



Responsible Investment Corporate Governance and SRI – Q4 2006

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Voting profile for Q4 2006

Over the course of the quarter, Newton exercised its clients' voting rights at 264 General Meetings. Votes were instructed against one or more resolutions at 7.9% of UK meetings and at 18.7% of meetings held outside of the UK. 26 separate resolutions were voted against at meetings in the UK. Outside the UK, 35 resolutions were voted against.

A major issue during the period, accounting for 23% of all votes against, was excessive dilution to existing shareholders' value. The proposed mechanisms, which Newton felt would result in

excessive dilution, included disapplication of existing shareholders' pre-emption rights, re-structuring of the company's share capital and overgenerous awards of share-based incentives.

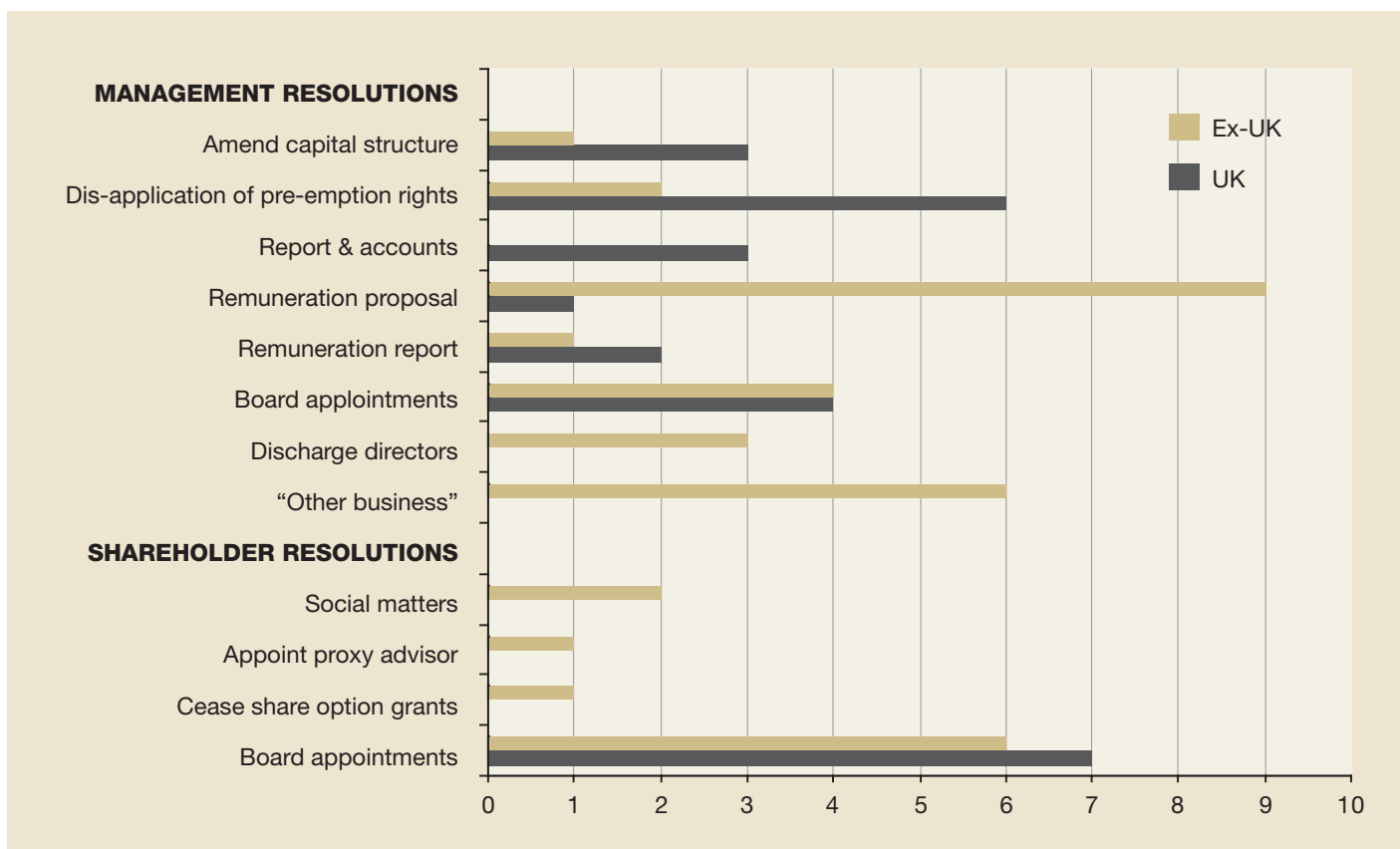
The table below summarises the exercise of voting rights during the fourth quarter of 2006. The chart following illustrates areas of contention where votes were instructed against resolution items.

Complete voting summary – Q4 2006	Total	UK	Ex-UK
AGMs			
Voted in favour of all resolutions	121	73	48
Voted against one or more resolutions	25	10	15
Took no action	1	0	1
Abstained	0	0	0
	147	83	64
EGMs			
Voted in favour of all resolutions	97	59	38
Voted against one or more resolutions	4	2	2
Took no action	3	0	3
Abstained	0	0	0
	104	61	43
Court Meetings			
Voted in favour of all resolutions	13	8	5
Voted against one or more resolutions	0	0	0
Took no action	0	0	0
Abstained	0	0	0
	13	8	5
Totals	264	152	112
Voted in favour	231	140	91
Voted against	29	12	17
Took no action	4	0	4
Abstained	0	0	0
Totals	264	152	112

Breakdown of resolutions where votes against were instructed during Q4 2006

In a number of instances, shareholder approval was sought for identical and, seemingly, routine resolutions. Many were consistent with the letter of the law but the spirit of good corporate governance was ignored. Examples of some of these

routine resolutions included seeking shareholder approval for “other business”, the dis-application of shareholders’ pre-emption rights over an acceptable level and the granting of retirement bonuses to independent non-executive directors.



UK Companies

Aegis Group PLC – EGM – 22 Nov 2006

At the company’s AGM on 14 June 2006, the company’s largest shareholder, Groupe Bollere, proposed two resolutions. These sought for the election of two of Groupe Bollere’s nominees to the company’s board. In June 2006, Newton voted against each resolution. The same resolutions were resurrected for this EGM in November, which was requisitioned by Groupe Bollere. Again, Newton voted against these resolutions for the same reasons as stated before...

“The proposed board members would be representatives of Groupe Bollere. It should be noted that Groupe Bollere is also a material holder of Havas, a direct competitor of Aegis. Also, Havas and Groupe Bollere share the same Chairman. Therefore, it could be argued that Groupe Bollere was seeking to potentially disadvantage current shareholders of Aegis and to control the company without paying an appropriate takeover premium to shareholders of Aegis.”

Air Partner PLC – AGM – 22 Nov 2006

Votes were instructed against the resolution that asked shareholders to accept the company’s Financial Statements and Statutory Reports. Newton felt that the executive chairman’s membership of the audit committee created a direct conflict of interest, which could inhibit the audit committee in its role of providing oversight and control of the audit function.

In addition, Newton voted against the proposed amendment to the company’s Share Option Plan. It was proposed that the overall dilution limit be increased from 10% to 15% of the company’s issued share capital. The company failed to provide any rationale for this abandonment of established best practice in this area.

iSoft Group PLC – AGM – 17 Oct 2006

On appointment, the company's Finance Director was awarded 250,000 share options. The vesting of these options would only be dependent upon the Finance Director's continued employment with the company. Newton considers that share based incentive awards should be subject to pre-determined performance conditions and should not be designed to allow for rewards for underperformance. Votes were instructed against the company's remuneration report and against two members of the remuneration committee, who were seeking re-election to the board.

Sibir Energy PLC – AGM – 12 Dec 2006

A member of the company's audit committee was a beneficiary of a trust that had a controlling stake in the company. As a member of the company's audit committee, Newton considered that this level of shareholding brought about a significant conflict of interest that would impede the individual's ability to act in shareholders' best interests. Consequently, Newton voted against the resolution that requested shareholders to accept the company's Financial Statements and Statutory Reports.

Newton also instructed votes against the resolution requesting shareholder approval for the company to issue additional shares, up to 46% of its issued share capital. Despite the company's intention to honour existing shareholders' pre-emption rights, Newton felt that, without any justification from the company as to the intended use of any raised capital, the level of requested issuance was excessive.

Spirent Communications – EGM – 22 Dec 2006

Newton voted against all seven resolutions proposed at this shareholder requisitioned EGM. The proponent, a shareholder group, sought to remove three of the company's non-executive directors and appoint four of its own nominees. Prior to this

EGM, the company had offered the proponent two seats on its board. However, this was not accepted by the proponent who wanted to take effective control of the board with the appointment of four of its own nominees. Newton agreed with the company's comment that a premium should be paid by the proponent for taking such control of the company.

Town Centre Securities PLC – AGM – 22 Nov 2006

Newton considers that companies' audit committees should be comprised of independent non-executive directors. However, one member of Town Centre Securities' audit committee controlled 8.8% of the company's share capital and was the brother of the CEO, who controlled 13.6% of the company's shares. Newton instructed votes against the resolution asking shareholders to receive and adopt the company's Financial Statements and Statutory Reports.

Votes were also instructed against the resolution seeking shareholder approval of the company's remuneration report. The CEO has a service contract that provides for at least 24 months notice. This is significantly outside the accepted best practice of a maximum of 12 months.

Dis-application of pre-emption rights at UK companies

In the UK, the Pre-emption Rights Group published a guidance note to companies and investors in the event of new issuances of shares. The guidance supports Newton's view that acceptable justification must be given to shareholders should a company seek to issue more than 5% of its issued share capital, without first offering the shares to existing shareholders. Without this level of protection, existing shareholders could face unacceptable levels of dilution to their holdings.

At the meetings listed below, Newton voted against the resolution seeking shareholder authority to dis-apply existing shareholders pre-emption rights.

Company	Meeting type	Date	Level of dis-application sought
Albemarle & Bond Holdings PLC	AGM	3 Nov 2006	10%
Cape Diamonds PLC	AGM	1 Nov 2006	50%*
Max Petroleum PLC	AGM	6 Oct 2006	164%*
Merrill Lynch Greater Europe Investment Trust PLC	AGM	21 Nov 2006	5%†
New Star investment Trust PLC	AGM	16 Nov 2006	5%†
SVM Global Fund PLC	AGM	19 Dec 2006	10%†

* Newton also voted against the resolution that sought shareholder approval to issue this same level of shares, whilst protecting existing shareholders pre-emption rights. However, Newton felt that, in the absence of any rationale from the company, the level of issuance was excessive.

† The terms of the issuance would allow for shares to be issued at a discounted price to their Net Asset Value. In theory, this could lead to shares being issued at a price below their trading price, which Newton feels is unacceptable.

Ex-UK Companies

Barclays Investment Funds; North American Equity – AGM – 30 Nov 2006

Shareholder approval was sought for the company to conduct “other business” that may arise at its General Meeting. Open-ended resolutions of this type, with no additional supporting information or shareholder protection measures, are generally considered to be unhelpful by institutional investors and other shareholders who vote by way of proxy. No explanation of this resolution or the motivation behind the proposal was disclosed. Therefore, Newton instructed votes against the resolution seeking shareholder approval of “other business”.

Echelon Resources Ltd – EGM – 16 Nov 2006

The company requested shareholder approval for a remuneration scheme that would grant 7.1% of the company's market capitalisation to two directors. Whilst Newton recognised that there was a real need for the company to incentivise these two directors, it was not felt that the structure of the incentive award was sufficiently robust to warrant the level of potential dilution of the company's existing shareholders. Concerns centred on the lack of performance conditions that would govern the vesting of the proposed share incentive awards. Newton instructed votes against this resolution.

Goldrea Resources – AGM – 21 Dec 2006

Two resolutions were proposed that related to the operation of the company's share option plan. The first requested shareholder approval for an increase in the number of shares available for granting under the company's share option plan to 20% of its issued share capital. Over the past three years, the average annual award of share options has been 8.39% of the company's share capital. Newton considers this policy to be unsustainable. It was also felt that the option plan was not sufficiently well structured to support such a high transfer of value from shareholders to the company's management. Very little information was disclosed about the share option plan, other than awards are able to vest on the date of grant (25%) and then 25% of any award at each 6 monthly interval. Also, the plan rules expressly permit the re-pricing of share options. The second resolution, detailing proposed amendments to the share option plan, was not considered to be in shareholders best interests. If approved, the proposal would give the company blanket permission to make any amendments to historic share option awards, including accelerated vesting.

A resolution entitled “Other Business” was put to shareholders for their approval. This would allow the board and shareholders to raise other issues at the AGM. While such requests are routine in certain jurisdictions, there is a possibility that certain items may be raised and approved under this resolution, which may not be in shareholders' best interests.

Harmony Gold Mining Co. Ltd – AGM – 10 Nov 2006

The company proposed a new share plan, for which shareholder approval was sought. From the limited detail provided on the proposal, Newton had issues with the proposed 14% dilution to shareholders' value, together with an ability for performance conditions to be re-tested should they not be achieved after the initial vesting period. These two key concerns led to Newton instructing votes against the proposed share plan. Newton also voted against a member of the remuneration committee, who was seeking re-election to the board.

Hopewell Highway Infrastructure Ltd – AGM – 19 Oct 2006

The company requested shareholder approval to issue up to 20% of its issued share capital, whilst dis-applying existing shareholders' pre-emption rights. As the company did not provide any comfort as to why shareholders should accept such a level of dilution, Newton voted against the resolution.

Fidelity Funds SICAV – AGM – 5 Oct 2006

Asian Special Situations Fund

Pacific Fund

European Growth Fund

At the time of the AGM, the Securities and Exchange Commission was considering bringing civil fraud charges against two of Fidelity's investment businesses. In addition, the company was also facing a gifts investigation by the National Association of Securities Dealers, along with a separate federal grand jury probe. Given these outstanding issues, Newton considered it prudent to instruct votes against the resolution seeking shareholder approval to discharge the board from liability.

Shareholders were also asked to approve the remuneration of the company's directors. Due to the company failing to provide details of the directors' remuneration arrangements, Newton voted against this resolution.

Finally, Newton also voted against a resolution that sought approval of “Other Business”. The unknown content of this resolution meant that Newton had to exercise a level of prudence by voting against its approval.

International KRL Resources Corp – AGM – 29 Nov 2006

A separate resolution, entitled “Other Business” was proposed. Newton felt unable to support this resolution given that, by its very nature, underlying actions and details would be unknown until the day of the meeting.

Japan Retail Fund Investment Corp – AGM – 22 Nov 2006

Votes were instructed against two members of the company's supervisory board, who were seeking re-election to the board. These two nominees had been board members for the period that covered the company receiving an administrative order for failure to conduct proper board meetings and carry out timely disclosure practices.

Microsoft Corp – AGM – 14 Nov 2006

Newton instructed votes against three resolutions that were proposed by certain shareholders of the company.

The first resolution requested that the company cease the sale of products or services that could be used to violate human or labour rights in foreign countries. Microsoft publicly discloses its current policies relating to government regulations on freedom of expression. The company also has a high level of awareness relating to this issue and its potential impacts on the company's operations. The company openly discusses the issue with interested parties and is engaged in dialogue with multiple stakeholders in an effort to develop industry-wide principles that would guide policy on this issue. Considering the proactive stance and transparent manner in which Microsoft already considers this topic, alongside concerns at the potential negative impact that actions, as requested by the resolution, could have on Microsoft's competitive position, Newton voted against accepting this resolution.

The second shareholder proposed resolution requested that the company explore ways to formulate an Equal Employment Opportunity (EEO) statement that complies with federal, state and local laws, but does not reference sexual orientation. Newton voted against accepting this resolution. Newton believes that companies should have policies in place that prevent workplace discrimination in all of its forms. Removing the sexual orientation clause from an EEO could lead to costly litigation and fines, low employee morale or increased employee turnover, a more limited pool of potential qualified employees and the alienation of certain client markets. These factors can all translate into real financial losses and strategic disadvantages for the company.

The final shareholder resolution, which Newton voted against, requested the company to hire a proxy advisor. The proponent requested that the company select and pay for a proxy advisor. Based on their research and analyses of the company's corporate governance, the proxy advisor would then be required to recommend voting actions to the company's shareholders. Newton failed to appreciate how the obvious conflict of interest could be avoided.

NWS Holdings Ltd – AGM – 21 Nov 2006

The company sought shareholder approval to issue up to 20% of its share capital. This would not be on a pre-emptive basis to the company's existing shareholders. The company failed to provide any information relating to the intended use of any share capital raised. Newton considered that potential dilution of 20% was excessive. Votes were instructed against this resolution.

Oracle Corp – AGM – 9 Oct 2006

In relation to the company's non-executive director share option plan, three amendments to the award policy were proposed for shareholder approval. The amendments would allow for a general increase in the levels of awards, together with enhanced awards for certain key board positions held. It was also proposed that the company have autonomy over any future

share-based awards to non-executive directors. Of concern was the potential level of dilution to existing shareholders of 14.4%, which Newton felt was excessive. Newton also felt that share-based incentive awards to non-executive directors would jeopardise the ability of non-executive directors to act independently of management and to act in the best interests of long-term shareholders. Newton instructed votes against the proposed amendments.

The Procter & Gamble Company – AGM – 10 Oct 2006

A resolution, proposed by one of the company's shareholders, sought for the abolition of any future share option awards. The resolution also requested that any existing share options should not be re-priced or renewed. Whilst Newton is in support of not allowing the re-pricing of share options, it was felt awarding share options should be at the discretion of the company's remuneration committee. Providing that share option awards are structured correctly, it is Newton's opinion that they can help to align managements' interests with shareholders' interests. Votes were instructed against this shareholder proposal.

Tabcorp Holdings Ltd – AGM – 27 Nov 2006

Newton did not support the election of a self-proposed candidate to the company's board. The nominee, an ex-gambling addict, sought to help the company fulfil its social responsibilities. The candidate provided a lack of detail as to what she would be able to bring to the board or how she would enhance shareholder value. Newton noted that the company has done much to address concerns surrounding responsible gambling practices, by way of strengthening its policies and procedures in this area.

In relation to the above resolution, the company proposed to increase the deadline for receiving proposed names for board nominees from the 35 days, recommended in the Australian Listing Rules, to 75 days prior to the general meeting. In practice, due to the requirement to gain regulatory approval for board nominees, candidates would need to begin the nomination process ahead of the publication of the company's report and accounts. Owing to the reduction in shareholders' ability to initiate board changes, Newton instructed votes against this management proposed resolution.

The final resolution that Newton voted against concerned the issuance of a significant number of share options to the company's CEO. Newton considered that the performance conditions were not sufficiently challenging to warrant the proposed award, especially given that the performance conditions could be re-tested should they not be achieved after the initial vesting period.

Tele Norte Leste Participacoes – EGM – 13 Nov 2006

The company sought shareholder approval for its six different share classes to be consolidated into one. This single share class would uphold the principle of one-share-one-vote and be listed on Bovespa's Novo Mercado and the New York Stock Exchange. This was felt to be a positive move by the company

in relation to it making a commitment to better principles of corporate governance. However, in the process of the restructuring, the company's proposal would lead to Newton's clients' value being diluted by 34%. In contrast, the controlling shareholders, who have nominated members to the board, (due to enhanced voting rights, rather than economic interest), would have their value increased by c.111%. Newton felt that this was a clear abuse of power, which warranted votes being instructed against the proposed restructuring.

Telstra Corporation Ltd – AGM – 14 Nov 2006

Newton voted against four proposed nominees to the company's board and against the re-election of a director, who was the chairman of the remuneration committee.

The four nominees Newton voted against did not have the backing of the company's board. Newton felt that these four nominees were too closely linked with the government, which was a majority shareholder of the company. Newton did vote in favour of a fifth shareholder nominee, who was not supported by the board. This nominee was a recognised corporate

governance activist in Australia, which Newton felt would help the board to act in shareholders' best interests.

The lack of focus on improving shareholder value was the main reason for Newton voting against the resolution that sought shareholder approval of the company's remuneration report. Whilst Newton was reassured by the robustness of the performance targets, which would govern the vesting of Long-Term Incentive awards, it was felt inappropriate for awards to vest in full in the event of a change in control. Instead Newton would expect awards to vest only to the extent that performance conditions had been achieved and then pro-rated to time. In addition, the remuneration committee stipulated that awards would vest in full should a third party attain 15% of the company's outstanding share capital. Newton failed to see how this would be an incentive for management to maximise shareholder value. Even if a third party were to acquire a 15% shareholding in the company, this third party would not be required to make a mandatory offer to the remaining shareholders of Telstra.

Examples of engagement – Q4 2006

Where clients provide Newton with discretion over the exercise of their voting rights, Newton undertakes corporate governance engagement activity in relation to their underlying investments. Below are examples of corporate governance engagement carried out during the quarter. This is not an exhaustive list of engagement activity.

UK Media company – September 2006

Contacts: **Chair of the Remuneration Committee**
Chief Executive Officer
Company Secretary
Remuneration Consultant

Following the introduction, in 2004, of its innovative Long-Term Incentive Plan (LTIP), a meeting was had with the company to review its progress. Discussions centred on the affects that the LTIP had had in helping the company meet its stated strategic objectives and how it had influenced the behaviour of the company's managers and its senior executives. The meeting also provided an opportunity to meet with the recently appointed chairman of the remuneration committee.

Newton questioned the CEO over the perceived significant culture change that the business had gone through since the introduction of the LTIP and how this had been influenced by the LTIP. At the time of its introduction and again at this meeting, Newton suggested that one of the performance conditions should be based on the company's generation of revenue per customer, rather than the use of net client retention. The company appreciated Newton's concerns over the longevity of some of the current performance conditions.

Given that some of the existing performance conditions are genuinely commercially sensitive, the company does not disclose specific targets. However, it was suggested to the company that it would be helpful if the targets were disclosed, at least, retrospectively.

UK Equity Investment company – October 2006

Contact: **Non-Executive Director**

The company held its first Annual General Meeting following its flotation on the London Stock Exchange. For this meeting, shareholders were asked to approve amendments to the company's Articles of Association and support nominees for re-election to the board. However, no information was disclosed relating to these resolutions. On being contacted, the company was able to provide the necessary detail relating to the proposed amendments to the Articles of Association, which Newton felt would be in shareholders' best interests. However, ahead of the AGM, there was no disclosure of details relating to the nominees for re-election to the board. Further conversation with the company secured a promise of an improved level of disclosure in order for shareholders to make informed and timely proxy voting decisions.

UK Support Services company – October 2006

Contacts: **Chairman-designate**
Chair-designate of the Remuneration Committee
Remuneration Consultants

Shareholders' views were requested on a proposed remuneration structure for a company that was expected to be spun-out from a larger company. Newton explained that the fixed remuneration elements seemed a little generous for what was expected to be a relatively small business that had, historically, performed below market expectations. Further queries were raised and assurances received relating to the setting and disclosing of challenging performance conditions, which would govern the vesting of share-based incentive awards. Detailed discussions were also had relating to a new remuneration structure proposed for the nominated Chairman of the company. It was proposed that the Chairman invest his own funds, which would then be matched by the company at a ratio of 1:1, over a three-year period. A fundamental concern with the Chairman's remuneration structure and all of the proposals was that the names of the board members, including the members of the remuneration committee, had not been formally disclosed. Little comfort was or could have been provided to shareholders on this matter.

UK Investment Trust – October 2006

Contact: **Company Secretary**

At its AGM, the company sought shareholder approval for it to issue in excess of 100% of its share capital, whilst dis-applying existing shareholders pre-emption rights. Newton's main concern centred on the ability for these shares to be issued at a discount to the price of the trading shares, thereby unnecessarily diluting existing shareholders' value. This point had not been considered by the company. Comfort was provided that it would not be the intention to dilute shareholders in this way. The company further stated that it would be reviewing this matter in time for next year's AGM.

UK Mining company – October 2006

Contact: **Company Secretary**

Newton contacted the company in relation to a special one-off award made to certain executive directors. These one-off awards were outside of the company's stated remuneration policy. Whilst the company provided additional information and rationale relating to the need for the awards to be made, Newton felt that the company handled the situation very poorly. The company admitted that the issue should have been dealt with better. A commitment was offered that, should the company need to deviate from its stated remuneration policy in the future, shareholders would be consulted in advance.

Singapore Food Producer – October 2006

Contact: General Manager, Corporate Affairs and IR

Newton wrote to the company with regard to a need for further information relating to two resolutions proposed at its Annual General Meeting. Newton was concerned that its clients' shareholdings could be unnecessarily diluted, due to proposed issuances of shares that would not respect existing shareholders' pre-emption rights. The company provided Newton with appropriate comfort. It was stated that the board would review and evaluate all factors before considering any capital raising exercises, including any effect on the company's shareholders. The company went on to state that it would be unlikely to issue such a large amount of shares, given that it has sufficient capital on its balance sheet to meet its 6-year growth targets. In addition, greater detail was provided in relation to the company's share option structure, which gave Newton a certain level of satisfaction as to the issuance that would be needed to meet potential obligations, should share option awards vest.

Singapore Healthcare Equipment & Services company – October 2006

Contact: Managing Director

In writing to the company, Newton sought further information surrounding proposals from the company to amend its long-term incentive structure. Newton was concerned that its clients' shareholdings could be unnecessarily diluted by up to 15%, by way of the company granting share options and performance shares. Also of concern was the inclusion of non-executive directors as recipients of awards under the proposed Performance Share Plan. Newton considers that such awards can undermine the requirement for non-executive directors to exercise the crucial role of independent oversight. The company stated that, historically, it has never issued more than 1% of its issued share capital by way of share-based incentive arrangements. Newton understood that this policy was unlikely to change. Assurances were also given that awards to non-executive directors would not be of such significance as to affect or compromise their independence.

UK Aerospace & Defence company – November 2006

Contacts: Chairman

Chair of the Remuneration Committee

Group Human Resources Director

Remuneration Consultant

The company proposed a new remuneration structure, on which it consulted with shareholders. The introduction of a deferred bonus share-matching plan was proposed, together with an increase in the maximum bonus potential and an increase in the level of share-based incentive awards. Whilst Newton recognised that the maximum potential payout from the awards would be much higher than from current arrangements, it was noted that the underlying performance conditions would be significantly increased. However, Newton stated that the proposed performance targets should be more challenging and that a return on capital measure should be incorporated.

UK Equity Investment company – November 2006

Contact: Investor Relations

It was requested by the company that shareholders approve the issue of shares, whilst dis-applying existing shareholders' pre-emption rights. The terms of any issuance would allow shares to be issued at the trading shares' Net Asset Value (NAV). This was of concern given that the shares trade at a premium to their NAV. Newton failed to appreciate why the company's existing shareholders should not be given an opportunity to purchase shares at a discount to their trading value. The company appreciated Newton's view and would take it into consideration should a future issuance of shares be made.

Newton is sympathetic to a policy of a company indemnifying its directors. However, it is not considered to be in shareholders' best interests for a company to indemnify its own, externally appointed, auditors. On examination of the details of a resolution, proposed by the company for approval at its AGM, it was discovered that the company would have an ability to indemnify its auditors should it choose to do so. Given that the company's auditors currently enjoy indemnification insurance from the company, the proposal would weaken the auditor's position by stating that the board "could" indemnify its auditors. This issue would be raised at the next board meeting. Newton stated that it expects the policy of being able to indemnify auditors to be removed in its entirety.

UK Investment Fund – November 2006

Contact: Chief Executive Officer

In an effort to increase the fund's market capitalisation, improve its performance and help it to become a market leader, Newton made a number of suggestions to the fund's board of directors. First, it was requested that shareholders be able to switch between the fund's different currency classes, as is available with most leading funds. Secondly, it was recommended that the annual management charge be amended to one that is less of an administrative burden on shareholders and one that is more in line with the rates charged by competing funds. Thirdly, Newton suggested that, in connection with the reduction in the management charge, any potential performance fee be more rewarding in the event of outperformance.

UK Fixed line Telecoms company – December 2006

Contacts: Chairman

Senior Independent Director

Following the introduction, earlier in the year, of a new remuneration structure, Newton met with the company's Chairman and Senior Independent Director (SID). The Chairman stated that the remuneration structure was providing the recipients with the necessary focus to take the company forward along the lines of its stated strategy. This comment was partly supported by the 50% increase seen in the company's share price since the remuneration structure was approved and awards were made to the key individuals. Newton also had the opportunity to discuss corporate governance matters with the SID, without the Chairman. This provided valuable insight into the dynamics of the board and its members. In particular, the role of the Chairman and his conduct were discussed.

Q406 SRI Focus The Pharmaceutical Industry:

The development of safe and effective medicines and the ethical considerations of clinical trials

Background

New medicines, vaccines and medical devices have brought significant benefits to the quality of life of millions of people over the last fifty years. However, there are still many serious and life-threatening illnesses for which there are no effective treatments or where treatments could be significantly improved.

The discovery and development of safe and effective medicines is a long, challenging and expensive process. In addition, biomedical and pharmaceutical research raises many ethical concerns relating to the testing of new drugs on animals and humans. Medical research trials are necessary to ensure that new medicines are both safe and effective. Both preclinical¹ and clinical trials² are integral to the development of any new medicine for human use. Currently, a new drug will only be approved if preclinical and clinical trials have demonstrated adherence to various ethical and scientific standards of best practice.

The pharmaceutical industry has a responsibility to manage the safety of those receiving its medicines. The industry is highly regulated specifically to ensure that patient safety is the number one priority of any company undertaking medical research. From a business perspective adherence to such regulations is important to protect the reputational, operational and financial risk of a company involved in the development of new medicines. The pharmaceutical industry has two major roles in managing the safety of medicines:

- To collect, investigate and proactively evaluate information relating to any side effects from administering medicines. This is for the purpose of protecting patients and advising on drug safety.
- To fulfil legal obligations to regulatory authorities by reporting individual adverse events³ that may occur during and post the drug development process.

This quarter's SRI focus begins with an outline of the drug discovery process. The ethical considerations of clinical trials that involve human participants are then discussed. Newton contacted three of the world's largest pharmaceutical companies, GlaxoSmithKline, AstraZeneca and Sanofi-Aventis, to discuss some of their policies and governance mechanisms when ensuring adherence to ethical and scientific regulations.

The drug discovery process

The drug discovery process is time-consuming, complex and risky. It is estimated that the average time taken to take a product from discovery to market is almost 15 years. This has increased almost 20% over the past 20 years⁴. This is largely due to an increasingly stringent regulatory environment that is designed to ensure patient safety.

The process of developing a new medicine is outlined below.

Discovery phase: The process of drug discovery begins with an understanding of a disease mechanism. A potential drug target is sought by attempting to develop a compound that interacts with a disease to form the basis of an effective treatment. Tens of thousands of molecules are screened in the search for a compound that could potentially have a pharmacological effect. However, only a handful may move forward for pre-clinical testing.

Preclinical Testing: Laboratory and animal studies are conducted to investigate biological activity of a compound against the targeted disease. The key pharmacological characteristics of a compound are determined to assess the safety and suitability of a compound to become a drug. Preclinical testing takes approximately three to four years.

Investigational New Drug Application (IND): After completing preclinical testing, the research company files an IND with the appropriate regional regulatory body. If the IND is approved, clinical trials to test the drug in people can begin. The IND must include the results of the preclinical trials, as well as details outlining how, where and by whom the new studies will be conducted. The IND must also include details of the chemical structure of the compound that is being tested, how it is thought to work in the body, any toxic effects found in the preclinical animal studies and how the compound is manufactured. In addition, the IND must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC performs a local oversight function in relation to scientific, ethical and regulatory matters which involve human subjects. An IRB/IEC has the authority to approve, request modifications to, or disapprove a particular study. Clinical studies in humans can begin once the regulators are satisfied that the preclinical animal data does not show an unacceptable safety risk to humans.

¹ Preclinical trial: a laboratory test of a new drug or a new invasive medical device on animal subjects; conducted to gather evidence justifying a clinical trial.

² Clinical trial: a rigorously controlled test of a new drug or a new invasive medical device on human subjects.

³ Adverse event: Any unwanted, unpleasant, negative, or dangerous effect in response to a treatment or intervention.

⁴ Deutsche Bank: Pharmaceuticals for Beginners, 5 August 2005

Clinical Trials, Phase I: These tests take approximately one year and involve normal, healthy human volunteers. The tests mainly study a drug's safety profile. The studies aim to determine how a drug is absorbed, distributed, metabolised and excreted from the body. The duration of a drug's action and its safe dosage range are also studied. Approximately 80-90% of Phase I drug candidates fail to progress to Phase II.

Clinical Trials, Phase II: In this phase, controlled studies of approximately 100 to 300 volunteer patients, with the disease being targeted, are undertaken. Studies assess the drug's safety, efficacy and side-effect characteristics. Typically the trials focus on dose response and dose frequency. Trials take approximately two years and fewer than 40% of drug candidates progress to Phase III.

Clinical Trials, Phase III: Phase III trials are typically conducted once the efficacy of a medicine has been demonstrated and the optimal dose range determined. The trials are conducted with patients for whom the drug is intended and are designed to demonstrate safety and efficacy in larger patient populations. This phase lasts approximately three years and usually involves 1,000 to 3,000 patients. The number of participants involved in the trial would be sufficient to statistically demonstrate efficacy and highlight any important side effects. Phase III trials are often described as pivotal trials and will form the major part of a drug approval submission to regulators.

New Drug Application (NDA): Following the successful completion of all three phases of clinical trials, the research company analyses all the data and submits a NDA to the appropriate regulatory body. The NDA requests approval to manufacture, distribute and market the drug. The NDA must contain all of the scientific information that the company has gathered.

Approval: Once the regulatory body approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to the regulator including any cases of adverse reactions and appropriate quality-control records.

Phase IV or post marketing surveillance: Even when the drug is approved, the clinical oversight does not come to an end. Sponsors are required to undertake post-marketing surveillance to monitor a drug's safety. This is a process that will continue for the life of a drug. Rare adverse events can become apparent once a substantial patient population gains exposure to a drug. Should serious adverse events occur the pharmaceutical companies must inform the regulatory agencies within fifteen days of discovery.

On average, it takes 15 years to take a product from discovery to market. Success rates are low. Only five in 5,000 compounds that enter preclinical testing make it to human testing. On average, only one of these five compounds tested on humans will be approved for launch.

Figure 2: Diagrammatical summary outline of the process of drug discovery

Phase	Discovery	Preclinical Testing	Clinical Trials			Regulatory Review	Total	Clinical Trials Phase IV
			Phase I	Phase II	Phase III			
Years	~5	1.5	1	2	3	1-2	~15	
Test Population	Laboratory	Animal Studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	Review Process/ Approval		Additional post-approval testing
Purpose	Develop compound to form basis of a treatment	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term drug use			
Success Rate	~10,000 compounds evaluated	~10 enter preclinical testing	5 enter clinical trials			1 approved		

Source: Newton Investment Management

Business pressures of drug development

The future profitability of a pharmaceutical company is determined by the success of its new drug pipeline. It is, therefore, no surprise that the progress of a drug is monitored closely by financial markets. Increasing amounts of information on a drug usually becomes available towards the end of Phase II clinical trials or at the beginning of Phase III. Success and setbacks can be met with significant movements in share price as was seen by Merck's experience with Vioxx, and, in a more recent example, Pfizer's experience with Torcetrapib.

• Merck and Vioxx

Vioxx is an anti-inflammatory agent prescribed for the treatment of arthritis, acute pain and primary dysmenorrhea⁵. The FDA approved Vioxx in May 1999. Trials evaluating the cardiovascular profile of the drug, as well as its impact on gastrointestinal safety, continued post approval. Merck also continued trials looking at the efficacy of Vioxx on other diseases such as the prevention of certain types of cancer. In September 2004, during one of the Merck sponsored trials, the incidence of cardiovascular events was discovered to be higher than expected. Based on these observations, an External Safety Monitoring Board recommended that the study be stopped and the data reviewed. This eventually led to a recommendation that Vioxx be withdrawn from the global market. The Management Committee and Board of Directors of Merck endorsed this conclusion and on September 30, 2004, Vioxx was voluntarily withdrawn from the market. The new data suggested that after 18 months of continuous use, Vioxx increased a patient's relative risk of sustaining a cardiovascular adverse event, such as a heart attack and/or stroke.

The following chart highlights how the share price of Merck responded to the news.

Fig 3: Merck Share Price, 31/12/03 – 31/12/04

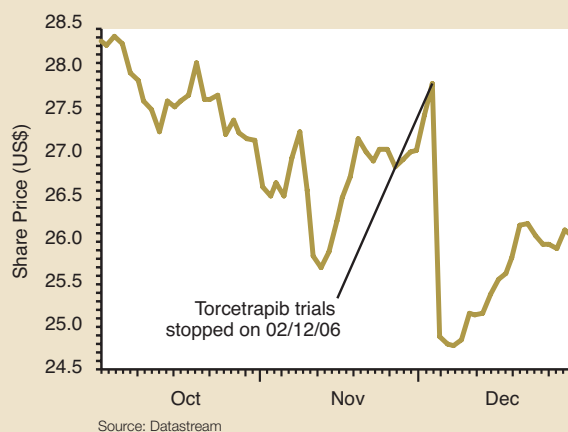


• Pfizer and Torcetrapib

The function of Torcetrapib is to block CETP (cholesterol ester transfer protein), a protein that regulates cholesterol. Scientists believe that CETP inhibition can lower cholesterol build-up on artery walls thereby reducing the potential occurrence of heart attack or stroke. On 2 December 2006, Pfizer announced that, in the interests of patient safety, it was stopping all Torcetrapib clinical trials. One day earlier, an independent Safety Monitoring

Board had recommended terminating the study due to an imbalance of cardiovascular and mortality events. Torcetrapib was in the last development stage of clinical trials. The clinical development programme, prior to the withdrawal of the drug, was estimated to have cost Pfizer approximately US\$800 million.

Fig 4: Pfizer Share Price, 30/09/06 – 31/12/06

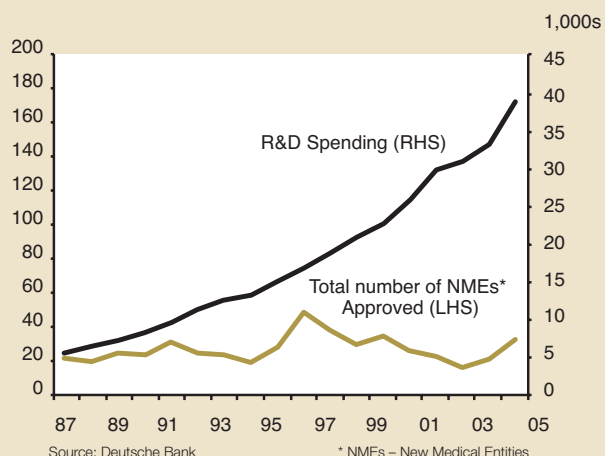


Increasing regulation and costs

Reflecting the increasing focus on drug safety, regulators will only approve a drug if clinical trials have demonstrated adherence to various ethical and scientific standards of best practice. On average, almost 70 clinical trials are now required for each new drug application. This is compared to nearer 30 at the start of the 1980s. Today, each new drug application requires over 4,200 patients to have participated in clinical trials compared to just over 1,300 twenty years ago⁶.

This has led to a major increase in the average costs incurred when developing a new drug (see Figure 5: Research and development spend versus drugs approved). Industry consultants estimate that, on average, a successful drug now costs US\$897m pre-tax to bring to market. This includes an estimated US\$150-200m to reflect the cost of drugs that fail in development⁶.

Figure 5: Research and development spend versus drugs approved



5 Dysmenorrhea: Pain or discomfort experienced just before or during a menstrual period.
6 Deutsche Bank: Pharmaceuticals for Beginners, 5 August 2005

Regulation

Clinical development of a new drug involves extensive collaboration with clinicians in many countries and participation, in many cases, of several thousand human subjects. From an ethical, scientific and business perspective, it is essential that clinical development is based on robust preclinical data so that efforts undertaken by clinical investigators, volunteers and patients are meaningful and productive.

Clinical research trials are usually performed or sponsored by the company that developed the drug being tested. Patient safety is the fundamental operating principle and takes precedence over commercial interests. Therefore, companies must ensure that volunteers and patients are not exposed to unnecessary risks. Continuous assessment of the balance between benefits and risks to trial participants must also be undertaken during clinical development and disclosed to regulators.

Three main markets

The three main markets for pharmaceutical products are North America, Japan and Europe. Separate regulatory bodies, legislative requirements and approval processes exist in each of these countries. In the US, the process of regulatory approval for a new drug falls under the supervision of the Food & Drug Administration (FDA). In Japan, the drug evaluation process for a new drug is overseen by the Ministry of Health Labour and Welfare (MHLW). In Europe, the central agency that coordinates and manages the drug approval process is the European Agency for the Evaluation of Medicinal Products (EMA).

Harmonisation

As things stand today, a new drug needs to go through each of these approval processes if it is to be launched in all three markets. This means that further clinical trials often have to be undertaken in order to meet the regulatory requirements of the authorities in the different territories. This is a feature that further increases the already substantial costs of the drug development and approval process.

Whilst regulatory obligations to protect public health are paramount, there is currently a project that aims to bring together the regulatory authorities of Europe, Japan and America, as well as experts from the pharmaceutical industry. The project is called the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The purpose of the ICH is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Improving harmonisation between the three countries could reduce the need for duplicate testing during the research and development of new medicines.

One objective of such harmonisation is a more economical use of human, animal and material resources. Another objective is to eliminate unnecessary delays in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy.

Global standards of best practice

For clinical trials involving human participants there are global standards of best practice that pharmaceutical companies can follow. These are in addition to specific regional regulations and include:

• The Declaration of Helsinki

In 1964, the World Medical Association established recommendations relating to the use of humans in biomedical research. These recommendations govern international research ethics and define rules for research that combines clinical care. The Declaration of Helsinki was most recently revised in 2000 and was used to develop very specific guidelines for good clinical practice, known as the Good Clinical Practice (GCP) Guidelines. The full Declaration of Helsinki can be found in the Appendix of this report.

• The International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP)

The Good Clinical Practice Guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with the GCP Guidelines assures protection of the rights, safety, and well-being of trial subjects. It also assures that the clinical trial data are credible. Over 45 guidelines have been developed. Some of the issues covered include:

- Having a clear and scientifically sound protocol that is signed by relevant investigators and approved by an independent Ethics Committee / Institutional Review Board (IEC/IRB);
- The selection and training of trial investigators;
- Gaining voluntarily-given informed consent from every trial participant;
- Demonstrating that the anticipated benefits justify the risks;
- Ensuring that the rights, safety and well-being of trial participants are the most important considerations.

Note. There are many other guidelines for best practice in such areas as laboratory practice and animal testing. This report only looks at guidelines and standards relating to the use of humans in biomedical research.

Ethical considerations of drug trials involving human participants and company contact

This section of the report discusses some of the significant ethical considerations of drug trials involving human participants. Newton contacted AstraZeneca (AZN), GlaxoSmithKline (GSK) and Sanofi-Aventis (SA) to discuss how they manage such issues. When conducting clinical research, all three companies adhere to the principles of the GCP guidelines as well as to the various regulations of the regional health authorities.

• Clinical Trial Protocol (CTP)

A CTP is a key document that describes the objectives, design, methodology, statistical considerations, and organisation of a clinical trial. For clinical trials sponsored by pharmaceutical, biotechnology or other medical device companies in North

America, the European Union or Japan, the structure and content of a protocol is governed by the GCP guidelines.

The CTP contains a plan on which all clinical development is based. The plan is designed to safeguard the health of participants as well as answer specific research questions. The CTP also describes what types of people may participate in the trial, the schedule of trials, procedures, medications, dosages and the length of the study. CTP's must be reviewed and approved by an Ethics Committee before the trial can begin. Once a trial has been approved, the Ethics Committee must be consulted about changes that could affect the study design and/or participants' safety. The Ethics Committee must also be informed if any unexpected or serious events occur.

Clinical trial protocols	
AZN	<ul style="list-style-type: none"> • Trial proposals are first subject to stringent internal review including consideration of the pre-clinical data, how safe the trial process is for participants, the information provided for participants and the procedures for gaining informed consent. • Before a trial begins, the protocol is approved by an appropriate external independent Ethics Committee and the relevant regulatory agency. • Trial protocols include strict guidelines to ensure that those taking part in trials understand their nature and purpose and are not exposed to unnecessary risks. They also include guidelines for the protection of the privacy of participant health information. • Standards of ethical practice apply worldwide.
GSK	<ul style="list-style-type: none"> • A detailed protocol is developed for each clinical trial. • Protocols are prepared in accordance with the internationally accepted Good Clinical Practices Guidelines developed by the International Conference on Harmonisation. • GSK will always seek formal approval for trials from independent Ethics Committees. • Trial protocols are reviewed by external regulatory agencies in the relevant countries when required. • Standards apply worldwide.
SA	<ul style="list-style-type: none"> • Each study protocol is reviewed by an Ethics Committee, as well as by scientific experts, to ensure adherence to the highest international standards. • Regulatory agencies are also involved in the consultation for development of CTP's. • Trials involving populations such as children and those who are incapable of exercising free will, as well as those in developing countries, must outline specific justification for undertaking the trial. This justification will be assessed by the Ethics Committee, scientific experts and regulatory agencies. • When designing a CTP, the company has a very thorough internal decision making process that utilises a great deal of external expertise.

• Information and consent

Before joining a clinical trial, a participant must qualify for the study by meeting strict criteria, such as age, gender, the type and stage of a disease and previous treatment history. Some trials seek participants with the condition that is to be studied while others need healthy participants.

Regulatory requirements aim to ensure that those taking part in a clinical trial understand its nature and purpose. They also aim to ensure that participants are not exposed to unnecessary risks and that the privacy of their health information is protected. Importantly,

it is a requirement that participants in clinical trials voluntarily decide to take part in a study by giving their informed consent.

Gaining informed consent is a process by which a potential clinical trial participant voluntarily confirms their willingness to participate in a trial after having been provided with information about the trial. This information must be presented in a format that is easily understood. In some situations information may need to be communicated in a non-technical style. The information provided should also include a summary of the clinical trial containing:

- The purpose of the trial;
- The treatment procedures and schedule;
- Potential risks and benefits to the participant;
- Alternatives to participation;
- Confirmation of confidentiality and data privacy;
- An explanation of participants' rights, including outlining that participation must be voluntary and that the participant can choose to end participation at any time.

Trial participants should be given full, truthful and understandable information that is in accordance with the general principles set out in the Declaration of Helsinki and in the GCP Guidelines. Informed consent should be documented in the form of a signed and dated informed consent form.

Once an individual decides to participate, the research team must update them with any new information that may affect their willingness to continue with participation. Before, during, and after the trial, opportunities must be provided for participants to

ask questions and raise concerns. Thus, informed consent is an ongoing, interactive process.

In some circumstances consent cannot be provided by the individual themselves. For example, when an individual may not have the capacity to consent to participation, or if a trial is to be undertaken with children who may be beneath the age of consent. In these circumstances consent must be provided by a legally acceptable individual. In situations when individuals are unable to read but are able to speak and understand the local language, an impartial witness must be present during the informed consent process. The witness can then attest, in writing, that the information in the informed consent form was accurately explained and that the potential participant was able to ask questions and gave consent voluntarily. Ethics Committees review and approve the informed consent information prior to the start of the clinical trial.

Gaining informed consent	
AZN	<ul style="list-style-type: none"> • Trial proposals are subject to stringent internal review before being accepted. Part of this process includes a review of what procedures will be in place for gaining informed consent from trial participants, including how any special circumstances, such as levels of literacy, will be addressed. • AZN has a specific mandatory Standard Operating Procedure, to ensure that ethical and legal requirements for the consent process are met. • AZN believes its policies enable it to receive truly informed consent from trial participants on a global basis. Standards are the same across the world. Extra measures are taken to ensure understanding of trial participants when there are language barriers and differing levels of understanding. • AZN is increasingly undertaking clinical trials in developing regions. One reason the company feels confident with this is because of its robust policies and procedures that ensure it can meet all internal and external regulatory requirements. • Neither doctors nor participants receive remuneration to participate in a clinical trial. Expenses incurred due to their efforts taken are covered.
GSK	<ul style="list-style-type: none"> • Voluntarily given informed consent is gained from every trial participant. • A trial will only proceed once informed consent, in a legally and ethically acceptable form, has been obtained from participants. • GSK understands that it is a big challenge ensuring that all participants of clinical trials are truly informed. GSK recognises that gaining informed consent goes beyond reading and signing a document. In some of the least-developed countries additional measures are often needed. For example, use of visual aids may be required when there are language barriers or additional steps may need to be taken to match the objectives of informed consent to local culture. For example local leaders and/or family members may need to be involved. • Where formal written informed consent from the participant is not possible in a GSK sponsored trial (due, for example, to poor literacy) investigators will work with independent witnesses who can formally verify that the purpose of the trial has been explained to the participant and that he/she has understood what is proposed and involved. • Full understanding must be ensured whilst complying with all ethical and legal requirements. • Due to the voluntary nature of trial participation, trial participants are not generally paid for their participation. However, reimbursement for costs incurred by the participant is provided to ensure that individuals do not suffer loss by involvement in a trial. Reimbursement offered to patients is appropriate to the local economy and submitted to independent ethics committees for consideration.
SA	<ul style="list-style-type: none"> • Informed consent is gained in accordance with the GCP guidelines. • Ethics Committees and scientific experts ensure patients are well-informed and that informed consent is given. • For all trials that involve children, informed consent must be obtained from the parents or legal guardians. In some cases, the relevant authority of the community involved may also be asked for consent. • SA states that patients should not be paid to participate in clinical trials. There is a possibility the patient can benefit from the treatment. Consent should be given freely and in writing. Reimbursement for costs incurred by the patient is provided. • For healthy volunteers, SA adheres to legislation relating to compensation. There is a limit to the number of studies a volunteer can participate in within one year. There is a global database to monitor trial participation to ensure participants do not become 'professional volunteers'. SA does not have direct contact with healthy volunteers in Phase I trials. The company has a contract with an external company that is in charge of identifying volunteers.

• **Location of the trial**

Clinical trials should be conducted in countries where the medicines are likely to be suitable for the wider community. Consequently, the majority of patients recruited into clinical trials have, in general, come from the main markets for pharmaceutical products. However, clinical trials are now increasingly conducted in other areas. This is, in part, to help develop new medicines more quickly. It is also to enable

access to a greater population of people that could be eligible as clinical trial participants. The need for clinical research outside Western Europe and America is questioned by some who argue that the industry is using some of the world's poorest populations as "guinea pigs" to trial drugs designed to target diseases of the developed world.

Choosing a trial location	
AZN	<ul style="list-style-type: none"> AZN's Global Project Team decides on where a trial should be undertaken. A decision is based on a variety of factors: <ul style="list-style-type: none"> The number of patients required for the trial; Resources available; The final end market of the drug; Which scientists are available to act as investigators of the trial. Special analysis is undertaken if the drug is to be sold in more than one geographical market. This is because different ethnic groups can respond differently to drugs.
GSK	<ul style="list-style-type: none"> GSK conducts clinical trials where: <ul style="list-style-type: none"> The population is relevant to the scientific question and where the results can be generalised to broader populations. High quality data can be obtained. Costs can be minimised. Clinical trials of investigational medicines are not conducted in countries when it is known at the outset that there is no intent to pursue registration and make the medicine available for use in that country. The majority of GSK's clinical trials are performed in Western Europe and the US. However, the company is increasing the number of trial participants from Central and Eastern Europe, Asia and South America. The main aim of this is to enable medicines to be developed more rapidly. This does not extend to recruiting trial participants from Least Developed Countries (as defined by the UN). GSK is consciously aiming to source clinical trial participants from a greater breadth of regions such as Eastern Europe. This is to increase access to potential trial participants. It is an ongoing challenge finding appropriate people to participate in trials.
SA	<ul style="list-style-type: none"> In 2005, c.33% of clinical trial participants were from the US, c. 33% were from the EU and c. 33% were classified as intercontinental. This includes trial participants from the Asia Pacific region, Latin America and Africa. Only limited studies are undertaken in Africa. A study will only be undertaken if it targets a disease that is specific to the area where the trial is being conducted. The company aims to develop innovative products that target diseases for which there are currently no effective treatments. A trial will only be conducted in an area if the community concerned will benefit from the drug once it has been approved. Availability of doctors and investigators with the appropriate knowledge is another key consideration. Other considerations include what infrastructure is in place and whether enough support staff are available. Clinical trials are not carried out in countries without Ethics Committees.

• **Safety reporting and monitoring**

One of the fundamental ethical aspects of clinical research is to guarantee that a clinical trial can be discontinued or modified if its objectives appear unobtainable or the risks encountered by participants appear to be too great. All pharmaceutical companies are required to make an immediate report to the health authorities about any serious and/or unexpected side effects reported to them by patients and healthcare professionals. The information must be communicated internationally.

In addition, health authorities in most countries require pharmaceutical companies to publish regular summary reports on all products. The reports must include all safety data relating to the use of the product. The information is used to re-assess the risk/benefit ratio of a drug to ensure that it does not change.

Companies must regularly analyse all the received data to ensure that the information given to consumers, patients and healthcare professionals corresponds to the most up-to-date information relating to any given product.

Collecting information relating to adverse events associated with a drug is a significant task. To outline the magnitude of the task, GSK alone, receives approximately 65,000 adverse events reports per year. Information on adverse events is collected from several sources, including:

- Unsolicited reports from health professionals and patients;
- Post-marketing trials or observational studies;
- Investigators who submit clinical study reports;
- Regulatory authorities;
- Medical and scientific literature;
- Newspapers and other media.

All information collected must be kept and entered into a global safety database. If any changes to the risk/benefit profile of a drug are detected, appropriate corrective action must be taken. This could include carrying out further clinical trials, modifying the prescribing information, communicating with physicians and

other healthcare providers or establishing a formal risk management programme. In some cases, it may be appropriate to stop a clinical trial or withdraw a product from the market. There are regulations outlining procedures for reporting on the safety of all drug products to regulatory bodies around the world.

Collecting and analysing data relating to adverse events	
AZN	<ul style="list-style-type: none"> • AZN has a team of over 500 clinical drug safety professionals dedicated to the task of ensuring that the company meets its commitment to drug safety. • Each of AZN's products, whether in development or on the market, have an assigned global drug safety physician who, supported by a team of drug safety scientists, is responsible for that product's continuous safety surveillance. • As an overriding principle, AZN strives to detect any new adverse reactions as early as possible and to update investigators, prescribers and volunteers/patients according to regulatory requirements. • AZN has an efficient network for collecting adverse event reports and for transmitting the information to the appropriate contact points within the company. • Processes and systems are in place to ensure regulatory compliance. • All reports concerning serious adverse events are scrutinised by a medically qualified individual. Cases that are judged to be potentially unsafe give rise to the appropriate ad hoc analyses of existing data for the project/product in question and possible ensuing actions. • Safety data from development projects, as well as marketed products, is periodically analysed to identify any significant new adverse reactions. Analysis is undertaken by both clinical and non-clinical sources. • The company has a defined process to ensure that significant new safety information is incorporated into product labelling. • Safety reporting is independent from clinical trials project teams and the commercial side of the business. Therefore the decision on whether there is a safety issue with data is made in an unbiased manner.
GSK	<ul style="list-style-type: none"> • GSK has policies that demand that an efficient and fully operational worldwide system for pharmacovigilance⁷ be maintained within the company. • The company has systems in place to collect data reports on adverse events of its products. When necessary, the company transmits the adverse event data to Global Safety Boards, forwards appropriate reports to the regulatory authorities and evaluates the safety data. The Global Safety Boards are made up of senior doctors and external consultants. The role of the Global Safety Boards is to advise and make decisions on the appropriate course of action regarding potential human safety issues. • Three central departments have responsibility for recording, investigating and evaluating adverse events and reporting these to the relevant regulatory authorities. These are: <ul style="list-style-type: none"> – The Global Clinical and Safety Pharmacovigilance team (GCSP). The team is responsible for the safety evaluation of all the company's pharmaceuticals and devices. – The Biologicals Clinical Safety and Pharmacovigilance Department. The department is responsible for the safety evaluation of the company's vaccines. – The Consumer Healthcare Product Safety Group. The group is responsible for the safety evaluation of consumer healthcare products. • The company has global labelling committees that review and approve the prescribing information for all products and ensures this is updated when appropriate. • The company has a policy requiring all staff to immediately report any issues that may find relating to the safety or quality of medicines.
SA	<ul style="list-style-type: none"> • Regular safety monitoring is conducted during all clinical trials. • Procedures are in place to ensure compliance with regulations and international standards as well as patient protection. • SA does not hire research companies to conduct trials but does so with its own resources. This way the company believes it has more control over the monitoring of clinical trials, expertise can be kept within the company and there are less intermediaries within the development process. This way, if there is any issue with a trial, it can be consolidated and the appropriate actions implemented as early as possible. • SA has a policy where a 'Data Monitoring Committee' monitors long-term trials. This advisory committee ensures that the trials follow the best ethical and methodological standards set out in international recommendations. • SA has pharmacovigilance divisions in each of its subsidiaries. These divisions are responsible for gathering, documenting, analysing and distributing information reported by patients, clinical trial investigators and healthcare professionals. They are also responsible for communicating information to local health authorities. • Alongside the pharmacovigilance divisions within the company's subsidiaries, it has two centralised pharmacovigilance units. One is dedicated to vaccines and the other is dedicated to all other drugs. These units collect all the information concerning a products safety that is available throughout the world. • All information relating to adverse events reported to the company is collected in a single database. • Operating procedures have been implemented to ensure compliance with current regulations relating to pharmacovigilance, regardless of the country of origin. • Immediate reporting of serious effects and periodical summary reports are prepared or validated by the central pharmacovigilance units. The reports are sent to all countries that market the product in question. • The same information is provided to all subsidiaries, marketing partners and health authorities. • The pharmacovigilance team is totally independent from the research and development side of the business.

⁷ Pharmacovigilance is the science and activities relating to the detection, assessment and understanding of adverse events or any other drug related issue.

• **Post trial availability of medicines**

If a trial participant derives a medical benefit from a drug that is being investigated, there may be medical rationale for that participant to continue to receive the drug before it is fully approved. Such a situation may occur if, for example, the illness being treated is life threatening or seriously debilitating, and there are no other treatments available. When this is the

case, post-trial treatment, with the investigational drug, could be provided with appropriate oversight. The issue of post trial treatment should be, where appropriate, addressed in pre-trial agreements, the trial protocol and as part of the informed consent process.

Post trial availability of medicines	
AZN	Information not obtained.
GSK	<ul style="list-style-type: none"> • Responsibility for post-trial provision of nationally licensed medicines used during a trial lies with governments as part of national healthcare programmes. • GSK-sponsored clinical trials of nationally licensed medicines will only be carried out if assurance is given that the healthcare system is able to take responsibility for the continued care of trial participants. • GSK-sponsored clinical trials of nationally licensed medicines will also only be carried out if assurance is given that, where there are no suitable alternatives, the drugs used in the trial will be made available after the trial to those patients who derived a measurable medical benefit. • In exceptional circumstances, if these nationally licensed medicines are not funded through the normal healthcare infrastructure, the medicines may be funded by GSK. This commitment is made pending the medicine being made available through the normal healthcare infrastructure or until the patient no longer requires them. • GSK recognises that there may be circumstances when patients who have derived a measurable medical benefit from a non-approved drug during a clinical trial should continue to receive the drug, even if it has not been approved and licensed for use. Under such circumstances, post-trial treatment with the drug will be provided with appropriate oversight, such as in a clinical trial setting. GSK commits to provide the drug for as long as necessary or until it is approved and licensed in that country. • The issue of post-trial treatment is addressed in pre-trial agreements, the trial protocol and as part of the informed consent process.
SA	<ul style="list-style-type: none"> • SA views it as essential that the population involved in the trial should benefit from the results after the trial is completed. • For long-term trials, it is normal behaviour for SA to provide continuing care and medication, post the trial, if the patient has derived a medical benefit. • When a vaccine clinical trial is carried out in a developing country, the infrastructure put in place for the trial should ideally continue to function after the trial in order to encourage the development of medical services over the long-term within the community involved.

• **Transparency**

There are important public health benefits associated with making clinical trial information more widely available to healthcare practitioners, patients, and others. Pharmaceutical companies have made significant progress over recent years in improving the transparency of data relating to clinical trials. Publicly available internet-based registration of ongoing clinical

trials can provide a stimulus for increased participation in clinical research. It can also provide an important reference point so interested parties can track the subsequent disclosure of clinical trial results. However, disclosure must maintain protections for individual privacy, intellectual property and contract rights, as well as conform to the regulations in relevant countries.

Transparency	
AZN	<ul style="list-style-type: none"> • AZN is committed to open communication of information regarding the company's clinical trials. • AZN provides appropriate information about its clinical trials on the website: www.astrazenecaclinicaltrials.com • The website enables information to be made public on all new and ongoing clinical trials that are sponsored by AZN. • The information currently available on the website covers core safety and efficacy registration trials for medicines approved since the formation of the company in 1999. Information on global trials completed since the formation of the company, and local trials completed since 1 January 2005, is also included.
GSK	<ul style="list-style-type: none"> • GSK makes the results of its clinical trials widely available to healthcare practitioners and others who use or evaluate the use of GSK medicines. • The company also publicly discloses information regarding ongoing trials. • GSK has an online Clinical Trials Register to supplement prescribing information and publications in scientific literature. The register contains results and protocol information from GSK-sponsored trials of marketed medicines. It also provides references to publications that have appeared in medical journals. It is accessible to anyone via the internet on: http://ctr.gsk.co.uk/welcome.asp.
SA	<ul style="list-style-type: none"> • SA is committed to increasing public access to clinical data through publication of trial details on the company's dedicated website. • Protocols for ongoing clinical studies have been accessible since September 2005. • The website includes information on trial results for drugs that are already on the market. • SA registers its clinical trials on the following web site: www.clinicaltrials.gov • SA publishes the results of its clinical trials on the following web site: www.clinicalstudyresults.org

All companies are subject to auditing procedures to ensure compliance with internal and external regulatory requirements.

**Comment from Newton's Pharmaceutical analyst:
Stephen Rowntree**

When a pharmaceutical company decides to initiate the development of a new drug, it is making an important commitment to its shareholders, the broader healthcare community and most importantly to future patients who may benefit from the work it undertakes.

The decision to begin development will be based on a number of years of prior scientific research and evaluation of a particular disease area. Once committed, the company faces an investment cycle that initially may stretch over a further 5-10 years. During this time the company must seek to demonstrate sufficient evidence of efficacy and a strong balance in favour of safety. It could cost the company in excess £500m to successfully bring the drug to a stage where it may be judged safe and effective enough to be launched to a broader patient population.

A decision to progress development is, therefore, not undertaken lightly and it is not a purely financial one. Development will also require the commitment of a potentially more scarce resource – the company's intellectual capital. It will involve many specialist teams that include amongst others, physicians, statisticians, project managers, manufacturing and regulatory experts. Each team will contribute to a specific area of development, be it patient safety, clinical evaluation or regulatory compliance.

Drug development is undertaken within a highly regulated framework, a framework that in Newton's view will only become more exacting going forward. Despite the high level of investment needed to demonstrate the effectiveness of a drug, the overriding principle of clinical development is the safety of those who volunteer to participate in trials and of future patients. Consequently, the decisions made to progress at the key stages of development are only made after close and careful scrutiny of the safety and effectiveness offered by the drug. These decisions are so important to the business that they are made or endorsed at the highest levels of management.

Demonstrable success in clinical development, as evidenced by the regular approval of new drugs, is one competitive advantage that we seek to identify when considering investments within the sector. Those companies that can achieve regular approvals are well placed to gain a return on their investment in drug development. As importantly, we see successful product approvals as an indication of an expertise and knowledge that in the long run should benefit not only shareholders, but also patients.

Conclusion

The future profitability of a pharmaceutical company is determined by the success of its new drug pipeline. Success and setbacks during drug research and development can cause significant movements in the share price of a company.

Regulations and standards of best practice define how pharmaceutical companies should undertake drug trials. Adherence to global standards of scientific research and development is necessary so there is confidence that data generated is clinically robust and reliable. This is important from an ethical perspective as well as from the perspective of the scientific community. Poorly conducted research misuses the efforts of scientists, resources and, most importantly, the time and commitment of trial participants and clinicians involved in the research.

The stringent regulatory environment surrounding human involvement in clinical trials is designed to ensure that patient safety is the number one priority. To be successful in drug development, companies must actively manage the commercial demands of business while taking time to remain scientifically and ethically vigilant during the research and development process.

Regulations are likely to become more demanding going forward as governments adopt an even stronger stance on patient safety. Companies must ensure they work with regulators to advance the risk/reward benefits offered by new drugs. One area that companies are focusing on improving is that of pharmacovigilance. By improving signal detection methodologies, companies can aim to detect potential adverse events well before the drug progresses to the stage where it is used by a large number of patients, thereby improving the safety of patients.

Next quarter

Next quarter's SRI report will look at some of the issues surrounding the world's water resources. Access to clean water is becoming increasingly constrained for many parts of the world. The report will look at some of the developing trends in this area. Risks that companies must manage, as well as business opportunities presented by such an environment, will be discussed.

Appendix 1: The Declaration of Helsinki

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
 22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
 23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
 24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.
 26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.
 27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
 28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
 29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote 1.
 30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote 2.
 31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
 32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
- Note 1: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
 - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
- All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.
- Note 2: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**
The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.
- The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.
9.10.2004.

SRI Activity

Please note that this activity log shows examples of SRI activity and engagement undertaken over the quarter. It is not an exhaustive list of all engagement. A complete list of how Newton voted on securities during the period is available upon request

BP

Subject: Operations in Alaska October 2006

BP has spent many years building a reputation as a leader in the areas of safety and environmental management. However, due to recent incidents such as the explosion in the Texas City refinery and the oil spill in Prudhoe Bay, Alaska, the company's commitments to corporate responsibility have been called into question.

On behalf of the Responsible Investors' Network, Newton wrote to BP requesting a meeting to discuss the problems the company had been experiencing in Prudhoe Bay. At this meeting, BP's Group Vice President for Existing Profit Centres and its Group Vice President for Safety & Operations gave an update on the cleanup of the oil spill that occurred in March 2006. Discussions were also had in relation to the ongoing investigation into the cause of the oil spill, the lessons learnt by the company and the changes being made to prevent such an incident reoccurring.

In response to the problems in Prudhoe Bay, the company increased its focus on the business processes that feed into safety systems. There is an increased emphasis on safety, managing people, planning for projects and maintenance of infrastructure. Every business must now deliver milestones according to a new 6-point plan. The company is also making efforts to improve the culture within the company by encouraging employees to be proactive in safety monitoring. Capital expenditure on maintenance has been increased and improvements to pipeline inspection methods have also been made.

In general, the company recognises that it needs to deliver some years of good performance to rebuild its track record in the areas of safety and operations. The company stated that safety and operational integrity continue to be a top priority going forward. Management remuneration has been adjusted to reflect this.

Newton took comfort in the efforts that the company has made to address the recent problems experienced. Newton also appreciated the company's openness when discussing these problems. Newton will continue to monitor BP's progress in this area.

Anglo American

Subject: Management of HIV/AIDS crisis October 2006

Newton attended an investor update on Anglo American's strategy for managing HIV/AIDS within its Southern African workforce. Anglo American estimates that HIV is prevalent amongst 23% of its Eastern and Southern African workforce. The company stated that prevention of new infections of HIV/AIDS is key in minimising the impact the virus has on employees and company operations. Therefore, the company vigorously pursues HIV prevention programmes. Whilst the company also offers treatment programmes, prevention of the spread of the virus is a significant area of focus. Anglo American has been collecting information on HIV/AIDS since 2003 and is now in a position to begin to assess the impact its HIV/AIDS strategy is having on company operations.

The company's strategy for managing HIV/AIDS revolves around encouraging all employees to know their HIV status. This can be achieved through undertaking voluntary counselling and testing (VCT). From here, treatment can be offered and wellness programmes for HIV positive employees can be implemented. Since 2003, the company has been offering anti-retroviral treatment (ART) for employees that have contracted HIV. By monitoring the number of employees who participated in VCT, the company is able to measure improvements and set targets for the future. The company's approach to managing HIV/AIDS is in line with the World Health Organisation's (WHO) priorities to reduce mortality of HIV/AIDS patients in low-income economies.

Anglo American is beginning to see some cost benefits of its HIV/AIDS management strategy. Alongside a reduction in drug costs, the group is seeing less employee absenteeism and is experiencing a reduction in HIV/AIDS related healthcare costs. The benefits of the company's strategy are beginning to outweigh the costs. Newton was encouraged to see Anglo American's proactive response to managing this issue.

Gildan

Subject: Responsible sourcing October 2006

Gildan is a Canadian tee-shirt manufacturer with low cost production facilities in Central America and the Caribbean. The offshore, low cost, production facilities allow the company to be competitive on price, whilst retaining attractive margins.

When assessing the company as a potential investment for Newton's client's, Gildan's responsible sourcing policy was discussed with the company's management. The management of Gildan are very aware of the need to responsibly manage the production and supply chain. The company has implemented a 'Social Compliance Programme' for labour practices and working conditions. This programme is designed to ensure that, at a minimum, all facilities comply with the company's internal Code of Conduct as well as local and international laws. The company also adheres to the codes of the Worldwide Responsible Apparel Production (WRAP) and Fair Labor Association (FLA). External suppliers to Gildan are also required to adhere to these codes.

Management is aware of the benefits that a well-structured corporate social responsibility policy can bring to its business. Therefore, the group has engaged the services of Verité, an international training, monitoring and auditing organisation. Verité is able to evaluate existing practices and make recommendations for improvement.

Newton took comfort in the company's strong strategies on the management of social and environmental matters.

First Group

Subject: Employee relations November 2006

Newton has been involved in ongoing discussions with First Group in relation to improving the company's policies on employee relations. In November, Newton met with the management of the company to discuss its progress with regard to this matter.

Following a review of its existing policies, the company had decided to incorporate the areas of Business Ethics, Safety & Security, Employment, Customer & Community and Environment, under one Corporate Social Responsibility (CSR) policy. Specific reference has been made to international standards as well as to the principle of freedom of association and collective bargaining. Newton found that the company had taken substantial efforts to ensure that its policies were understood and integrated into its daily operations. A training programme for local management, relating to the implementation and management of the adopted policies, had been undertaken. The company had also taken significant measures to train staff with regard to its policy on neutrality for union membership. Independent CSR auditors have also been employed to review and measure the company's CSR performance against best practice standards.

The group has shown it is committed to open communications with staff and stakeholders. Whilst the policies are in the early days of implementation, Newton is happy with the commitment that the company has made and will continue to monitor developments.

Attendance at corporate responsibility updates

Subject: Investor updates

Over the quarter, Newton attended investor updates on corporate responsibility by Sony, BHP Billiton, Xstrata, Eurofins Scientific, RWE, Petrobras, Centrica, Tesco and SABMiller.

Company Meeting Log: Q4 2006

During the quarter, Newton analysts and fund managers had individual meetings with the management of 284 companies to initiate or maintain dialogue around financial performance and/or responsible investment matters. The insights gained through this engagement are used when making investment decisions. Meetings were held with the following companies:

Abacus	Cemex	FKI
Abercrombie & Fitch	Centurion Energy International	FLSmith & Company
Acambis	China Comms Construction	Foster Wheeler
ACOM	China Over's Land & Invst	Futuris
ActivBiotics	Chinatrust Financial	Galaxy Entertainment
Agnico-Eagle Mines	Chloride	Genus
Airgas	Civica	GlaxoSmithKline
Alcatel-Lucent	Clapham House	GoIndustry
Alexon	Clerkenwell Ventures	Goldman Sachs
Alliance Boots	Clinphone	Great Southern Plantations
Alpha Bank	Cooper Companies	Gulliver International
Amadeus Fire	Coretronic	Hain Celestial
Amlin	Creston	Haitian International
Andhra Bank	Cyrela Brazil Realty	Halfords
Aqua America	Danske Bank	Halma
ARA Asset Management	Datamonitor	Hana Financial
Arriva	Debenhams	Hang Lung Properties
Arrow Energy	Detica	Harley-Davidson
Ashtead	Deutsche Boerse	Hengan International
Associated British Foods	DIC Entertainment	Hess
Asustek Computer	Digi.com	Hong Kong Land
Atkins	Diploma	Hopson Development
Aveva	D-Link	Hornby
Aviva	DNO	Hospira
Axa	Domestic & General	Hovnanian Enterprises
Babcock & Brown	Dong-A Pharmaceutical	HSBC
Babcock & Brown Infrastructure	Dragon Oil	Huntleigh Technology
Banca Monte Dei Paschi	DSM	Hysan Development
Bangkok Bank	DuPont	ICAP
Bango	Dyson	Imagination Technologies
Bank of the Philippine Islands	EDF Energies Nouvelles	Imperial Energy
BBA Aviation	Elisa	Informa
Beckman Coulter	EMAP	Inmet Mining
BG Group	Encana	InterContinental Hotels
BHP Billiton	Endesa Chile	International Paper
Block Shield	Enersis	Interserve
BrazAlta Resources	Enodis	Investec
Brewin Dolphin	Enterprise Inns	Isotron
Britvic	E-Pay Asia	Jackson Hewitt Tax Service
Brulines	Eurocastle Investment	Japan Tobacco
Brunswick	Famsa	Jollibee Foods
Burger King	Far Eastern Textile	Just Retirement x 2
Cable & Wireless	Fast Search & Transfer	K + S
Care UK	Findel	Keefe Bruyette & Woods
Carlsberg	First Choice Holidays	Kemira
Carnival	First Gen	Kia Motors
Carphone Warehouse	First Quantum Minerals	Kimberley Diamond
Catlin	First REIT	Kohls

KT & G	Premier Foods	Symrise
Laurel Pub	Premier Research	Syner Food
Lite-On Technology	Procter & Gamble	Synergy Healthcare
Lloyds TSB	Promise	Synexus Clinical Research
Lonza	ProPharma	Syngenta
Lotte Shopping	Protherics	Synthes
Lukoil	Pulmuone	Taiwan Semiconductor Mfrg
Macquarie MEAG Prime REIT	Punch Taverns	Takefuji
Mapletree Logistics	Qiagen	Tanfield
March Networks	QinetiQ	Tangent Communications
McDonalds	Quantmetriks Research	Teck Cominco
Melco PBL Entertainment	Quarto	Telstra
Midland Realty	Raffles Education	Tenaga Nasional
Mizuho Financial	RDF Media	Terna Participacoes
MobileOne	Renewable Energy	Thomson Intermedia
Mosaic	Renovo	Three Seven
Motech Industries	Republic Services	Timbercorp
Mothercare	Royal & Sun Alliance	Total
Motorola	Royal Caribbean Cruises	TotalCat
Mouchel Parkman	RR Donnelley & Sons	Touchstone
Nanya Technology	RWS	Tractebel Engineering
National Australia Bank	Ryanair	Tribal
National Grid	S1	Unilever
Natixis	SABMiller	United Overseas Bank
Navigant Consulting	Sage	UTi Worldwide
Neste Oil	Salamander Energy	Vanguard Environmental
Nicholas Piramal India	Sampo	Varian Medical Systems
Norfolk Southern	Scientific Games	Vectura
Northern Foods	Scottish & Southern Energy	Vertu Motors
Old Mutual	Severn Trent	Vocento
Open Business Club	SGS	Vodafone
Opsec Security	Shanghai Jin Jiang Int'l Hotel	VT Group
Oriflame Cosmetics	Shanks	Weatherford International
Oxford Instruments	Shed Productions	West Japan Railway
Paddy Power	Shui On Land	West Pioneer
Paragon	Shinhan Financial	Wimpey (George)
PayPoint	Singapore Tech Engineering	Wincanton
Pentair	Singapore Telecom	Wistron
PetroChina	Sinopec	Wolverhampton & Dudley Breweries x 2
Phoenixtec Power	Soitec	Woolworths
Pico Far East	Somero Enterprise	Woongjin Coway
Plasmon	Sonda	Woori Financial
Polynt	SSL International	YouGov
Powerleague	Statoil	Yuanta Core Pacific Securities
Powertech Technology	Sun Hung Kai Properties	Yuhan
Praktiker	Sunplus Technology	Zyxel Communications
Premier Farnell	Supporta	

In addition, the analysts and fund managers attended a large variety of external meetings arranged by the companies or by brokers and other research providers.

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