

## Background Briefing

### CONTENTS

Questions and Answers.....	2
Key Points:.....	2
Stem Cells for Safer Medicines.....	2
Q. 1    What is “Stem Cells for Safer Medicines”?.....	2
Q. 2    What is the purpose of the collaboration? .....	2
Q. 3    How much will this cost and how is it funded? .....	3
Q. 4    What is a public-private collaboration?.....	3
Q. 5    Why are you setting up such a collaboration? .....	3
Q. 6    Who are the Members? .....	3
Q. 7    How is the public-private collaboration being run? .....	4
Q. 8    Why create a company?.....	4
Q. 9    Why should pharmaceutical companies join? .....	4
Q. 10   Why is Government supporting this collaboration? .....	4
Q. 11   Are there other benefits? .....	4
Q. 12   How will research be facilitated? .....	5
Q. 13   What will happen in the pilot phase? Why do you need one? .....	5
Q. 14   What will happen beyond the pilot phase? .....	5
Stem Cells in Drug Discovery .....	5
Q. 15   Why use stem cells in developing new medicines?.....	5
Q. 16   How will the consortium allocate research projects?.....	6
Q. 17   Will the consortium fund research to use stem cells in therapies?.....	6
Q. 18   Will this research replace the use of animals in research? .....	6
Ethics Policy.....	6
Q. 19   What is the ethics policy .....	6
Q. 20   Why does this differ from the UK national position? .....	7
Science .....	7
Q. 21   What is predictive toxicology? .....	7
Q. 22   What are stem cells? .....	7
Q. 23   What type of tool can be made from stem cells?.....	7
Q. 24   What type of stem cells will you be using? .....	7
Q. 25   What is a stem cell line? .....	8
Q. 26   Why is this research important? .....	8

## QUESTIONS AND ANSWERS

### KEY POINTS:

- Stem Cells for Safer Medicines Ltd is a unique public-private collaboration with membership from UK Government and pharmaceutical companies.
- The initiative was developed as a direct follow up to the report of the UK Stem Cell Initiative, chaired by Sir John Pattison and published in November 2005.
- Initial research will enable the use of stem cells in early drug discovery by focusing on key scientific challenges and developing open standards and protocols.
- The long-term objective of the collaboration is to develop a bank of differentiated human cell lines to be used in early drug discovery to provide early identification and elimination of potential toxicity issues before clinical testing.
- Research will be funded in academe and participation by biotechnology SMEs encouraged.
- The initiative has real potential to assist with drug development, by identifying potential medicines that may have unexpected safety issues in clinical studies.
- The advantage for participating companies is that they will help define standards in line with their specific needs and be in the lead in utilising such technologies in the development of new medicines.

### STEM CELLS FOR SAFER MEDICINES

#### **Q. 1** *What is “Stem Cells for Safer Medicines”?*

Stem Cells for Safer Medicines is a public-private collaboration with membership from UK Government and pharmaceutical companies. Government includes participation of the Department of Health, the Department for Innovation, Universities and Skills, the Scottish Government, the Medical Research Council and the Biotechnology and Biological Sciences Research Council.

AstraZeneca, GlaxoSmithKline and Hoffman-La Roche are the founding private sector members of the consortium, but further members will be sought in the next 12 months during the pilot phase.

The consortium has been established as a not-for-profit company limited by guarantee called *Stem Cells for Safer Medicines Ltd*.

The consortium was developed following recommendation 1 in the report of the UK Stem Cell Initiative chaired by Sir John Pattison, which was published in November 2005<sup>1</sup>. In July 2006 the DTI and DH asked the ABPI to lead a Task Force to provide a more detailed report on the best way to progress a public-private partnership. This report was submitted in November 2006 and after agreement by all parties in December, the ABPI was asked to establish a collaboration working closely with both the private and public sectors.

#### **Q. 2** *What is the purpose of the collaboration?*

The objective of the company is:

- *To enable the creation a bank of stem cells, open protocols and standardised systems in stem cell technology that will enable consistent differentiation of stem cells into stable homogenous populations of particular cell types, with*

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<sup>1</sup> <http://www.advisorybodies.doh.gov.uk/uksci/>

*physiologically relevant phenotypes suitable for toxicology testing in high throughput platforms.*

The Stem Cells for Safer Medicines consortium is therefore interested in the potential of differentiating human embryonic stem cells into normal human cells, such as those in the liver (hepatocytes) and heart muscle (cardiomyocytes). If this is possible in a reproducible and consistent way, these cells could be used to evaluate the effect a potential new medicine has on specific cells, and to provide a more accurate prediction of drug metabolism and toxicity outcomes in man. We believe this would represent a significant step forward in increasing the human relevance of studies at an earlier stage of development of a potential new medicine and would help us to overcome the current limitations that a restricted supply of normal cells presents.

The consortium will draw upon scientific expertise within the pharmaceutical companies – especially in relation to safety assessment of new medicines – academic stem cell experts in the UK and third parties including biotechnology companies.

**Q. 3 How much will this cost and how is it funded?**

The initiative is split into an initial pilot phase – to address fundamental scientific challenges in relation to the differentiation and validation of stem cells into different cell types. For this first phase, £1,050,000 in funding will be available - £100,000 from each of the industry partners and £150,000 from each of the five Government departments and agencies (Department of Health, the Department for Innovation, Universities and Skills, the Scottish Government, the Medical Research Council and the Biotechnology and Biological Sciences Research Council). It is a matched funding arrangement with Government providing up to 72% of total funds, with the rest provided by contributions from the private sector partners.

During the first phase the Scientific Advisory Board – comprising academic and industry experts on stem cells and medicines safety assessment – will be preparing a more detailed road map for the full programme: a further four years. The road map will identify the scientific challenges of developing the technology from small scale differentiation of stem cells to validated and consistent high throughput platforms that can be used routinely in drug discovery and development.

**Q. 4 What is a public-private collaboration?**

Public-private collaboration is where government and its agencies can work together with industry and third parties; in this instance to fund research of mutual interest and with shared objectives.

**Q. 5 Why are you setting up such a collaboration?**

In the March 2005 budget, the Chancellor announced the establishment of the UK Stem Cell Initiative (UKSCI), led by Sir John Pattison with members from both academic and commercial sectors, charged with developing a strategy to make the UK a global leader in stem cell research. The UKSCI report, published in December 2005<sup>1</sup>, recommended that part of the strategy should be the establishment of a partnership to develop predictive toxicology tools from stem cell lines. The Government accepted the recommendation and, following round table discussions with stakeholders throughout 2006, asked ABPI to report on how to deliver this.

**Q. 6 Who are the Members?**

The founding members from Government are the Department of Health, the Department for Innovation, Universities and Skills, the Scottish Government, the Medical Research Council and the Biotechnology and Biological Sciences Research Council. The pharmaceutical industry partners are GlaxoSmithKline, AstraZeneca and Hoffman-La Roche. *Stem Cells for Safer Medicines* is open to new members and a number of other companies are considering joining.

**Q. 7 *How is the public-private collaboration being run?***

The collaboration has been set up as a company limited by guarantee, rather than by shares. Any income from the company's activities will be used to fund future research rather than being distributed to its members. It has a Board, comprising of a Chairman, CEO, non-Executive Directors from the Founding Members and the Chairman of the Scientific Advisory Board, which comprises of academic and industry scientific experts in stem cell research and the safety assessment of new medicines. Strategic direction will be supplied by the Members and the Scientific Advisory Board.

The consortium is open to new members and these will be actively sought during the first year. A number of companies, in addition to those established as founding members, are very interested in the work and are considering how they can participate.

In addition we will be seeking to engage smaller companies in specific projects – this is very important and will provide benefit to them by access to cross-company industry expertise.

**Q. 8 *Why create a company?***

A not-for-profit company provides a good mechanism for the consortium to fund research projects, widen membership and manage a broad collaboration. Beyond the first phase of funding, financial support could also be sought from alternative sources, such as European research programmes.

**Q. 9 *Why should pharmaceutical companies join?***

There are a number of advantages in joining for members including:

- having the opportunity to influence the direction of the work;
- making real progress in early drug safety screening that will create standards for tools of direct relevance for human safety;
- sharing scientific expertise and knowledge as part of the SC4SM network;
- spreading the risk in what is a significant research and technology challenge; and
- being able to adopt the technologies rapidly to assist with drug discovery.

**Q. 10 *Why is Government supporting this collaboration?***

There are clear benefits in terms of UK Government strategy and for the public good that justifies Government support:

- in the longer term, if successful this will lead to improved patient safety, in clinical trials and in clinical practice;
- enhancing basic research capability in the UK and maintaining the UK's global lead in stem cell research; and
- to help speed the development of new medicines to patients, though this pre-competitive research collaboration.

**Q. 11 *Are there other benefits?***

Yes. The benefits to the UK of such an initiative may well be substantial, including:

- enhancing academic-industry collaboration;
- acting as a focus for UK stem cell expertise and international experts in safety assessment;
- opening up exploitation opportunities for small and medium enterprises, who will be encouraged to engage with the collaboration; and

- enhancing UK competitive advantage to retain and attract more pharmaceutical companies to locate their research and development and safety assessment activities in the UK, promoting future inward investment.

**Q. 12 *How will research be facilitated?***

Calls for proposals will be made, applications received from research groups, and selections and funding made. The first call is published with the intention to run a one-year research programme focused on key scientific challenges that were identified in a report to Government by the ABPI in late 2006. A further application was submitted to the then Department of Trade & Industry for consideration under the Technology Strategy Programme.

The Scientific Advisory Board will develop the programme of long-term scientific research to prepare calls for research proposals against set objectives and also, in the first year, to define the longer term strategy for the consortium.

**Q. 13 *What will happen in the pilot phase? Why do you need one?***

The initial pilot phase will concentrate on liver cells and has two priorities: first the consortium has identified a number of scientific hurdles in relation to the differentiation of stem cells into liver cells (hepatocytes); second, further work will need to be done to map out the detailed scientific and technical programme for the remaining four years.

The first year will also allow the consortium to build the networks amongst the scientific experts in the companies academe and SMEs. This will be the first time where companies' global expertise in medicines safety assessment and stem cell scientists have been brought together to work so closely on a project in a consortium type approach.

Although the stem cell research funded will be focused in the UK, we will try to facilitate the participation of non-UK experts and collaborators.

The pilot phase will run to late 2008 or early 2009, depending upon how quickly research programmes can be initiated.

**Q. 14 *What will happen beyond the pilot phase?***

If key scientific hurdles to differentiate stem cells into liver cells are achieved, then further work will be required to:

- understand physiological indicators of the cells
- identify key indicators of toxicity to develop standards that can be used in high throughput screens
- scale up production protocols of cell lines and integrate into high throughput cell assay systems
- screening of multiple compounds of known toxicity, again to create open standards that can be used in benchmarking and validating the cells lines in safety screens.

## **STEM CELLS IN DRUG DISCOVERY**

**Q. 15 *Why use stem cells in developing new medicines?***

The attrition of medicines in clinical studies remains a critical issue for pharmaceutical companies. Unexpected safety issues remain a key reason for failure in first in man and larger late-stage clinical studies. While animals continue to give essential information on safety, efficacy and dosing calculations for first in man studies, human cell based assays offer the opportunity of early identification of those that are likely to fail when first tested in volunteers or patients.

**Q. 16 How will the consortium allocate research projects?**

This will mostly be by open competitive tendering by scientific groups. The Scientific Advisory Board will advise on the calls for proposals which will be approved by the Members of the company. The SAB will be especially important in mapping out the calls for research proposals beyond the pilot phase.

In later stages company laboratories, working in partnership with academics and third party organisations, will carry out research to assist identifying the standards and protocols that would be useful for drug discovery research. Validating these technology platforms, standards and protocols will be critical in realising the vision for the project.

**Q. 17 Will the consortium fund research to use stem cells in therapies?**

No, the collaboration is only interested in developing stem cells for early screening in predictive toxicology to assess the safety of medicines. However, the knowledge developed in the programme could also be relevant to the use of Stem Cells in medicine particularly since validation of differentiation protocols is a common issue.

**Q. 18 Will this research replace the use of animals in research?**

The concept is not directly to replace the use of animals in safety testing and for the foreseeable future they will remain an essential element of developing a new medicine. Animals research will continue to give critical information on safety and efficacy of candidate medicines in whole animals (as opposed to organs, which the stem cell assays are akin to), as well as provide results that allow the first dose in man to be calculated safely.

However by screening out compounds with possible human safety issues early in the drug discovery process, the number of animals used in research for compounds that fail in clinical studies should be reduced and refine the use of animals by focusing their use only in areas where animal data adds value.

**ETHICS POLICY****Q. 19 What is the ethics policy**

Companies operate in a global environment and must take account of their employees, public and patient views, not just in the UK but around the world.

The UK is a global leader in the regulation of human stem cells research and has a strong ethical framework in which companies can operate. In particular the Human Fertilisation and Embryology Authority and UK Stem Cell Bank leads the world in overseeing the creation and banking of stem cells lines. This is a key advantage for the UK.

The full ethics policy is available on the [www.sc4sm.org](http://www.sc4sm.org). An independent Ethics Advisory Board will be developed to advise the consortium on its policy and the impact of new technologies and advances – the policy will need to evolve as science and technology progresses and the social and political environment changes. Understanding employee, public and patient perception across the world is an important element.

The collaboration will operate in accordance with the standards established by UK Stem Cell Bank and will only use lines already banked, or registered to be banked, in the facilities. Specifically, the guiding principles of the Ethics policy are:

“Research sponsored by or co-ordinated through the Stem Cells for Safer Medicines consortium will only utilise stem cell lines that are fully compliant with

the following criteria and reflect the conditions for inclusion in the NIH Registry<sup>2</sup> in the USA and the UK Stem Cell Bank<sup>3</sup>.

- The stem cells must have been derived from adult, cord-blood sources or unused fertilised eggs created for reproductive purposes (embryonic stem cells).
- Fully informed consent must have been obtained prior to the donation of a fertilised egg or other source of stem cell lines for scientific research.
- There must be no financial or other inducements for donation of a fertilised egg, cord-blood or source of adult stem cells.
- Donation, management and distribution must comply with guidance and ethical codes in the countries from which the stem cell lines were sourced.
- Only stem cells lines already banked or registered to be banked should be used.
- Prior to any research utilising cell lines derived from human embryonic stem cells, there must be a clearly defined purpose to increase knowledge about serious disease and/or to apply such knowledge in developing treatments for serious disease.
- Stem Cells for Safer Medicines and research funded by the consortium will not use human-animal hybrid cloned stem cell lines or cytoplasmic hybrids.”

**Q. 20** *Why does this differ from the UK national position?*

Companies operate in a global environment and must take account of their employees, public and patient views, not just in the UK but around the world. Therefore the Ethics Policy reflects the principles set out by the companies.

## SCIENCE

**Q. 21** *What is predictive toxicology?*

Predictive toxicology is the term used to describe pre-clinical experiments to ascertain any toxic effects of drugs to guide subsequent research in patients or healthy volunteers.

**Q. 22** *What are stem cells?*

The human body contains different types of cells that usually have a specific purpose (e.g. liver cells, brain cells etc). Stem cells are different in that they have not yet developed in to a specific type of cell. If we can create liver cells in a consistent manner, then these could be used in *in vitro* assays – high throughput screens to test a large number of compounds in early drug discovery.

**Q. 23** *What type of tool can be made from stem cells?*

It is hoped that we will be able to produce standardised systems in stem cell technology leading to stem cells to be consistently developed into stable populations of particular cell types, especially liver cells. These can then be used in tests and trials to predict what toxicity effects new medicines might have on humans.

**Q. 24** *What type of stem cells will you be using?*

During the pilot phase, the work will look to develop a tool to predict the toxicity of new medicines, utilising human embryonic stem cells that are already banked with the UK

<sup>2</sup> <http://stemcells.nih.gov/research/registry/>

<sup>3</sup> <http://www.ukstemcellbank.org.uk/>

Stem Cell Bank. Any cells used must comply with the Ethics Policy and research groups will be audited to ensure this has been followed.

Liver cells are the most relevant to toxicity for most medicines and therefore in the first year, those most likely to be able to be differentiated into liver cells (hepatocytes) will be the most relevant.

**Q. 25 *What is a stem cell line?***

A stem cell line is a stable population of stem cells maintained in a culture for successive generations. Once the cell line is created no further samples are required from sources for stem cells.

Not all stem cells are equal though. Some can only give rise to particular cell types (for example bone marrow contains stem cells that can only give rise to blood cells, these are adult stem cells). Others, such as those sourced from human embryonic stem cells typically give rise to a much wider range of cell types. It has been very difficult to derive liver cells from adult sources.

A number of research groups around the world are looking to identify alternative sources of stem cells, such as from umbilical cord blood. However it is not the intention of the consortium to utilise these at the current time. The Scientific Advisory Board will keep relevant developments under review and the Ethics Advisory Board, when created in 2008, will advise on the framework in which such cells lines could be considered in the longer-term scientific strategy.

**Q. 26 *Why is this research important?***

If stem cells can be developed in a consistent way to enable their use in predicting such adverse effects then failures could be detected at a lot earlier stage, reducing investment loss and improving the safety of medicines for patients in the longer term.

Pharmaceutical companies invest huge amounts of money in developing new medicines. Due to the nature of the development process, much of this investment can be lost if unexpected reactions occur when candidate medicines are first tested in man. Such failures mean that the investment is not successful.