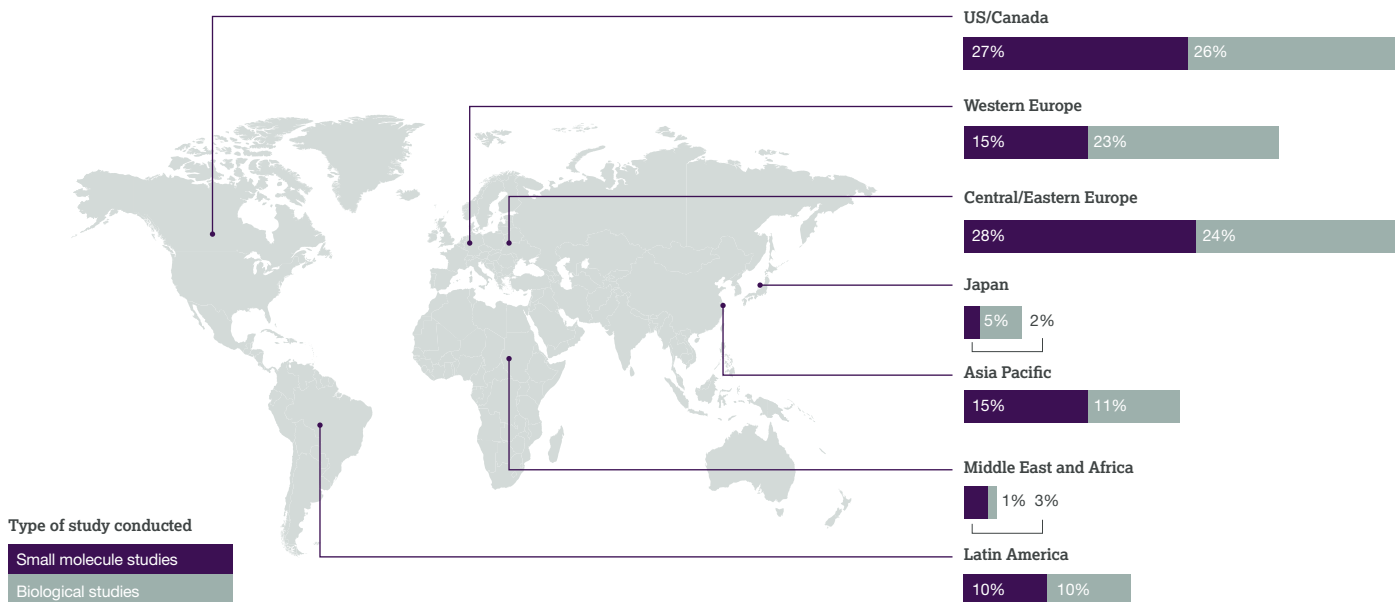
We can't eliminate all the risks to clinical trial participants, but we aim to minimise risks as much as possible. Our top priority is to make sure that those taking part in our studies are not exposed to any unnecessary risks and that, before they give their consent, they understand fully what taking 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 in the patients' local language or, if literacy is an issue, we provide the information verbally. We use independent witnesses to ensure patient safety and that the consent process is verified. 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 to participate in any AstraZeneca Group research study.

All our clinical studies are designed and finally interpreted in-house. Some are conducted by contract research organisations (CROs) on our behalf. In 2016, approximately 48% of patients in our small molecule studies and 44% 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 2016



Ethics and transparency
Patient safety and product security

Our approach
Bioethics

Compliance
Antimicrobial resistance

Supply chain management

Implementing to the highest standards

Our standards are global and apply to all AstraZeneca Group 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

Since 2015, our dedicated Clinical Trial Transparency office has been working to ensure our compliance with clinical trial policies and all legal requirements. We have committed to allow external parties to request patient-level data as part of the Commitment to Responsible Data Sharing. Sharing more data will help the industry as a whole improve existing and develop new products and treatments, and will save money by avoiding duplication of research. More information can be found on our company website located at www.AstraZenecaClinicalTrials.com.

Calls for 'open access' to clinical data raise complex practical, legal and ethical issues around full disclosure of patient information. Decision-makers, as well as academia and industry, have a duty to consider all the implications that could arise from such proposals. These include ensuring scientific rigour, safeguarding patient privacy and protecting innovation and medical progress. We continue to engage with regulators, legislators, industry, medical and scientific bodies to streamline and implement policies, standards, processes and systems to support responsible clinical trial data sharing that deliver real benefits to medical science and patients.

The Commitment to Responsible Data Sharing is a voluntary, industry-wide scheme designed to improve transparency across the pharmaceutical industry.

To communicate better with clinical trial patients, AstraZeneca developed a suite of 95 different patient engagements. For example, our lay language summaries put research findings into language that patients and the general public can understand. In 2017, we will launch a website for lay language summaries which are interventional studies. The purpose of the website is to allow greater access to these summaries. The website will include summaries that are from 2015 onwards and can be accessed by visiting www.TrialSummaries.com.

We implemented new global standards this year, which give patients and researchers more information about our research. Every patient who participates in a study sponsored by us receives a note recognising their contribution as well as a copy of the study's Trial Results Summary. We also launched the [AstraZeneca Group Data Request Portal](#) to allow external researchers to request our clinical data and reports. We have responded to over 50 requests so far.

In 2016, we prepared to meet the Redacted Clinical Report Package of the EMA Publication of Clinical Data Policy. The policy is designed to further improve transparency and access to research information. 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. At the end of the year we submitted the first package to the EMA for our subsidiary group Ardea. The process and work in this area is new to the industry and will quickly develop in 2017 to meet the submission requirements.



Animals in science

We are committed to helping the public understand our use of animals in research. This remains a challenging issue for many people, but animal studies are a critical stage in the development of new life-saving and life-improving medicines and treatments.

This year, we continued to support the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). Our commitment to the 3Rs (Reduction, Refinement and Replacement) is reflected in our [Global Bioethics Policy](#).

We have enhanced our approach to animal research governance in recent years, revising our policies and processes, and making sure our internal systems and structures reflect our responsible approach to the use of animals in science. Under the leadership of our Chief Veterinary Officer, our Council for Science and Animal Welfare (C-SAW) now oversees all issues relating to the use of animals in science. We are confident that we have robust governance and oversight mechanisms that will allow us to drive continuing improvement in laboratory animal science and welfare.

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.

The Concordat on Openness on Animal Research

We are 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. Now in its second full year, we have again contributed to the [Concordat's annual report](#) in 2016.

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

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

Organ on a chip: the direction of future travel

Organ on a chip might well be the most exciting scientific advance towards eventually eliminating the need for the use of animals in science. So far, it is the closest we have come to replicating the biological functioning of a human organ outside the human body and being able to use it as a test subject.

The organ-on-chips are self-contained units, typically about the size of a memory stick, that contain hollow microfluidic channels lined by human cells, which recreate the physiological functions of human organs.

Scientists are currently developing lung, liver, kidney, pancreas, blood-brain barrier and bone marrow organ-on-a-chip systems. There is also a major effort to integrate these organ chips to create a virtual 'human-body-on-chips'. This will enable us to test new discoveries in a way that would provide us with scientifically relevant results and help us better understand how a medicine might ultimately impact patients.

Although the Concordat is a UK initiative, we welcome and engage in open and constructive dialogue with stakeholders worldwide who have a legitimate interest in our use of animals in research. As well as providing funding to organisations and working groups that educate the public about the use of animals in research, we take active steps to be open about our own animal programmes. For instance, we conducted over 30 UK facility tours to staff and external representatives from UK universities and animal welfare organisations.

Our UK Animal Welfare and Ethical Review Body (AWERB) meetings, where we discuss past, present and future animal work to ensure appropriate ethical review, are open to all staff on site, not just those involved in the animal programme. In the US, we have invited groups of schoolchildren to our site to learn more about the crucial role animals play in bringing new drugs to patients.

Implementing and sharing high standards

Our C-SAW is the expert decision-making group accountable for animal welfare and compliance across the AstraZeneca Group of companies.

Our annual C-SAW Global 3Rs awards, which ran for the third time in 2016, recognise efforts to reduce, refine and replace the use of animals in research.

The judging panel, which included a lay member and an external expert from the NC3Rs (Dr Vicky Robinson CBE) as well as representatives of science, veterinary and laboratory leads from across the geographic business, reviewed 30 very high-quality entries.

The panel elected three winners who were able to demonstrate outstanding efforts and success in applying the principles of the 3Rs in their work:

- > A team from the US and Japan who built a successful case to reduce primate studies that received regulatory agreement
- > A UK team who have established a battery of applications including in vitro tissue slices to better address tumour progression
- > Another UK team that established the science to support group housing of ferrets during essential batch efficacy testing of FluMist®.

Many of the submissions represent significant efforts at the grass roots of laboratory animal care. To recognise the efforts of these teams in doing the right thing, the panel chose to recognise an additional two teams for the 2016 C-SAW Culture of Care Award.



Science, animal welfare and our reputation all go hand in hand when it comes to animal research. The 3Rs wholly represent our Values to put patients first, follow the science and do the right thing."

Pascal Soriot,
CEO, AstraZeneca



In Focus:

How are we improving the ethical use of animals in science?

We rely on animal studies in order to create new and improved medicines. Some types of animal studies are required by regulators before they approve a new medicine to be tested in humans during clinical trials. We are also still working to understand fundamental biological processes, where often there is no alternative to the use of live animals. Until we have a good understanding of these processes, we can't look at ways of replicating those using non-animal models.

But that doesn't mean that we are relaxed about how many or what kind of animals we use. Our scientists are constantly looking to find better, more accurate models that can reduce our reliance on animal studies, with the hope of one day replacing them altogether. For the time being the use of animals remains a necessity, so we are equally committed to improving the care and welfare of the animals we do have to use.

We have a proud history of reducing, refining and replacing animals in scientific studies and have made further progress in 2016. Our scientists collaborate and communicate to share innovative practices with our peers to continue to advance the 3Rs. Recent examples include:

- > Ongoing strategic collaborations working to develop new technologies (e.g. '[organ on a chip](#)' on page 17) that may one day replace many types of animal studies
- > Working with academic collaborators to develop a new model of human heart cells to help provide a better indication of the potential effects of new drugs. We hope this will be more widely used by others and work towards reducing the number of animal studies in this important field
- > Publishing and sharing refinements we developed in animal welfare to benefit animals more broadly, for instance with regard to social housing and refined methods of blood sampling.

We support and advocate for the NC3Rs, and work with them on many of the innovations that advanced the 3Rs.



Improving ferret welfare through group housing – 2016 C-SAW Global 3Rs Awards Winner



As a requirement for licensing, each batch of Fluenz/FluMist® must be tested. This involves the use of several hundred ferrets each year because like humans, ferrets are susceptible to flu virus.

Ferrets are social animals and we usually house them in groups. However, regulators have expressed concerns that increased play and proximity could be seen to increase body temperature, which would make interpretation of test results difficult. Elevated temperature is also a symptom of flu, so we had to be able to show that any temperature increases in our animals were as a result of the flu, not from play or other activity.

The team worked with the contractor to demonstrate that group housing did not affect body temperature. By providing this compelling scientific evidence to support our stance, we were able to persuade the regulatory agency to allow us to group house ferrets for Fluenz and FluMist® testing. This is an example of how we are always seeking ways to apply our high animal welfare standards in practice.

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, reduces variation and produces better quality data from fewer animals.

To reduce stress in the animals we use, we work to high standards of animal welfare and are constantly looking for ways to improve. We provide mandatory training, ongoing competency assessments and continuing professional development opportunities such as certifications and ratifications for employees involved in our animal research. To work towards comparable animal care standards around the globe, we employ a single consistent Global Standard for all animal work, whether carried out in our own facilities or by third parties acting on our behalf. We require the work to be:

- > Compliant with laws or regulations in the location where the work is conducted
- > Consistent with the principles of the 8th Edition of the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research) – internationally respected good practice guidelines for animal care
- > Wherever possible, conducted in facilities accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

We undertake a range of due diligence activities, overseen by the C-SAW, to ensure that this is the case.

Rat Playtime – 2016 Global 3Rs ‘Culture of Care’ Award Winner



Long-term housing of rats in caging that does not give them the opportunity to fully carry out valuable natural behaviours such as standing fully upright, climbing, burrowing and foraging has been shown to affect rat behaviour. In order to allow our rats the chance to experience an environment that provides them the opportunity to carry out these natural behaviours, socialisation pens were created, where they could spend time out of their home cage and socialise, exercise, explore and play with each other.

The design of the pen and the provision of enrichment materials within it was carefully considered to encourage and allow the rats to carry out natural behaviours while allowing them to feel secure. Access to different enrichment materials, covered areas and tunnels to hide in were provided, as well as furniture that allowed them to climb and explore the vertical space. Food treats were hidden around the pen to promote foraging behaviour, and some treats were hand fed, encouraging the rats to see hands as a good thing and increasing interaction.

It became very apparent that there was an increase in the confidence and friendliness of the rats. They became more used to and amenable to being handled and were much more likely to voluntarily interact with people. Refining their environment proved to be of great value to both the rats' and their carers' wellbeing. This activity will be shared more broadly through a jointly hosted NC3Rs/AstraZeneca workshop in March 2017.

Measuring compliance

The Institute Risk Assessment Tool is designed to assist PARTNER Coordinators with determining if an on-site inspection is warranted. The template calculates risk factors to provide an overall risk score, which can then be used to quantify the degree of risk and provide the PARTNER Coordinators with an objective course of action.

Factors for evaluating risk include:

- > Species being used
- > Whether the study involves novel or sensitive procedures
- > Our track record with the facility

- > The reputation and standing of the facility
- > AAALAC accreditation status
- > The nature of regulatory oversight and the laws or regulations that apply to the facility.

Inspections can be done virtually or physically and inspectors use our Facility Inspection Template to guide their analysis. Inspectors must evaluate the information that is critical to the success or failure of a project, so the question list is just a baseline for inspecting an institute. Inspectors are empowered to use their professional judgement and experience to build upon this where necessary.

Approving animal studies

Internal studies: Each country where we have internal animal facilities has a different requirement for the in-house ethical review of internal studies. In the United Kingdom the committee responsible is AWERB. In Sweden it's the Djurskyddsorgan and in the United States and China it's the Institutional Animal Care and Use Committee. Each of these committees has slightly different requirements and responsibilities to regulatory authorities, but their shared remit is to ensure proposals for research involving animals are properly reviewed and to assure the welfare of the animals.

External studies: Review and approval of external animal research is performed by representatives from each site that have been appointed by the C-SAW. This group is known as the PARTNER (Platform for Animal Research, Tracking, and External Relationships) Site Coordinator Team.

The PARTNER Site Coordinator is the primary contact at each site responsible for animal study ethical review and tracking. Their key responsibilities include providing training in the requirements of the AstraZeneca Global Standard: Animal Care and Welfare, reviewing study submissions and being a point of contact for incident reporting.

The PARTNER Site Coordinator may also perform the duties of an Institute Inspector and manage the relationship between third-party institutes and AstraZeneca. Above all the inspector's role is to ensure that third-parties acting on our behalf have bioethical standards consistent with our own, and that the requirements of the Global Standard are being met.

100% of staff working with animals are appropriately trained in animal care, use and welfare.



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

Understanding Animal Research: www.understandinganimalresearch.org.uk

Americans for Medical Progress: www.amprogress.org/animal-research/faqs

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



Number of animals used in research

The majority of animals we use – over 97% – 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.

Year	In-house	External contract research	Total
2013	260,930	19,676	280,606
2014	194,162	15,634	209,796
2015	182,055	33,220	215,275
2016	193,451	25,651	219,102

Nagoya Protocol

AstraZeneca is supportive 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 research and development programmes on the path to finding a new medicine.

The Nagoya Protocol is an international treaty which helps to ensure fair reward is given to the country that originally supplies the biological material. In accordance with the Protocol, we, as users of biological resources, have to record our access and use of the

material and keep a record of this for 20 years ('due diligence'). We 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 protects indigenous and local communities, by ensuring that their rights to their natural resources are protected, and promotes a measured and transparent approach to the use of natural resources, which supports the sustainability of our planet's biological diversity.

We are committed to ensuring these communities understand their ownership of and associated rights to their natural resources, and that they are giving informed consent before the removal of these materials and understand the equitable benefits they will

receive in return. We do this with consideration for and adherence to local laws, procedures and customs wherever we work.

Whenever a researcher wants to use biological material that is in the scope of the Nagoya Protocol, our internal processes ensure they meet the appropriate requirements. We have created a dedicated e-tool to help researchers establish whether or not the resource they want to use is in scope and provide guidance. Our procurement team can help the research team contact appropriate suppliers, our business development team oversees the process to ensure it is fair and our Nagoya governance team guides the research team through the process.

Antimicrobial resistance

The increasing resistance of infectious diseases to antibiotics is a global issue. We have previously 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 global threat that antimicrobial resistance (AMR) poses to society and the barriers that prevent new antibiotics coming to the market.

At the World Economic Forum in Davos in early 2016, we signed the Davos Declaration on Combating Antimicrobial Resistance along with over 100 other companies. The Declaration acts as a collective call on governments to commit to the investment needed to support the development of new antibiotic technologies.

We sold the antibiotics part of our business to Pfizer this year, but, recognising the impact of AMR now and in the future, have committed to continuing to share our research and use our influence to contribute to addressing this global challenge.



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, is 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 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.

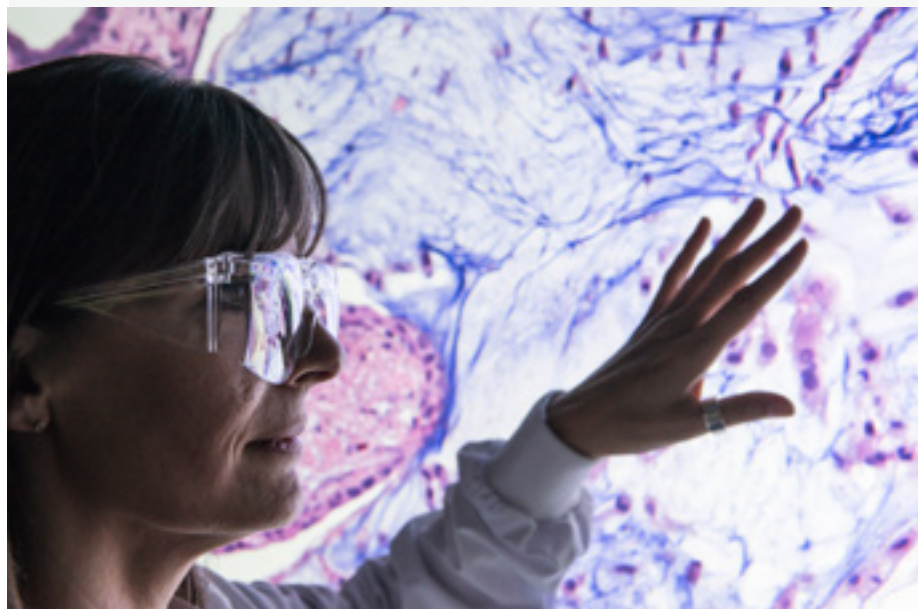
Antibiotics need to be viewed as a public good, similar to the firefighting system in place in all communities, and will require a reimbursement strategy that recognises the reality of the insurance value of antibiotics.

The AMR roadmap

In September 2016, we became one of 13 signatories to the Industry Roadmap for Progress on Combating Antimicrobial Resistance. The roadmap includes a series of commitments made by pharmaceutical companies to work towards a sustainable and predictable market for antibiotics, vaccines and diagnostics that enhances conservation for new and existing treatments. It also called for coordinated action to improve prevention of infections, hygiene, stewardship and conservation measures.

These commitments include:

- > Implementing measures to reduce environmental pollution from production of antibiotics
- > Working with partners to ensure antibiotics are only used in patients who need them
- > Improving access and ensuring affordability for existing and future antibiotics, diagnostics and vaccines
- > Exploring new opportunities for open collaborations between industry and the public sector to address challenges in the research and development of new antibiotics, vaccines and diagnostics, recognising the value these bring to society.



Preventing pneumonia to reduce the antibiotic burden

Among the most problematic multidrug resistant bacterial pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. These are frequent causes of hospital infections and often result in death or significant illness and a longer stay in hospital.

MedImmune, the biologics research and development arm of AstraZeneca, is currently conducting two Phase 2B studies of MEDI4893 and MEDI3902 to prevent patients with one of these pathogens from going on to develop pneumonia.

This approach may well spare the use of antibiotics in the first place or improve outcomes in patients who do develop pneumonia, further preserving the usefulness of antibiotics.

MedImmune is also continuing to work to discover new kinds of antibacterial agents that work against the most resistant strains of bacteria.

