EXPLANATORY MEMORANDUM TO

THE MEDICINES FOR HUMAN USE (ADVANCED THERAPY AND MISCELLANEOUS AMENDMENTS) REGULATIONS 2010

2010 No. 1882

1. This explanatory memorandum has been prepared by the Department of Health and is laid before Parliament by Command of Her Majesty.

This memorandum contains information for the Joint Committee on Statutory Instruments.

2. Purpose of the instrument

Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products (the ATMP Regulation) entered into force on 30 December 2007 and applied from 30 December 2008. The Regulation is directly applicable in Member States. This instrument principally implements certain enforcement obligations laid down in the Regulation and the arrangements that will apply in the UK under the hospital exemption scheme under the Regulation and laid down in Article 3 (7) of Directive 2001/83/EC.

2.1 This instrument also implements Commission Directive 2009/120/EC of 14 September 2009 of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products (ATMPs). 2009/120/EC flows from the ATMP Regulation and introduces the specific technical requirements that will apply to ATMPs and which are mentioned in Recital 12 in the ATMP Regulation.

2.2 The instrument also gives effect to the decision of the European Court of Justice in C-143/06 Ludwigs-Apotheke München Internationale Apotheke V Juers Pharma Import–Export GmbH by permitting price lists to be issued that do not make representations in respect of a product supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patient on his direct personal responsibility, in order to fulfil the special needs of those patients. The instrument also amends the Medicines for Human Use Clinical Trials Regulations so that the procedures for giving an ethics committee opinion and for authorising clinical trials apply to trials involving tissue engineered products in the same way that they apply to trials involving gene therapy and somatic cell therapy.

3. Matters of special interest to the Joint Committee on Statutory Instruments

There are no matters of special interest.

4. Legislative Context

4.1 This instrument is made under Section 2 (2) of the European Communities Act 1972 and implements the ATMP Regulation and Commission Directive 2009/120/EC. The Parliamentary scrutiny committees were kept fully informed of progress when the

ATMP Regulation was under negotiation and scrutiny clearance was granted before final agreement was reached on the Regulation in June 2007.

5. Territorial Extent and Application

5.1 This instrument applies to all of the United Kingdom.

6. European Convention on Human Rights

As the instrument is subject to negative resolution procedure and does not amend primary legislation, no statement is required.

7. Policy background

- ***What is being done and why***

7.1 The ATMP Regulation entered into force on 30 December 2007 and applied from 30 December 2008. The Regulation is a new piece of European legislation and groups together three categories of medicinal products called ATMPs – those categories are tissue engineered products, gene therapy and somatic cell therapy products. The Regulation does not change the definition of medicinal product but introduces specific requirements for ATMPs. The overall aim of the Regulation is to improve access to ATMPs by increasing the research, development and authorisation of ATMPs. The lack of a clear European regulatory framework had led to considerable uncertainty in the sector. Operators found that in the absence of a clear cut regulatory regime they were unable to attract sufficient investment. This instrument implements legislative revisions which are required to ensure the requirements laid down in the Regulation can be enforced in the UK including the national arrangements that will apply under the hospital exemption scheme. Products categorised as ATMPs fall under the centralised European marketing authorisation procedure (except where the exemption applies) which is granted by the European Medicines Agency (EMA).

The exemption is for ATMPs which are prepared on a non routine basis and used within the same Member State in accordance with a medical prescription for an individual patient. The Regulation stipulates that manufacture of ATMPs under the hospital exemption must be authorised by the Member State. In addition, traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to ATMPs for which a centralised marketing authorisation would be granted by the EMEA. The specific parameters that are laid down in the Regulation for the exemption are intended to ensure minimum standards. The MHRA considered whether additional provisions were necessary and considered that requirements in respect of patient information and advertising are necessary under the exemption. Those additional provisions are also reflected in the SI. The exemption was included in recognition of the small scale and developmental nature of activity carried out in some hospitals which argued for a degree of flexibility over the nature of regulatory requirements. The Medicines and Healthcare products Regulatory Agency (MHRA) is

responsible for the regulatory requirements under the exemption in the UK and this instrument implements those requirements.

Commission Directive 2009/120/EC flows from the ATMP Regulation (1394/2007) which applied from 30 December 2008. The Regulation does not change the definition of medicinal product but introduces specific requirements for ATMPs. The detailed technical requirements that will apply to ATMPs are introduced by 2009/120/EC which amends part IV of Annex 1 to Directive 2001/83. Part IV of Annex 1 includes updated definitions for gene therapy and somatic cell therapy products and lays down the clinical documentation that must be provided when market authorisation applications are submitted.

- ***Consolidation***

7.2 A consolidation of the 1968 Medicines Act is currently underway so there may be some implications in the future.

8. Consultation outcome

8.1 The MHRA consulted extensively with a range of stakeholders during the negotiations on the ATMP Regulation and since the Regulation was agreed. The case for the Regulation was well supported by UK stakeholders. Hospitals, research interests and small spin off companies were strongly supportive of the hospital exemption. A public consultation exercise on the Regulation and the UK's proposed national arrangements under the hospital exemption scheme was launched in July 2008. 10 responses were received. Most respondents were supportive of the hospital exemption scheme and the proposed requirements. Some respondents said it would be important for MHRA to issue guidance on the new regulatory arrangements. Further information about the results of the consultation exercise is included in the impact assessment (IA).

The European Commission consulted on the proposed revisions to Annex 1 of 2001/83 which are introduced by Commission Directive 2009/120/EC.

9. Guidance

9.1 The MHRA consulted on draft guidance on the arrangements that will apply under the hospital exemption scheme in July 2009. Guidance and information on the new Regulation has been published on the MHRA website. A programme of seminars/events to raise awareness of the new regulatory requirements will take place in 2010. The EMA has published guidance for those ATMPs that would fall under the centralised authorisation procedure.

10. Impact

10.1 The impact of the hospital exemption scheme on business, charities or voluntary bodies is expected to be low. While there will be some costs associated with the provisions under the exemption scheme, the overall effect of the exemption should be to reduce costs that hospitals would otherwise incur were they subject to the full

provisions of the Regulation, including the requirement for a centralised marketing authorisation.

10.2 The impact on the public sector is expected to be minimal though there may in the future be an indirect impact on public health budgets through pricing and reimbursement of ATMPs.

10.3 An IA is attached to this memorandum which covers the UK's hospital exemption scheme arrangements. A separate IA has not been prepared for Commission Directive 2009/120/EC. A full IA for the main ATMP Regulation was published by the MHRA in October 2007; a copy of which is also attached.

11. Regulating small business

11.1 The legislation applies to small business. In the UK, producers of ATMPs are typically small spin-off companies emerging from university research in specialist hospitals, charities and a few larger companies. The hospital exemption was included in the Regulation in recognition of the small scale, developmental nature of activity carried out in some hospitals for which a degree of flexibility from the requirements from a centralised marketing authorisation would be necessary. However, it was recognised that safety standards would be important given the potentially high risk nature of some ATMPs and so the Regulation requires Member States to put in place a number of safeguards within certain parameters to protect public health. In addition, a range of incentives including reduced fees are available to small and medium sized enterprises (SMEs) who apply to the EMA for a centralised marketing authorisation.

12. Monitoring & review

12.1 The European Commission has given a commitment to review the ATMP Regulation including the hospital exemption within five years of the Regulation coming into force at which time the Commission will publish a report on the operation of the legislation. The MHRA will monitor activities under the UK's exemption scheme and proposes to seek the views of stakeholders in advance of the date set for the Commission's review to identify UK experience of operating under the exemption and the Regulation.

13. Contact

Caroline Brennan at the MHRA (telephone number 020 7084 2525 or email address caroline.brennan@mhra.gsi.gov.uk) can answer any queries regarding the instrument.

Title:	Impact Assessment (IA)
Impact assessment of the UK's proposed national arrangements under the hospital exemption laid down in Regulation (EC) No 1394/2007	**IA No:**
Lead department or agency: MHRA	**Date:** 01/07/2010
	Stage: Final
	Source of intervention: EU
Other departments or agencies:	**Type of measure:** Secondary legislation
	Contact for enquiries: Caroline Brennan MHRA

Summary: Intervention and Options

What is the problem under consideration? Why is government intervention necessary?

Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 entered into force on 30 December 2007. The main provisions contained in the Regulation are at Annex A. Under the Regulation, there is an exemption for advanced therapy medicinal products (ATMPs) which are prepared on a non routine basis and used in a hospital in accordance with a medical prescription for an individual patient. There is a requirement for Member States to put in place national arrangements for the exemption, within parameters laid down in the Regulation. This IA sets out the UK's proposed legislative provisions for a national scheme.

What are the policy objectives and the intended effects?

The exemption was included in the Regulation in recognition of the small scale, iterative developmental nature of activity carried out in some hospitals for which a degree of flexibility from the requirements for a centralised marketing authorisation (MA) would be necessary. However, it was recognised that safety standards would be important given the potentially high risk nature of some ATMPs and so the Regulation requires that Member States put in place a number of safeguards at national level within certain parameters in order to protect public health. Member States must ensure that the standards applicable to ATMPs made and used under the exemption are equivalent to those provided for at Community level in respect of ATMPs which would be centrally authorised under the Regulation.

What policy options have been considered? Please justify preferred option (further details in Evidence Base)

Option 1 - do nothing.
Option 2 - introduce voluntary arrangements for provisions that would apply under the scheme.
Option 3 - introduce specific national requirements in legislation within the parameters laid down in the Regulation.
Option 4 - introduce specific national requirements in legislation within the parameters laid down in the Regulation but also including some additional features not specifically required by the Regulation in order to protect public health and to ensure consistency with other regulatory provisions. Option 4 is the only approach that would put in place appropriate safeguards to protect public health and ensure consistent, coherent regulation and is considered the preferred option.

When will the policy be reviewed to establish its impact and the extent to which the policy objectives have been achieved?	It will be reviewed 12/2012
Are there arrangements in place that will allow a systematic collection of monitoring information for future policy review?	Yes

SELECT SIGNATORY Sign-off For final proposal stage Impact Assessments:

I have read the Impact Assessment and I am satisfied that (a) it represents a fair and reasonable view of the expected costs, benefits and impact of the policy, and (b) the benefits justify the costs.

Signed by the responsible SELECT SIGNATORY: Earl Howe..... Date: 21st July 2010.....

Summary: Analysis and Evidence

Policy Option 1

Description:

Option 4: Introduce specific national requirements in legislation within the parameters laid down in the Regulation as well as some additional patient information provisions

Price Base Year	PV Base Year	Time Period Years	Net Benefit (Present Value (PV)) (£m)		
			Low: Optional	**High:** Optional	**Best Estimate: Not know**

COSTS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low	Optional		Optional	**Optional**
High	Optional		Optional	**Optional**
Best Estimate	Not known		Not known	**Not known**

Description and scale of key monetised costs by 'main affected groups'

Other key non-monetised costs by 'main affected groups'

There will be some costs attributable to hospitals/operators meeting the proposed requirements. There may in the future be an indirect impact on public health budgets through pricing and reimbursement of ATMPs. Further information is outlined in the document.

BENEFITS (£m)	Total Transition (Constant Price)	Years	Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	Optional		Optional	**Optional**
High	Optional		Optional	**Optional**
Best Estimate	Not known		Not known	**Not known**

Description and scale of key monetised benefits by 'main affected groups'

Other key non-monetised benefits by 'main affected groups'

The costs to hospitals/operators will be lower than those that will apply to ATMPs that will be authorised under the Regulation for which the full provisions laid down in the Regulation will apply. The scheme will ensure appropriate safeguards are in place to protect public health. Further information is outlined in the document.

Key assumptions/sensitivities/risks **Discount rate (%)**

The hospital exemption scheme introduces certain provisions which are outlined in this document. The overall effect of the exemption should be to reduce costs that hospitals would otherwise incur were they subject to the full provisions of the Regulation, including the requirement to obtain a centralised European marketing authorisation. This is an innovative and developing area and based on current intelligence the current volume of activity is very low. It will take a number of years for new innovative ATMPs to be developed. It will therefore take some time to make a robust assessment of the regulatory impact.

Impact on admin burden (AB) (£m):			Impact on policy cost savings (£m):	In scope
New AB:	**AB savings:**	**Net:**	**Policy cost savings:**	Yes/No

Enforcement, Implementation and Wider Impacts

What is the geographic coverage of the policy/option?			United Kingdom		
From what date will the policy be implemented?			July 2010		
Which organisation(s) will enforce the policy?			MHRA		
What is the annual change in enforcement cost (£m)?			Negligible		
Does enforcement comply with Hampton principles?			Yes		
Does implementation go beyond minimum EU requirements?			Yes		
What is the CO_2 equivalent change in greenhouse gas emissions? (Million tonnes CO_2 equivalent)			**Traded:** N/A	**Non-traded:** N/A	
Does the proposal have an impact on competition?			No		
What proportion (%) of Total PV costs/benefits is directly attributable to primary legislation, if applicable?			**Costs:** N/A	**Benefits:** N/A	
Annual cost (£m) per organisation (excl. Transition) (Constant Price)	**Micro**	**< 20**	**Small**	**Medium**	**Large**
Are any of these organisations exempt?	No	No	No	No	No

Specific Impact Tests: Checklist

Set out in the table below where information on any SITs undertaken as part of the analysis of the policy options can be found in the evidence base. For guidance on how to complete each test, double-click on the link for the guidance provided by the relevant department.

Please note this checklist is not intended to list each and every statutory consideration that departments should take into account when deciding which policy option to follow. It is the responsibility of departments to make sure that their duties are complied with.

Does your policy option/proposal have an impact on…?	**Impact**	**Page ref within IA**
Statutory equality duties[1] Statutory Equality Duties Impact Test guidance	No	14
Economic impacts		
Competition Competition Assessment Impact Test guidance	No	14
Small firms Small Firms Impact Test guidance	Yes	13
Environmental impacts		
Greenhouse gas assessment Greenhouse Gas Assessment Impact Test guidance	No	14
Wider environmental issues Wider Environmental Issues Impact Test guidance	No	14
Social impacts		
Health and well-being Health and Well-being Impact Test guidance	No	
Human rights Human Rights Impact Test guidance	No	14
Justice system Justice Impact Test guidance	No	
Rural proofing Rural Proofing Impact Test guidance	No	14
Sustainable development Sustainable Development Impact Test guidance	No	14

[1] Race, disability and gender Impact assessments are statutory requirements for relevant policies. Equality statutory requirements will be expanded 2011, once the Equality Bill comes into force. Statutory equality duties part of the Equality Bill apply to GB only. The Toolkit provides advice on statutory equality duties for public authorities with a remit in Northern Ireland.

Evidence Base (for summary sheets) – Notes

Use this space to set out the relevant references, evidence, analysis and detailed narrative from which you have generated your policy options or proposal. Please fill in **References** section.

References

Include the links to relevant legislation and publications, such as public impact assessment of earlier stages (e.g. Consultation, Final, Enactment).

No.	Legislation or publication
1	Regulation (EC) No 1394/2007 (http:ec.europa.eu/enterprise/pharmaceuticals/indexen.htm
2	Final regulatory impact assessment for the Regulation on advanced therapy medicinal products published by the MHRA in October 2007 (http://www.dh.gov.uk)
3	Impact assessment published by the European Commission in November 2005 (http://ec.europa.eu/enterprise/pharmaceuticals/indexen.htm)
4	

+ Add another row

Evidence Base

Ensure that the information in this section provides clear evidence of the information provided in the summary pages of this form (recommended maximum of 30 pages). Complete the **Annual profile of monetised costs and benefits** (transition and recurring) below over the life of the preferred policy (use the spreadsheet attached if the period is longer than 10 years).

The spreadsheet also contains an emission changes table that you will need to fill in if your measure has an impact on greenhouse gas emissions.

Annual profile of monetised costs and benefits* - (£m) constant prices

	Y_0	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9
Transition costs										
Annual recurring cost										
Total annual costs										
Transition benefits										
Annual recurring benefits										
Total annual benefits										

* For non-monetised benefits please see summary pages and main evidence base section

Evidence Base (for summary sheets)

1. TITLE OF PROPOSAL

Implementation of the exemption scheme as laid down in Article 28 (2) of Regulation No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. This impact assessment covers the provisions that will apply in the UK under the exemption laid down in the Regulation. A partial impact assessment was published in July 2008 when the MHRA consulted on the proposed provisions that would apply under the exemption in the UK. A final regulatory impact assessment (RIA) in respect of the general Regulation was published in October 2007.

2. PURPOSE AND INTENDED EFFECT OF MEASURE

(i) The objective

The Regulations [2] will implement the hospital exemption scheme in the UK. Under Regulation 1394/2007, there is an exemption for ATMPs which are prepared on a non routine basis and used in a hospital in accordance with a medical prescription for an individual patient but there is a requirement for Member States (the MHRA for the UK) to put in place national arrangements within certain parameters set out in the Regulation. This exemption was included in recognition of the fact that activity in this new innovative sector is typically iterative, developmental and on a very small scale.

(ii) Background

Regulation 1394/2007 was agreed at the Health Council in May 2007 and entered into force on 30 December 2007. The Regulation applied from 30 December 2008. The overall aim of the Regulation is to improve access to ATMPs by increasing the research, development and authorisation of gene therapy, somatic cell therapy and tissue engineered products (TEPs). The specific objectives are:

- to protect public health;
- to provide legal certainty in order to foster development in the European bioscience industries; and
- to harmonise market access in the European Union by establishing a comprehensive regulatory framework for ATMPs.

Under the Regulation, TEPs falling within the definition of medicinal product will be grouped alongside gene therapy and somatic cell therapy medicinal products and called ATMPs. ATMPs that fall under the definition will be centrally authorised by the European Medicines Agency (EMEA). The first two categories are already covered by existing European medicines legislation. The Regulation does not change the definition of a medicinal product but introduces specific requirements for ATMPs.

Article 28 (2) of the Regulation amends Article 3 of Directive 2001/83/EC and includes an exemption for ATMPs which are prepared on a non routine basis and used within the same Member State in a hospital under the professional responsibility of a medical practitioner in order to comply with an individual prescription for an individual patient. Under the Regulation, Member States are required to introduce national measures for ATMPs made and used under the exemption. The agreed exemption was included in the Regulation in recognition of the fact that there should be some flexibility in terms of requirements for small scale operators including

[2] The Medicines for Human Use ATMP Regulations, etc…

hospitals in this area. Consultation with stakeholders in the UK indicated that there are currently a small number of hospitals collaborating with other parties in a range of different arrangements in this area.

(iii) Rationale for Government intervention

The UK Government supports research and development on the basis that this activity can generate financial gains not only to the parties undertaking the research but also to others that benefit through the provision of new knowledge, technologies, or processes created. The literature on R&D suggests that the private rate of return to R&D may equal as little as a quarter of the social returns to R&D as a result of such 'spillovers'[3]. For this reason, the Government tries to ensure that the right conditions are put in place to support private sector R&D.

The MHRA received strong and consistent feedback from UK interested parties that the market for ATMPs cannot develop and function without effective Government intervention in the form of regulation. This feedback was consistent with the feedback received by the European Commission in their consultations with stakeholders. Operators have found that in the absence of a clear cut regulatory regime they are unable to attract sufficient investment – the scientific risks of investing in the development of innovative new medical products will usually be large anyway, so from an investor's perspective it is imperative that the regulatory regime facilitates an effective market for successful innovations. The development of innovative therapies based on bioscience is an important priority for the UK and more widely for the EU and there is a clear rationale for the Government to take measures that will help the market to work effectively and to support socially beneficial R&D. So far as public health is concerned there is a range of possible public health risks associated with ATMPs. The risk to public health is high if ATMPs are made in situations where there is inadequate expertise or investment. Of greatest concern is exposure to a wide range of infectious agents arising from the donor or from contamination during processing.

The exemption for ATMPs prepared on a non-routine basis and used in a hospital within the same Member State was included in the Regulation in recognition of the fact that there should be some flexibility in terms of requirements for small scale operators including hospitals in this area. It was recognised that it would not be appropriate for the full provisions of the ATMP Regulation to apply in such situations but certain requirements were deemed necessary in the interests of patient safety (manufacturing/quality, traceability and pharmacovigilance).

(iv) The proposal

Under the Regulation, there is an exemption for ATMPs which are prepared on a non routine basis and used in a hospital in accordance with a medical prescription for an individual patient. Manufacture of ATMPs which are made and used under the hospital exemption scheme must be authorised by the Member State. Under the scheme traceability, quality and pharmacovigilance standards must be equivalent to ATMPs for which a centralised market authorisation would be granted by the EMEA.

The text for the exemption reads:

> *Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual prescription for a custom-made product for an individual patient.*

[3] A summary of the empirical literature is provided by BERR at http://www.berr.gov.uk/files/file14768.pdf

Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary used and establishing a European Medicines Agency.

Good manufacturing practice (GMP) and quality

The hospital exemption requires that Member States shall authorise manufacture and ensure that the specific quality standards applied are equivalent to those provided for at Community level in respect of ATMPs which would be centrally authorised under the Regulation. In accordance with the Regulation we propose that in order to operate under the hospital exemption the manufacturer must obtain a manufacturing licence from the MHRA as the UK national competent authority. The licence will authorise the manufacture of particular categories of ATMPs rather than individual products. The MHRA will be able to make use of its extensive experience in the granting of manufacturer's licences for unlicensed products.

ATMPs that are made and used under the exemption must comply with the principles of GMP. The European Commission will develop new GMP guidelines for ATMPs. We do not envisage additional quality requirements beyond those guidelines and the general requirements of GMP. The MHRA will inspect for compliance with GMP standards which will be applied appropriately to the nature of the products involved. Inspections will be risk-based and in accordance with Hampton principles.

Pharmacovigilance

For ATMPs that are centrally authorised under the Regulation, the pharmacovigilance requirements laid down in Articles 21 to 29 of Regulation (EC) No 726/2004 (as well as Article 14 of the ATMP Regulation) shall apply. While meeting the requirement in the Regulation for equivalent pharmacovigilance standards under the hospital exemption it is necessary to recognise that certain requirements cannot readily be applied to unlicensed products. In particular, it would not be realistic to apply the requirement for periodic safety update reports for products under the hospital exemption that are produced on a non routine basis. Likewise, given that there is not an authorised indication for the product under the hospital exemption, we propose that follow up of efficacy should be viewed in the context of the normal professional obligation for clinicians to monitor closely the effects on patients of relatively innovative, complex or high risk treatments.

Therefore, under the hospital exemption, the pharmacovigilance requirements will cover the notification of adverse reactions and the possibility for MHRA to ask for a risk management plan. Initial consideration of the need for such a plan will be instigated at the point that a manufacturer's licence is sought to operate under the exemption and will reflect the nature of the proposed activity. In addition, the MHRA may request a risk management plan from the manufacturer at any point (if, for example, safety concerns were raised about a product which was not known at the point that the application was made for a manufacturer's licence).

Traceability

For ATMPs that are centrally authorised under the Regulation, a traceability system compatible with the traceability requirements under the Tissues and cells Directive (2004/23/EC) and the Blood Directive (2002/98/EC) is required. Additional traceability provisions are laid down in Article 15 of the Regulation. Under the exemption, in view of the absence of a marketing

authorisation holder (MAH), traceability obligations will fall to the manufacturer of the ATMP. As the manufacturer will not always be a hospital there will be defined responsibilities for the hospital administering or using the ATMP. Under Directives 2004/23/EC and 2002/98/EC the tissue/blood establishments are required to maintain traceability records from donor to the point of dispatch of the tissues/cells/blood to the organisation where it will be used/transfused/administered/applied (for example a hospital, other healthcare establishment or manufacturer). The "user" organisations are required to keep traceability records from receipt of the material from the establishment to its final use or destruction. This approach will apply for ATMPs manufactured, supplied and administered under the hospital exemption.

In the case of bankruptcy, responsibility for holding the traceability data for 30 years in respect of centrally authorised ATMPs would lie with the EMEA. In the case of bankruptcy for ATMPs made and used under the exemption, it is proposed that it should be a condition of operating under the hospital exemption that arrangements are put in place by the manufacture and hospital for holding records in the event of a cessation of operations. In cases where a hospital is the manufacturer, the records would be kept with the residual records of that hospital. In other cases, as a last resort, it is proposed that MHRA would take responsibility for holding traceability data.

Ethical issues

The MHRA and DH have considered whether specific ethical review requirements would be applicable to ATMPs made and used under the exemption. Provided it did not involve xenotransplantation (which, under existing Department of Health guidance, it is recommended should be presented, conducted and managed as research), administering an ATMP as part of a patient's clinical treatment would not require a favourable research ethics committee opinion. Clinical ethical issues presented by using ATMPs in clinical practice would be covered by the NHS trusts' clinical governance arrangements. In addition, the terms of reference of the Gene Therapy Advisory Committee (GTAC) which is sponsored by the DH were revised in 2008. GTAC is a Ministerial advisory body and the UK nation research ethics committee for gene therapy under the UK's Clinical Trials Regulations. This would mean that GTAC could be called upon to provide ethical advice to medical practitioners on the use of gene therapy and stem cell line derived materials made and used under the exemption, if necessary.

Other requirements not specified within the Regulation

The specific parameters that are laid down in the Regulation for the exemption are intended to ensure minimum standards. The MHRA has considered whether additional provisions are required. The criteria considered for additional provisions were:

- are they necessary to protect public health;
- are they fully consistent with purpose of the hospital exemption; and
- are they necessary on grounds of ensuring clarity of the regulatory arrangements.

The MHRA's view is that there is a strong case for provisions in two areas set out below and that the arrangements proposed clearly avoid the risk of unnecessary over-implementation of European legislation:

(a) product information requirements, including labelling and advertising for ATMPs made and used under the exemption.

This reflects the need to protect public health as well as the lack of clarity in regulatory arrangements if there were to be no provisions in this area. The specific provisions that will apply are included in the annexes.

(b) adjusting provisions in the UK Specials scheme, as they apply to any Specials that are ATMPs, to align standards (manufacturing/quality, pharmacovigilance, traceability, patient information and ethics) with those of the hospital exemption

This is a complex area and is explained below.

The relationship between the hospital exemption and Article 5 (1) of Directive 2001/83/EC

There are some apparent similarities between the kind of activities falling within the hospital exemption and those covered by the provisions of Article 5 (1) of Directive 2001/83/EC[4]. The two schemes are legally distinct. Article 5 (1) is the derogation from the Directive that the UK uses as the basis for its national "Specials" scheme (including the linked import notification scheme) which applies to unlicensed medicinal products commissioned by an authorised healthcare professional to meet the special needs of individual patients. In principle, this scheme would be available for ATMPs as for any other category of medicinal product.

Summary of some of the main differences in scope between the hospital exemption and "specials" schemes	
Hospital exemption	**The "specials" scheme**
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a "non- routine basis"	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)
The ATMP must be used in a hospital	There is no stipulation as to location

From fieldwork carried out by the MHRA at the time the European Commission brought forward its proposals for a Regulation, the Agency considers it likely that in the developmental stages of advanced therapy products, especially tissue engineering, it may not always be straightforward to establish which is the applicable regulatory scheme.

The MHRA considers that it is important to ensure that regulation is coherent and understandable to operators in the field and that there is a consistent level of public health protection in relation to identical or very similar products. In the interests of ensuring this the MHRA proposes that there should be coordination of regulatory requirements of the two schemes on issues where this is consistent with the separate underpinning requirements of European legislation for the two schemes. It is proposed to align the UK's Article 5 (1) scheme as it applies to ATMPs with the hospital exemption scheme later in 2010/11.

[4] Article 5 (1) of Directive 2001/83/EC provides that "a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility".

Accordingly, we propose that in the following areas, the specific proposals for the hospital exemption set out in this document should also be applied where ATMPs are supplied under the Specials regime:

- Good manufacturing practice/quality
- Pharmacovigilance
- Traceability
- Patient information (labelling and advertising)
- Ethics

In all other respects the existing arrangements for Specials would continue to apply to those ATMPs supplied under the Specials regime. Specials that are not ATMPs would be unaffected by any of these proposals.

We also propose that at the point where operators need to apply to the MHRA for a special manufacturers licence (whether to operate under the hospital exemption or the Specials Article 5.1 scheme specifically in relation to ATMPs) there should be an opportunity for dialogue with the MHRA in order to help ensure that operators apply under the appropriate scheme and in order where feasible to contain the likelihood of operators needing to switch between the two schemes. This would be particularly important in situations where both schemes may appear to be applicable.

3. OPTIONS

Option 1 - do nothing. Under this option, the UK would fail to meet its obligations under European Community law and could result in infraction proceedings by the European Commission. This option could also perpetuate the current fragmented approach to regulation in this area. This option has been discounted.

Option 2 - introduce voluntary arrangements for provisions that would apply under the scheme.

The sector could be encouraged to adopt the proposed provisions through a voluntary scheme. This option would rely entirely on the goodwill of the sector and would not provide the necessary public health protection assurances. This option has been discounted.

Option 3 - introduce specific national requirements in legislation within the parameters laid down in the Regulation. This approach would put in place appropriate safeguards to protect public health and would ensure the UK meets its obligations under European legislation.

Option 4 - implement the exemption laid down in the ATMP Regulation by introducing the Regulations; including several additional features not specifically required by the Regulation in order to protect public health and ensure the clarity and coherence of the regulatory regime.

4. COSTS AND BENEFITS

(i) Sectors and groups affected

The sector in the UK is relatively small. Producers are typically small spin-off companies emerging from university research, specialist hospitals, charities and a few larger companies. The current scale of activity is very small, iterative and developmental. According to the European Commission's assessment of activity in the UK, Germany and France, this type of activity is currently undertaken by relatively few hospitals and tissue banks. We know from consultation with stakeholders in the UK that activities of this nature carried out in hospitals in

the UK involve co-operation between hospitals and other parties such as spin off companies and medical charities in a range of different arrangements.

(ii) Analysis of costs and benefits

Benefits

Option 1 - do nothing:

- would avoid the effort of introducing change; and
- would avoid any costs associated with compliance with new regulatory provisions under the exemption scheme.

Option 2 - introduce voluntary arrangements for provisions that would apply under the scheme:

- would provide flexibility for the sector in developing new arrangements for self regulation of ATMPs made and used under the exemption scheme; and
- would avoid any costs associated with compliance with new regulatory provisions.

Option 3 - introduce specific requirements in legislation within the parameters laid down in the Regulation:

- would ensure minimum standards are in place;
- would provide clarity and legal certainty to those in the sector; (except in those additional areas covered by Option 4)
- would minimise the costs to the sector as without the exemption scheme the full provisions of the ATMP Regulation would apply; and
- would ensure the UK meets its obligations under European Community law.

Option 4 - implement the exemption laid down in the ATMP Regulation by introducing the Regulations; including several additional features not specifically required by the Regulation in order to protect public health and ensure the clarity and coherence of the regulatory regime:

- would ensure appropriate safeguards are in place to protect public health;
- would help to create confidence in the sector given that known safeguards are in place;
- would provide legal certainty to those in the sector; specifically providing a way of addressing the complex issues that operators with similar or even identical products would face under Option 3 over the interface of the hospital exemption and the Specials scheme
- would minimise costs as without the exemption scheme the full provisions of the ATMP Regulation would apply; and
- would ensure the UK meets its obligations under European Community law.

Returns to R&D activities

- More clarity in regulatory arrangements should enable a greater amount of medical R&D activity and as such may provide private, social, and health returns. The financial returns to medical research and development can be large - for example, the Medical Research

Council and its technology transfer company, MRC Technology (MRCT), have been involved in the creation of 17 start-up companies, including two of the UK's biggest biotechnology companies UCB-Celltech and Cambridge Antibody Technology (CAT), and in the last eight years royalties arising from the licensing of MRC intellectual property to industry has generated £234 million and has been the foundation of the global monoclonal antibody business, which has more than £5.3bn in sales annually.

- In addition to financial returns to companies, medical research also has the potential to improve the health of society through the provision of new treatments and technologies. A recent study - Medical Research: what's it worth?[5] - estimated that the total annual returns to publically funded medical research in cardio-vascular disease in the UK were around 39% - 30% financial return to companies and 9% health gain returns to patients.
- At the same time, it is important to note that not all R&D will be very productive, either in terms of private or social financial gains or health returns, and some R&D may provide no returns at all.

Costs

Option 1 - do nothing:

- would not change the current situation so the current unregulated fragmented arrangements would continue;
- the sector would continue to experience difficulties given the lack of legal certainty;
- there would be a risk to public health given the lack of regulatory requirements in place; and
- would carry the risk of infraction proceedings against the UK for failing to put in place national provisions for ATMPs made and used under the exemption.

Option 2 - introduce voluntary arrangements for provisions that would apply under the scheme:

- would introduce new costs associated with a self regulatory system;
- would reduce the overall coherence of medicines legislation not least in that statutory regulatory arrangements are already in place in relation to the UK scheme under Article 5 (1) of Directive 2001/83/EC;
- would rely entirely on the goodwill of the sector; and
- would carry the risk of infraction proceedings against the UK for failing to put in place national provisions for ATMPs made and used under the exemption.

Option 3 - introduce specific requirements in legislation within the parameters laid down in the Regulation:

- the main effect of the proposed provisions would be to transpose into national legislation the requirements that would apply to ATMPs made and used under the exemption scheme;
- some specific costs would be attributable to meeting those requirements but the costs should be lower than those that would fall to ATMPs that would otherwise be authorised under the Regulation which would be subject to all of the provisions laid down in the Regulation; and
- the financial impact has yet to be determined but overall the effect should be to reduce costs that hospitals would otherwise incur.

[5] http://www.wellcome.ac.uk/About-us/Publications/Reports/Biomedical-science/WTX052113.htm

Option 4 - implement the exemption laid down in the ATMP Regulation by introducing the Regulations; including several additional features not specifically required by the Regulation in order to protect public health and ensure the clarity and coherence of the regulatory regime:

- the main effect of the requirements under the Regulation will be to transpose into national legislation the requirements that will apply to ATMPs made and used under the exemption scheme;
- some costs will be attributable to meeting the requirements (including the additional features that are proposed) but the costs should be lower than those that will apply to ATMPs that will be authorised under the Regulation for which the full provisions laid down in the Regulation will apply; and
- the financial impact has yet to be determined but overall the effects should be to reduce costs that hospital would otherwise incur.

Costs to public health budgets

- There may in the future be an indirect impact on public health budgets through pricing and reimbursement of ATMPs. It is likely that the cost of such treatments may in some cases be high in relation to existing treatments. However, where such treatments find an ongoing place in the market it is likely that this will be because the costs are offset by savings where treatments prove more effective than existing treatments. In developmental work seen by the MHRA at spin off companies working in collaboration with hospitals there has been a strong emphasis on developing products to tackle conditions for which existing treatments have not proved successful.
- When considering costs attached to the hospital exemption it is helpful to make the comparison with the costs that would have applied if an exemption had not been included in the Regulation. If the Regulation had not included a hospital exemption the default position is that an industrially produced ATMP placed on the UK market would require a marketing authorisation under the centralised procedure. In this comparison the costs associated with the hospital exemption would be very much lower. However, it is also likely that without the exemption a number of products could be supplied as “Specials” – in which circumstance any cost differential per product should be very limited.

5. CONSULTATION WITH SMALL BUSINESS: THE SMALL FIRMS’ IMPACT TEST

In the UK, producers of ATMPs are typically small spin-off companies emerging from university research, in specialist hospitals, charities and a few larger companies. The MHRA has engaged with a range of stakeholders, including hospitals, since late 2004 before the Commission’s proposal for a Regulation was adopted in November 2005.

According to the Commission’s original proposal ATMPs which were prepared in full and used in a single hospital, in accordance with a medical prescription for an individual patient would have fallen under the hospital exemption. In negotiations, the UK argued that it would be overly restrictive to limit the exemption to manufacture and use within the same hospital. This was based on discussions that had taken place with stakeholders in the UK who confirmed that typically this type of activity carried out in hospitals (albeit on a very small scale) was undertaken in a range of different arrangements which included co-operation between different hospitals and in some cases with medical charities. The exemption that has been agreed has so far been welcomed by hospitals involved in this type of activity.

Public consultation exercise

In July 2008, the MHRA consulted on proposed provisions under the UK's exemption scheme. 10 responses were received. Some respondents said it would be important for MHRA to issue guidance on the new regulatory arrangements. Comprehensive guidance has since been developed and has been published on the MHRA website. No information was provided by stakeholders about the possible costs associated with the proposed requirements though some respondents raised concerns about the fees that would be applicable to those organisations who would need to register as a tissue bank with the Human Tissue Authority (HTA) and also apply to the MHRA for a manufacturing licence to operate under the exemption. The MHRA and the HTA are currently collaborating with a view to carrying out joint inspections where this is possible bearing in mind inspections are required against different criteria/legislation.

It should be noted that, even without the hospital exemption, there would still normally be a requirement for a manufacture's licence in relation to such medicinal products following the regulatory requirements relating to marketing authorisations or the "specials" regime.

6. COMPETITION ASSESSMENT

The Cabinet Office's competition filter test has been applied to determine whether a simple or more detailed competition assessment is required. A simple assessment seems appropriate on the basis that the sector is not dominated by a single or small number of companies. In addition, the overall effect of the exemption scheme should be to reduce costs that hospitals would otherwise incur should all of the provisions of the ATMP Regulation apply to their activities.

7. EQUALITY IMPACT ASSESSMENT

Equality impacts have been considered. The proposed provisions will have no discernable effect on any of the following issues: race, disability, gender, sustainability, carbon assessment or other environmental issues, human rights or rural issues.

8. ENFORCEMENT, SANCTIONS AND MONITORING

The MHRA is responsible for operating the national arrangements under the exemption scheme in the UK and will check for compliance with the requirements through normal inspection arrangements in line with the principles of better regulation. Specific penalties will apply for non compliance with the provisions laid down in national legislation. Monitoring of activities under the exemption scheme will be undertaken by the MHRA The European Commission has given a commitment to review the ATMP Regulation within five years of coming into force at which time the Commission will publish a report on the operation of the legislation. The MHRA will monitor activities under the UK's exemption scheme and proposes to seek the views of stakeholders in advance of the date set for the Commission's review to identify collective UK experience of operating under the exemption and the Regulation.

9. IMPLEMENTATION AND DELIVERY PLAN

The Regulation's provisions are directly applicable and applied from 30 December 2008. The Statutory Instrument that is attached implements the Regulation in the UK. The amendments that are proposed to the UK's "Specials" scheme under Article 5 (1) as they apply to ATMPs will follow at a later stage. We envisage this will take place later in 2010/11.

10. POST IMPLEMENTATION REVIEW

The European Commission has given a commitment to review the ATMP Regulation within five years of coming into force at which time the Commission will publish a report on the operation of the legislation. The MHRA will monitor activities under the UK's exemption scheme and proposes to seek the views of stakeholders in advance of the date set for the Commission's review to identify collective UK experience of operating under the exemption and the Regulation.

11. SUMMARY AND RECOMMENDATION

Overall, the proposed regulatory framework does not change which products would be subject to medicines legislation but provides clarification of the specific requirements that would apply. The exemption scheme imposes certain provisions which are outlined in this document. The overall effect of the exemption should be to reduce costs that hospitals would otherwise incur were they subject to the full provisions of the Regulation, including the requirement for a centralised marketing authorisation. There will, however, be some costs associated with the proposed provisions. Collaboration between hospitals and private operators will be permissible under the exemption. In addition, the provisions that would apply under the proposed UK scheme would put in place appropriate safeguards to protect public health and are considered necessary given the possible risks associated with ATMPs. Those additional measures that are proposed under Option 4 would provide the necessary safeguards to protect public health which should in turn help to develop confidence in the sector.

This is an innovative and developing area and based on the intelligence that is available the current volume of activity is very low. It will take a number of years for new innovative ATMPs to be developed. It will therefore take some time to make a robust assessment of the regulatory impact. We invite the sector to provide estimates of the costs associated with the proposed provisions as well as those associated with the additional measures proposed in respect of patient information/labelling.

While Option 3 would mean that the UK would meet its requirements under European Community law, Option 4 is the recommended option since, in addition to meeting those requirements it would include important provisions on patient information in the interests of patient safety and would ensure a coherent approach to the interface between the hospital exemption and the UK Article 5.1 Specials Scheme.

Annexes

Annex 1 should be used to set out the Post Implementation Review Plan as detailed below. Further annexes may be added where the Specific Impact Tests yield information relevant to an overall understanding of policy options.

Annex 1: Post Implementation Review (PIR) Plan

A PIR should be undertaken, usually three to five years after implementation of the policy, but exceptionally a longer period may be more appropriate. A PIR should examine the extent to which the implemented regulations have achieved their objectives, assess their costs and benefits and identify whether they are having any unintended consequences. Please set out the PIR Plan as detailed below. If there is no plan to do a PIR please provide reasons below.

Basis of the review: [The basis of the review could be statutory (forming part of the legislation), it could be to review existing policy or there could be a political commitment to review];

The European Commission has given a commitment to review the ATMP Regulation (including the hospital exemption) within five years of coming into force. This is laid down in the Regulation. In addition, the MHRA proposes to identify collective UK experience of operating under the exemption and the Regulation (in consultation with stakeholders) in advance of the date set for the Commission's review.

Review objective: [Is it intended as a proportionate check that regulation is operating as expected to tackle the problem of concern?; or as a wider exploration of the policy approach taken?; or as a link from policy objective to outcome?]

The main focus of the review will be to ensure that the regulatory arrangements are working as intended under the Regulation and to review the impact of scientific/technical progress on the application of the regulatory framework.

Review approach and rationale: [e.g. describe here the review approach (in-depth evaluation, scope review of monitoring data, scan of stakeholder views, etc.) and the rationale that made choosing such an approach]

The MHRA will monitor activities under the UK's exemption scheme and intends to seek the views of operators in advance of the date set for the Commission's review to identify collective UK experience of operating under the exemption and the Regulation.

Baseline: [The current (baseline) position against which the change introduced by the legislation can be measured]

Prior to the introduction of the Regulation, there was no specific regulatory framework in place for this category of medicines.

Success criteria: [Criteria showing achievement of the policy objectives as set out in the final impact assessment; criteria for modifying or replacing the policy if it does not achieve its objectives]

Qualitative information about the perceived value of the scheme to its users, supported by quantitative information on the use of the combined provisions of the hospital exemption and the Article 5 (1) scheme as they apply to ATMPs. In this highly innovative area of technology the rate of progress cannot be predicted and therefore qualitative information will be particularly important in illuminating the extent to which particular quantitative information, eg about the number of operators using the hospital exemption, represents success. Qualitative information about the sector's understanding of the regulation applying to ATMPs will also be significant.

Monitoring information arrangements: [Provide further details of the planned/existing arrangements in place that will allow a systematic collection systematic collection of monitoring information for future policy review]

The MHRA will be responsible for authorising manufacture of ATMPs made and used under the exemption, and will check for compliance with the requirements through normal inspections in line with the principles of better regulaton. In addition, operators will be required to submit an annual return to the MHRA so the Agency will have systematic information about the operation of the national scheme for review purposes.

Reasons for not planning a PIR: [If there is no plan to do a PIR please provide reasons here]

REGULATION NO 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS

KEY PROVISIONS

- TEPs falling within the definition of medicinal product will be grouped along with gene therapy and somatic cell therapy products and regarded as ATMPs;
- a TEP means a product that contains or consists of engineered cells or tissues and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue;
- a centralised Community marketing authorisation procedure will apply to ATMPs;
- ATMPs which are prepared on a non routine basis and used within the same Member State in a hospital in accordance with a medical prescription for an individual patient will be exempt from the Regulation;
- a new committee for advanced therapies (CAT) will be established within the EMEA to provide scientific advice on ATMPs of which at least two members must have medical devices expertise;
- for combination advanced therapy medicinal products, the device element will have to conform to the essential requirements as in devices legislation, and the overall product evaluated by the EMEA;
- where the medical device or implantable device has already been assessed by a notified body, the EMEA will recognise the results of that assessment in its evaluation of the product concerned;
- where a notified body's assessment has not taken place, the EMEA will seek an opinion from a notified body unless CAT, advised by its devices experts, decides that an opinion is not required;
- the Tissues and Cells Directive (2004/23/EC) will apply to donation, procurement and testing of human tissues and cells contained in ATMPs;
- detailed guidelines in line with the principles of good manufacturing practice and good clinical practice specific to ATMPs will be published by the Commission;
- specific technical guidelines will be developed for ATMPs;
- there will be specific labelling and packaging requirements for ATMPs;
- post-authorisation monitoring will be required via pharmacovigilance and risk management;
- the Regulation recognises that there is no consensus among Member States upon which harmonised decisions could be taken on the use or prohibition of certain types of cells (such as embryonic stem cells) so the option of prohibition or restriction of products containing particular kinds of cells will remain a national responsibility;
- a range of incentives is proposed for small and medium sized enterprises (SMEs) including a reduction in fees payable to the EMEA for provision of scientific advice and deferral of fees until notification of final decision; and

- there will be 3 or 4 years transitional protection for products legally on the market at the time the Regulation applies. 3 years will apply for gene therapy and somatic cell therapy products and 4 years for TEPs.