



DG INTERNAL POLICIES OF THE UNION

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**Proposal for a Regulation of the European Parliament
and of the Council on Advanced Therapy Medicinal
Products and amending Directive 2001/83/EC &
Regulation (EC) No.726/2004 (COM(2005)567)**

(IP/A/ENVI/OF/2005-051)

Briefing Note

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EXECUTIVE SUMMARY

The Commission's proposal on advanced therapy medicinal products envisages the compulsory use of the centralized (EMA) marketing authorization procedure for all advanced therapy – gene, cell and tissue-based - medicinal products. The compulsory use of the centralized procedure is proposed on the grounds that there is a lack of expertise in advanced therapies in some national regulatory authorities; there is a need to improve patient access to new medicines across Europe; and as this would build on existing regulatory practice. The proposal should also benefit the (often small) companies involved in developing and manufacturing advanced therapy products. It will make available to them the prospect of access to a large European market rather than often small national territories. Whereas gene and cell therapy products are already covered by EU pharmaceutical law, tissue therapy products would be covered for the first time.

The Commission has consulted widely during its development of this proposal. Its comprehensive consultation exercises on this proposal are well documented and it appears that significant support exists for the approach adopted by the Commission. Various legislative options were addressed during the Commission's consultation processes. Overall, support was demonstrated during these consultations for a specific, harmonized and coherent EU regulatory framework along the lines proposed.

The presence of manipulated tissues and cells in advanced therapy products and the associated risks requires there to be strict hurdles for licensing these products. It is proposed that all advanced therapy products be grouped together within a single framework rather than in several different ones. This will also help overcome the problem of potential borderline products (in respect of which the proposal also provides that a scientific opinion may be requested of the EMA).

A major concern that Parliament will need to address is the approach taken by the Commission in responding to the lack of consensus in Europe about research involving embryonic stem cells and xenogeneic products. The Commission proposes that legislation on advanced therapy medicinal products should be without prejudice to decisions taken by member states concerning the use or non-use of specific types of cells (such as embryonic stem cells). Parliament will no doubt wish to consider whether it is appropriate for access to medicinal products developed for patients with at best intractable and most often incurable illnesses, and licensed by the European Commission, to be denied to patients in parts of the European Union. While this approach may be legitimate in the context of legislation on the quality and safety of cells (as in directive 2004/23), denying patients access to medicinal products resulting from such technologies, whilst others in Europe benefit, is going a step further. At the very least Parliament will need to take political responsibility for confirming that the logic of non-Europe should apply in this case, to the likely detriment of some patients.

Other major concerns that Parliament is likely to wish to address concern: traceability, incentives, the impact of this legislation on hospitals and tissue banks, the proposed EMA Committee on Advanced Therapies, and donor consent.

Introduction

1. Recent years have witnessed significant scientific advances in the area of gene and cell therapy and tissue engineering. It is likely that such advanced therapies will increasingly lead to marked improvements in medical treatment by providing better outcomes than can be achieved with currently available techniques or by making available treatments for diseases or conditions for which there are none currently. However, the application of such scientific developments to clinical use carries significant risks, including types of risk that have hitherto not been seen in healthcare. In some cases, scientific developments in this area also raise difficult ethical and social challenges.

Objectives of the Commission's proposal

2. The Commission presented its proposal for a Regulation of Parliament and Council on advanced therapy products on 16 November 2005¹. The proposal is intended to bring the authorization, supervision and pharmacovigilance of advanced - gene, cell and tissue-based - therapy products within a single, integrated and tailored European legislative framework and to ensure consistency across the member states.

3. The main elements of the proposal are:

- compulsory use of the centralised marketing authorisation procedure for all advanced therapy products;
- creation of a new Committee for Advanced Therapies (CAT) within the European Medicines Agency (EMA), to assess advanced therapy products;
- introduction of a comitology procedure to establish the main technical requirements specific to advanced therapy products; in addition, further detailed technical guidance is to be published by the Commission and/or EMA following “extensive and thorough consultation with all interested parties”² (see further below);
- account is taken of the absence of consensus within Europe about the use or prohibition of embryonic stem cells;
- specific risk management, pharmacovigilance and traceability requirements for advanced therapy products;
- incentives for all applicants and an additional incentive for small and medium-sized enterprises (SMEs).

¹ http://pharmacos.eudra.org/F2/advtherapies/docs/COM_2005_567_EN.pdf

² *ibid.*, p. 6

Scope of the proposal

4. There is an extremely strong case for advanced therapy medicinal products being authorized via the centralized (EMA) procedure. Gene and cell therapy products are already classified as medicinal products under EU law and regulated as such (Annex 1, Part IV, Commission directive 2003/63/EC amending directive 2001/83/EC – Community Code relating to medicines for human use).³ In contrast, tissue-engineered products are not currently classified either as medicinal products or medical devices and, accordingly, for the present lie outside any EU regulatory framework. Tissue-engineered products are currently classified and authorized differently by each member state, often through opaque and lengthy procedures. Some member states have sought to regulate tissue engineered products with specific, dedicated rules; others apply medical devices legislation; still others regulate them as pharmaceuticals. As a result products circulate only with difficulty in the EU and, ultimately, patients may be prevented from having access to them.
5. There is also a lack of advanced therapy expertise in some national regulatory authorities; as a result it may be difficult for manufacturers to bring some products to market. This shortage of expertise across Europe points strongly to the need for member states to share resources for the evaluation of advanced therapy products via the EMA.
6. Currently, patients may be prevented from having access to new therapies as a result of an incomplete EU legislative framework. Indeed, patients today may have access to new therapies in some EU member states while the same therapies are not available in other member states. Use of the centralized procedure for advanced therapy products should improve this situation, in particular to the benefit of patients.
7. There appears to be widespread support for the principle of establishing a specific regulatory framework to address the current lacunae in EU law regarding tissue therapy products. Opinions canvassed during the Commission's consultation processes (see below) differ on details but there is a very little evidence of significant opposition in principle to a specific EU framework covering tissue engineered and other cell/tissue based products.
8. The main impact of the proposal would be to bring tissue engineered products within EU pharmaceutical law for the first time, and this within the broad area of advanced therapies, which henceforth will group together gene and cell therapy products as well as tissue engineered products.
9. The Commission posits that the advanced therapies proposal does not modify the regulatory system applying to gene and cell therapy products, which is already laid down in Annex I to directive 2001/83, except insofar as it would create the new Committee on Advanced Therapies within the EMA to oversee these products. It does add to it, however, most notably through providing that the provisions of the human cells and tissues directive (directive 2004/23) relating to donation, procurement and testing, will apply unambiguously to all advanced therapy medicinal products, and through introducing the complete traceability of patients, products and starting materials.

³ http://europa.eu.int/eur-lex/pri/en/oj/dat/2003/l_159/l_15920030627en00460094.pdf, p. 88 ff

10. Examples of advanced therapy products covered by this proposal include:

Gene therapy

Gene therapy refers to treatments obtained through transferring a gene (a piece of nucleic acid) to human or animal cells and its subsequent expression *in vivo*. Though in its infancy, possibilities for future gene therapy are widely regarded to include *inter alia*, the treatment of cancer, CVD, neurodegenerative and auto-immune diseases. By way of example, in July 2005 the Commission granted orphan drug status to an adeno-associated viral vector containing a modified small nuclear RNA gene for the treatment of Duchenne muscular dystrophy. This viral vector is regarded as having the potential to address the underlying cause of the disease, in contrast with current treatments that temporarily slow disease progression or provide only palliative benefit. No clinical trials in patients have yet been initiated but evaluation is ongoing.

Cell therapy

Autologous (the original tissue being drawn from the recipient of the product) cells and tissues are often used therapeutically. Restoring defects to knee cartilage is possible through growing patients' own cartilage cells to repair cartilage defects. The regeneration and repair of bones, nerves, tendons and ligaments through cell therapy products may be possible in future.

Some 45,000 people across the world receive haematopoietic cell transplants each year to replace diseased blood-forming cells produced in bone marrow. Umbilical cord blood cells, rich in stem and progenitor cells, are already being used in patients with haematologic disorders including genetic diseases.

Research is currently in progress to treat epidermolysis bullosa (EB) through cell and gene therapy. EB is a group of genetic disorders causing blistering and shearing of the skin. EU funded research (FP 6) is directed at genetically modifying epidermal stem cells to produce skin implants for clinical use, and to undertake a pilot clinical trial of genetically modified autologous cell grafts over a limited skin surface in patients. This will serve as proof-of-principle for the treatment of EB and as a model for the treatment of genetic disorders by *ex vivo* gene therapy.⁴

Tissue engineered products

A Commission JRC IPTS report (see below) identified about 35 tissue engineered treatments available within the EU in 2003. These were mainly skin replacements and cartilage and bone products. The vast majority are autologous and were placed on the market by SMEs. The report also found patient access to tissue engineered treatments in Europe to be localized and fragmented: according to the JRC there is not a single tissue engineered product which is available in every member state.⁵

⁴ See for example, <http://www.debra-international.org/research11.htm>

⁵ See <http://pharmacos.eudra.org/F2/advtherapies/docs/2nd%20IPTS%20report.pdf>, p. 8

A few hospitals per member state also produce tissue engineered products, usually for in-house or local treatments. Tissue banks might also consider tissue engineering in the future and in some cases have research projects in progress (for example, corneal epithelial cells to reconstruct the surface of the eye, at the East Grinstead Eye Bank, UK; the development of tissue engineered heart valves, by the UK National Blood Transfusion Service) or a manufacturing authorization for human tissues (tissue transplants such as bone, amniotic membranes, de-mineralized bone matrix, tendons, and ligaments, at the Institute for Transfusion Medicine, University Hospital Charité, Berlin).⁶

⁶ For a summary of tissue engineering in Europe, see *ibid.*, section 2.

The development of the Commission's proposal - a long, comprehensive and wide ranging consultation process

11. The gestation period of this proposal has been long and appears to have involved extensive, careful, open and thorough public consultation. An important early event in the evolution of the proposal was the October 2001 Opinion of the Commission's Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) on *The State of the Art Concerning Tissue Engineering*⁷. This opinion argued strongly for the establishment of an EU Tissue Engineering Regulatory Body to oversee the introduction of tissue engineered products in Europe, emphasized that new products and processes were evolving rapidly, clinical trials were already underway, patents were starting to be granted and systems were being got ready to be implemented. It is worthwhile to quote the SCMPMD's 2001 opinion at length:

In view of the significant risks to patients under certain circumstances, it is considered essential that some form of regulatory process is introduced on a European basis. It is fully recognised and accepted that regulatory processes should not inhibit or indeed interfere with scientific progress in this area, but at the very least, regulatory control should be exercised at the stage when tissue engineering enters clinical trial phases and/or involves a commercial process. Under some circumstances, it may be necessary for such control to be applied to the point at which a tissue engineered product or process is utilised in man for the first time. Although some aspects of complex tissue engineering processes may well be suitable for regulation under an existing European Directive, for example in relation to medicinal products, or medical devices, or clinical trials, it is unlikely that all aspects of tissue engineering can be encompassed by current legislation.⁸

The 2001 Opinion of the SCMPMD provided the initial impetus for the Commission to start considering an appropriate EU legal framework for tissue engineered and other advanced therapy products.

12. In addition to the identified lack of a specifically designed European-wide regulatory mechanism or legal framework for the introduction of tissue engineering into clinical practice, many developments have occurred outside Europe (principally in the US and Japan). European governments are faced with making decisions on the importation of products from overseas and the granting of permission for clinical use. Regulatory frameworks and standards have evolved elsewhere also, especially in the US but also in individual member states.

13. In June 2002 the Commission launched a public consultation on the need for a legislative framework on human tissue engineering and cell engineering products. This consultation, like those which followed, highlighted a broad consensus amongst industry and expert respondents that a specific and uniform EU legal framework was needed for tissue-engineered products. Government and public institution respondents also in the main advocated a new regulatory framework, though some proposed to use existing EU pharmaceutical legislation.⁹

14. A later consultation undertaken by the Commission in 2004 revealed widespread support for specific EU legislation on human tissue engineered products, as did a stakeholder conference convened by the Commission in April 2004. This consultation highlighted broad

⁷ See http://europa.eu.int/comm/food/fs/sc/scmp/out37_en.pdf

⁸ *ibid.*, p. 8.

⁹ For a summary of results of 2002 consultation see:

<http://pharmacos.eudra.org/F2/advtherapies/docs/2002%20Public%20consultation%202002%20-%20summary%20of%20results.pdf>

public, official and industry consensus in favour of a specific, harmonised and coherent EU regulatory framework covering human tissue engineered products, as well as other cell/tissue based products and stressed the need to establish legal certainty in an emerging field as rapidly as possible. Respondents to the consultation recommended that any new initiative should comprehensively address not only existing, but also future cell/tissue-based products. Comments received during the consultation were also generally in favour of a regulation, rather than a directive. Key procedural and technical aspects (notably scope, definitions, marketing authorisation requirements, borderline issues and post-authorisation issues) were thoroughly addressed.¹⁰

15. Finally, in May 2005, in advance of the formal presentation of its legislative proposal, the Commission launched a third and final consultation on the details of the legislative approach it intended to propose. The 2005 consultation went further than the earlier ones in setting out essentially the specific legislative and regulatory strategy found today in the Commission's Advanced Therapy Products proposal. It even gave respondents to the consultation the opportunity to comment on a detailed preliminary draft of the proposal, itself now before Parliament and Council.¹¹

16. In addition to the Commission's extensive consultation process summarized above, two supporting studies have been conducted by the Joint Research Centre's Institute for Prospective Technological Studies, one on the market and future prospects for human tissue engineered products¹² and the other on the potential socio-economic impacts of a new European regulatory framework for human tissue-engineered products.¹³

17. The Impact Assessment (SEC (2005)1444) undertaken with regard to this proposal draws heavily on the wide-ranging consultation exercise and the associated studies commissioned by the Commission.¹⁴ It is comprehensive and reviews fully the various legislative options considered by the Commission (see also below). In places where there are gaps in the impact assessment (in the case of confidentiality and traceability, for example), these are addressed below.

¹⁰ For a summary of results of Commission's 2004 consultation see:

<http://pharmacos.eudra.org/F2/advtherapies/docs/Summaryofresultsfinal2004.pdf>

¹¹ For a summary of results of the Commission's 2005 consultation see:

<http://pharmacos.eudra.org/F2/advtherapies/docs/2005Consultation-Outcome-2005-11-18.pdf>. For individual responses to the consultation see: <http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005.htm>

¹² <http://pharmacos.eudra.org/F2/advtherapies/docs/ipts21000en.pdf>

¹³ <http://pharmacos.eudra.org/F2/advtherapies/docs/2nd%20PTS%20report.pdf>

¹⁴ See http://pharmacos.eudra.org/F2/advtherapies/docs/SEC_2005_1444_EN.pdf, p. 17

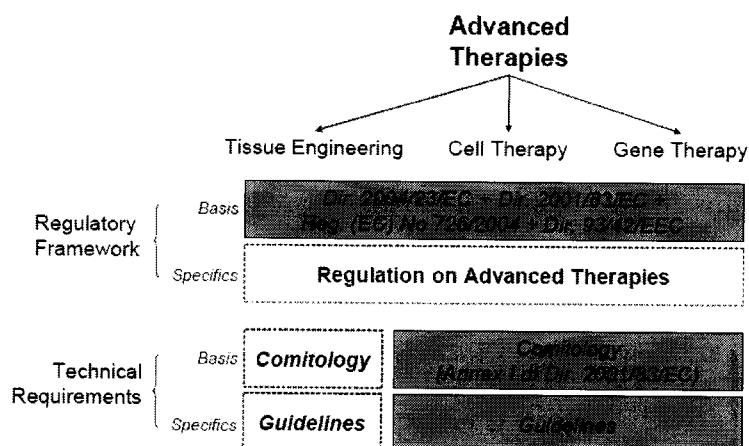
The Commission's legislative strategy for advanced therapy medicinal products

18. The legislative strategy proposed by the Commission is depicted in the diagram below.¹⁵ The Commission argues that its approach will provide for a global and integrated legislative structure addressing all advanced therapies (gene therapy, cell therapy, tissue engineering) in a single framework while allowing, in the Commission's view, for regulatory and technical specificities to be taken into account.

19. The Commission's impact assessment summarizes the alternative regulatory options considered by the Commission during the development of the proposal, in the following diagram¹⁶. These are shown on the chart below.

20. The Commission's consultation exercises conducted during the drafting of this proposal 2002 – 2005 found general support for avoiding the regulation of tissue engineered products separately from somatic cell therapy and gene therapy. Extension of the medical devices legislation, minimal regulation through a "new approach" regulatory method, a decentralized "concertation" type approach and a specific regulatory framework for tissue engineered products alone, were also found to have more disadvantages than advantages (see chart below).

The proposed legislative strategy for advanced therapy medicinal products



Existing elements are highlighted in orange; elements to be established by the advanced therapies proposal or which would result from it (ie. via comitology and guidelines) are highlighted in white dashed boxes.

Directive 2004/23: Standards of quality and safety for donation, procurement, testing, processing etc. of human cells and tissues

Directive 2001/83: Community Code regarding pharmaceutical products for human use

Regulation 726/2004: Community procedures for the authorisation and supervision of medicinal products and establishing a European Medicines Agency

Directive 93/42: Medical devices

¹⁵ From <http://pharmacos.eudra.org/F2/advtherapies/docs/ConsultationPaper-AdvancedTherapies-2005-May-04.pdf>, p. 5.

¹⁶ http://pharmacos.eudra.org/F2/advtherapies/docs/SEC_2005_1444_EN.pdf, p. 17

Regulatory options

	Pros	Cons
Status Quo	Does not require any change	<ul style="list-style-type: none"> –Current situation is unharmonised –Stakeholders in favour of a specific EU framework
Extension of the Medical Devices legislation	Existing framework with demonstrated practicability	<ul style="list-style-type: none"> –Tissues/cells raise specific safety, efficacy and ethical issues –Scarcity of expertise / Notified bodies –Community harmonisation may not be ensured
'New Approach' legislation	<ul style="list-style-type: none"> –Concept of 'New approach' has worked well in other sectors –'Essential requirements' system provides for flexibility 	<ul style="list-style-type: none"> –Scarcity of expertise / Notified bodies –Community harmonisation may not be ensured
Semi-centralised and 2-tier authorisation	<ul style="list-style-type: none"> –Flexible system, match the need of local/national producers –Use of existing resources and expertise at national level 	<ul style="list-style-type: none"> –Scarcity of expertise –National authorisation implies mutual recognition; Community harmonisation might not be ensured –2 layers of bureaucracy; overall complexity of the system
'3rd pillar'	<ul style="list-style-type: none"> –Specificity of TEPs emphasised and addressed –New framework allows flexibility 	<ul style="list-style-type: none"> –Creates artificial border between TEPs and other, 'similar' products (e.g. cell therapy) –Duplication of existing and applicable regulatory concepts; 'reinvent the wheel' risk
'Advanced Therapies' approach	<ul style="list-style-type: none"> –Builds on existing and applicable frameworks –Focus on specificities –Allows for flexibility 	<ul style="list-style-type: none"> –Need for special attention to small/local actors –Existing framework need to be adapted to match specificities

21. The Commission argues, rightly, that processes applicable to evaluating and authorizing gene and cell therapies are equally relevant to tissue engineered products. Creating a separate regulatory system for tissue engineered products would be duplicative, confusing and uncertain. Questions of definition recurred throughout the consultation processes, as did concern about grey areas or indistinct borderlines between different processes and therapies (see also below). Moreover, tissue engineering, somatic cell therapy and gene therapy share much more common scientific and economic features than they do differences: they all aim at modifying genetic, physiological or structural properties of cells and tissues; they are based on complex and innovative manufacturing processes; there is very limited regulatory and scientific expertise available for the evaluation of advanced therapies; traceability from donor to patient, associated long-term patient care, and thorough risk management, are crucial aspects in advanced therapies; and the major economic actors involved are young, small research-based and technology-oriented biotechnology companies, highly specialized divisions of large companies, as well as some hospitals and tissue banks.

Outstanding issues

Drawing the borderlines

22. Policy making relating to pharmaceuticals, cosmetics, medical devices and often food products frequently raises questions concerning the borderline between different kinds of products and therefore which regulatory system should apply. The potential for an indistinct borderline between medical devices and tissue engineered products was an important feature of discussions during the Commission's development of this proposal. While the definitions used by the Commission in its proposal are clear, the Commission acknowledges that they may not be perfect¹⁷:

It must be acknowledged that even the best possible definition of advanced therapy medicinal products may not fully eliminate the risk of grey areas, given the highly innovative and rapidly evolving nature of the advanced therapies sector. To address this, the proposal foresees the possibility for applicants to request a scientific recommendation from the EMEA on the classification of any product based on cells or tissues, with a view to resolving borderline issues.

23. Borderline issues will be reduced as a result of all advanced therapies being grouped together within a single regulatory framework rather than many different ones or none at all. In addition, the possibility for applicants (and, presumably, *potential* applicants) to request a scientific recommendation of the EMEA with a view to determining whether the product falls within the definition of an advanced therapy product is an appropriate way forward (see Article 18). Questions relating to drawing the borderlines between products will be able to be anticipated and definitions adapted as science develops. In particular the publication of summaries of recommendations (Article 18) concerning definitions will allow regulatory practice to develop in parallel with the evolution of science and medicine.

24. The Commission's proposal also addresses cases where medical devices might be part of an advanced therapy product. In such cases the whole "combined advanced therapy medicinal product" will be evaluated by the Agency, which may request information related to the results of the assessment of the medical device in accordance with the medical devices legislation.

25. While it is expected to change in the future, currently it is companies within the medical devices sector which produce the majority of products affected by legislation on advanced therapies, namely those which manufacture human tissue engineered products. It is not impossible that parts of the medical devices industry sector will argue that it faces difficulty in adapting to the very much more stringent and tightly regulated pharmaceutical licensing framework, created for advanced therapy products as a result of this proposal, than that which currently exists for medical devices.

¹⁷ Explanatory memorandum, COM (2005) 567 final, p. 6.

26. During the latest stage of the Commission's consultation process on this proposal the trade association representing the medical devices sector, Eucomed, recognized that EU pharmaceutical legislation should indeed be the basis for regulating human tissue engineered products¹⁸. The organization did, however, maintain its opposition to tissue engineered products becoming, strictly speaking, medicinal products as such, as a result of this proposed new legislative classification. While this is mainly a question of semantics, it might suggest some outstanding concern among medical device manufacturers about facing the strict hurdles associated with pharmaceutical licensing in the EU.

27. Ultimately, in the case of tissue engineered products, strict hurdles are justified in view of the presence of manipulated tissues and cells and associated risks. Indeed, Council has also already recognized (during adoption of the *in vitro* diagnostic medical device directive, 98/79/EC) that the use of substances of human origin in tissue engineered products inherently raises specific issues due to safety and ethical questions. This suggests again that advanced therapy products should undoubtedly be regulated as pharmaceuticals rather than medical devices.

28. Including tissue engineered products within the EU's centralized licensing process for pharmaceuticals also allows what limited scientific expertise exists in this area to be pooled for the authorization and supervision of such products. This is welcome in an area of medicine which is young, evolving rapidly, is highly complex and often cuts across several scientific disciplines.

29. Competitiveness issues can also be mentioned. The centralized authorization system proposed by the Commission will benefit (the often small) companies involved in developing and manufacturing advanced therapy products. In future these companies would have the prospect of having access to the large European market, rather than often small national territories. While some companies and economic operators might be reluctant to make this transition, this nevertheless points to the value of this proposal as an instrument supporting the modernization the European economy.

30. Borderline and definitional issues appear therefore to have been addressed appropriately and the correct balance found by the Commission.

¹⁸ http://www.eucomed.be/docs/EUCOMED_POSITION_PAPER_HTP_June05.pdf

Comitology and guidelines

31. The Commission proposes that guidelines be established by the EMEA on post authorization risk management (Article 15), and by the Commission on traceability (Article 16), good clinical practice (Article 4), and good manufacturing practice (Article 5). Additionally, the proposal provides for comitology procedures for the amendment of Commission directive 2005/28 (guidelines relating to clinical trials) in order to take account of advanced therapy products (Article 4), to amend Annex I to Directive 2001/83 to lay down technical requirements specific to tissue engineered products and to take into account scientific evolution (Article 8), to establish provisions for the scientific evaluation and certification of data generated by SMEs by the EMEA (Article 19), and to adapt the annexes to scientific and technical evolution (Article 24).

Guidelines to be established subsequent to adoption of directive on advanced therapies

Reference in COM (2005) 567	Subject	Adopted by
Article 4	Clinical trials	Commission
Article 5	Good Manufacturing Practice	Commission
Article 15	Post authorization risk management	EMEA
Article 16	Traceability	Commission

Comitology provisions within Commission's advanced therapies proposal

Reference in COM (2005) 567	Subject
Article 4	Amendment of Commission directive 2005/28 (guidelines relating to clinical trials) to take account of advanced therapy products
Article 8	Amendment of Annex I to Directive 2001/83 to lay down technical requirements specific to tissue engineered products
Article 19	Provisions for scientific evaluation and certification of SME data
Article 24	Adaptation of annexes to scientific and technical evolution

32. As noted above, the development of further detailed guidelines and technical guidance underpins the Commission's legislative strategy for advanced therapy products. The development of detailed guidelines and technical guidance by the Commission and/or by the EMEA is an important part, which generally works well, of EU pharmaceutical policy. The authorization of medicines in the EU – and through it the protection of public health and maintaining patient safety - requires the submission and assessment of very large amounts of complex, scientific and highly specific quality, safety and efficacy data. For years the Commission and EMEA have established technical requirements and guidelines relating to the data needed for medicines licensing. In the case of advanced therapy products it will be particularly important for such technical and practical requirements to be able to be adapted promptly, within the framework laid down in primary legislation by Parliament and Council.

33. There may be some specific concern about the inter-relationship between the duration of the proposed transitional period (2 years – Article 29) and the need for guidelines to be developed by the Commission and the EMEA actually entering into force during this two year period. If the guidelines do not enter into force early in the transitional period products already on the market may need to be withdrawn. Frankly, it is unlikely that the Commission and the EMEA will succeed in developing the guidelines required within two years (those required by the pharmaceutical review 2001-2003 are still being developed today). Parliament should ensure that the Commission and EMEA recognize the need either for urgency in developing the guidelines suggested or, alternatively, the Commission should acknowledge the need for the transitional period to be longer. Products currently in use should not be denied to patients on the grounds that the details of their future licensing have not been finalised.

Traceability

34. Another area proposed by the Commission to be subject to the development of guidelines warrants significant further consideration by Parliament. This relates to traceability.

35. According to the proposal (Article 16) the holder of a marketing authorization will be required to “establish and maintain a system ensuring that the individual product and its starting and raw materials ... can be traced ... to the hospital, institution or private practice...”. The hospital or clinic where the product is used is in turn required to maintain a system for patient and product traceability. This dual approach, based on the blood and blood products legislation, is presumably intended to balance the need for donor and patient privacy, anonymity and confidentiality, with traceability. The rationale for a dual approach is not, however, explained in either the Commission’s explanatory memorandum or in its Impact Assessment.

36. Concerns were expressed in connection with the Commission’s preliminary draft proposal that it had provided for (private sector) marketing authorization holders to be entirely and alone responsible for managing a system allowing complete traceability of products and patients. This would obviously have raised important concerns about the confidentiality of donor and patient healthcare related data – and was contested by some patient and industry organizations and government bodies during the Commission’s 2005 consultation exercise.¹⁹ It is this that underlies, presumably, the choice of a dual approach to traceability.

37. As the Commission acknowledges, precise traceability is central to achieving a high level of safety in this area of medicine. And, as the Commission notes in its Impact Assessment for this proposal, there

“may be conflicting interests between, on the one hand, respect of the donor’s privacy, anonymity and confidentiality of information collected during tissue procurement and, on the other hand, safety of treatment for the recipient, which implies traceability requirements”.²⁰

The Commission also recalls that Opinion 11 of the European Group on Ethics in Science and New Technologies (EGE) indicated the necessity for strict personal data protection provisions in this field, aimed at reconciling both the donor’s and recipient’s interests and to prevent misuse of personal data and/or transmission of health data to third parties.

¹⁹ See, for example,

<http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Patients%20associations/Eurordis-%20European%20Organisation%20for%20Rare%20Diseases.pdf>,

<http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Healthcare%20professionals/Centro%20Nazionale%20Trapianti.pdf>,

<http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EFPIA-European%20Federation%20of%20Pharmaceutical%20Industry%20Associations.pdf>,

<http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/Spanish%20Ministry%20of%20Health.pdf>

²⁰ Op Cit., fn 14., p. 33.

38. The privacy and data protection of donors are already addressed comprehensively in directive 2004/23, on human cells and tissues (see annex for the relevant provisions). These provisions in the human cells and tissues directive already apply to the donation and procurement of human cells and tissues intended to be used in gene, cell and tissue therapy products. This proposal would also effectively extend this to the hospital, institution or private practice where such products are used through requiring their traceability systems to be complimentary to and compatible with the human cells and tissues directive (Article 16.3).

39. The Commission proposes adopting guidelines on the detailed application of the traceability rules set out in the proposal. However, it might be worthwhile for Parliament to ensure that the privacy of patients receiving gene, cell and tissue therapy products has been sufficiently taken into account by the Commission and that the planned Commission guidelines, once adopted, will do the same. Notwithstanding the requirement that will be placed on hospitals and clinics to establish systems for patient and product traceability, rather than (usually private sector) marketing authorization holders (as originally envisaged), it is important that strict data protection rules apply not only to donors but also to patients. This in turn also raises the issue of healthcare professionals being required to maintain strict patient confidentiality and privacy. Moreover, hospitals and treatment centres may of course also be private sector organizations.

40. Related to the above, it is surprising that the explanatory memorandum for the proposal says remarkably little (one short paragraph) about traceability and privacy. It is also remarkable that there is only one passing reference (at the end of recital 20) in the Commission's proposal to the requirements of directive 95/46 on the protection of individuals with regard to the processing of personal data and the free movement of such data.

41. While donor and patient confidentiality are paramount so too is safety. It is appropriate that commercially-oriented private sector organizations are not entrusted with ensuring traceability from hospital and clinic to individual patients. However, the Commission's approach runs the risk of allowing a void to open between the traceability system established by a marketing authorization holder and applying from starting materials to individual hospitals, and the traceability system created by hospitals and clinics for patient and product traceability.

42. It is difficult to envisage a better system than that proposed by the Commission. Some respondents to the Commission's consultations suggested that the EMEA or national competent authorities should be directly responsible for traceability. Parliament should consider whether it is realistic and/or desirable to establish such a publicly-run and possibly pan-European traceability system for gene, cell and tissue therapy products rather than the potentially fragmented compromise that the Commission has proposed. Indeed, Parliament needs to ensure that the requirements of both traceability and donor and patient privacy have been sufficiently and appropriately addressed by the Commission during the development of this proposal. Parliament may also want to ensure that the Commission has fully assessed all the options for guaranteeing traceability and donor and patient privacy. This is particularly important as the detailed guidelines for traceability are intended to be developed subsequently by the Commission, once the regulation is adopted. The Commission is also less than clear in setting out what the role of member states will be (if any) in supervising traceability and compliance by hospitals – it might be better for this to be set out clearly in the Regulation rather than (presumably) in guidelines. There may also be a need to ensure that the Commission/EMEA ensure compliance with traceability rules through, for example, requiring

that the eventual traceability guidelines encompass periodic inspection of hospital record keeping, etc.

43. Finally, Article 16.5 provides that in the event of the bankruptcy of the marketing authorization holder and in the event that the marketing authorization is not transferred to another legal entity, the data retained by it for product traceability to hospitals will be transferred to the EMEA. The proposal does not refer to what would happen to traceability data in the eventuality of a hospital, institution or private practice where the product is used closing. This should be rectified.

The Non-Europe in bio-Ethics

44. **Embryonic stem cells.** Directive 2004/23 on human cells and tissues (in recital 12 and Article 4(3)), provides that European law

“should not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells” (recital 12)

The advanced therapies proposal applies the restrictions relating to stem cells enshrined in that directive to the use of advanced therapy products. The lack of a consensus in Europe about research involving embryonic stem cells becomes in this proposal grounds for a member state to prohibit the sale, supply or use of medicinal products containing or derived from stem cells. In other words, patients in a country which does not allow stem cell research will not necessarily have access to medicines licensed under the EU framework to be created by this proposal.

45. Parliament will no doubt wish to consider whether it is appropriate for access to medicinal products developed for patients with at best intractable and most often incurable illnesses to be denied in parts of the European Union, despite those products having been authorized by the EMEA and being in use elsewhere in the Union. It is one thing to enshrine this kind of restriction in the context of legislation on the quality and safety of cells (as in directive 2004/23); allowing patients in Europe to be denied access to products resulting from such technologies, whilst others benefit, is going a step further.

46. Neither is it sufficient to suggest that patients may travel from one member state to another to gain access to treatment: ethically restrictive member states would presumably prevent reimbursement of such treatment also. Hence, access would be limited to those patients who were able to afford treatment themselves, those with supportive families and friends, and those able to travel. The non-Europe in bio-ethics therefore runs the risk of opening new social divisions, and of undermining the idea of social solidarity in access to healthcare.

47. It will be important for Parliament and Council to debate this issue again as in this case the non-Europe in ethics will cut directly across patient access to authorized medicinal products. At the very least, Parliament and Council should take political responsibility for confirming that the logic of non-Europe should apply in the case of this legislation as it does for the human cells and tissues directive.

48. One thing that should be uncontested, however, is the requirement that member states which do not allow patients on their territory to have access to certain advanced therapy products should be required to make this known. The Commission’s proposal provides that in such cases “Member States shall communicate the national legislation concerned to the Commission” (Article 28). This information should also surely be published.

49. *Xenogeneic products.*

Products derived from cells or tissues of animal origin raise further ethical tensions. In connection with xenogeneic transplants, for example, the Bioethics Discussion Group of the Commission of the Bishops' Conferences of the European Community (COMECE) noted in 1999 that²¹

“Problems of identity or a compromise of the “spiritual personality” could arise as transplants expand to cover the nobler organs with a heavier sentimental or emotional charge”, and added that “Humanity also concerns the spirit and there are therefore likely to be identity reflexes”.

50. It is necessary to contrast such sentiments with the development in future of life saving treatments for patients which, in many cases, will be their only hope of life. According to the Commission's proposal, xenogeneic cell and tissue therapy medicinal products would be covered by the same logic of non-Europe as that applying to embryonic stem cells namely, xenogeneic products are included in the proposal but without prejudice to national legislation prohibiting or restricting the sale, supply or use of such cells. An EMEA marketing authorization would be valid only in those member states where such a marketing authorization does not contradict national legislation.

51. Some religious organizations have suggested excluding xenogeneic products entirely from this proposal. Were xenogeneic products to be excluded the current fragmentation of regulatory approaches in Europe would be perpetuated and the shared scientific and assessment resources of the EMEA would be prevented from contributing to patient safety. Nobody doubts that risks exist in the use of xenogeneic cell and tissue products. However, excluding such products from this proposal would succeed only in making their regulation and assessment less stringent and most likely lead to patients in some member states being exposed to risks that otherwise could be avoided. Indeed, cell therapy medicinal products based on animal cells have in any case been covered by EU pharmaceutical legislation since 2003 and medical devices incorporating animal cells since 1993.

52. The inclusion of xenogeneic cell and tissue products in the Regulation will make available the resources of the EMEA for the assessment and regulation of such products. This is likely to be to Europe's common benefit in reducing and avoiding risks to patients. However, it is for Parliament and Council to review the ethical issues surrounding xenogeneic products, in particular with a view to taking political responsibility for the possibility that access to potentially life-saving therapies could be denied in parts of Europe, on the grounds of ethical unease.

²¹ http://www.comece.org/upload/pdf/work_bio_pv4_990304_en.pdf

Incentives

53. This proposal brings advanced therapy products within the regime of incentives established for centrally authorized medicinal products. During Parliament's review of EU medicines licensing rules during 2001 - 2003 this system of incentives was a point of significant political disagreement. Eventually Parliament opted for a harmonized data protection period of eight years of data exclusivity, two years of marketing exclusivity, with an additional year of exclusivity for new indications (the 8+2+1 formula). In addition to this incentive advanced therapy products will also be able to be designated as orphan medicinal products and to benefit from the incentives offered for such medicines. As for other centralized licensing procedures, accelerated assessment will be possible in the case of major public health interest in particular from the viewpoint of therapeutic innovation, as will marketing authorizations in exceptional circumstances and conditional marketing authorizations. A 90 per cent fee reduction for EMEA scientific advice is also proposed for advanced therapy products, as are special incentives for SMEs.²²

54. In the case of the proposal before Parliament relating to pediatric medicines (COM (2004)599 – Grossetete report) the Commission has insisted that the incentive proposed to encourage pediatric medicine research and development (an additional six months extension of exclusivity) should only become available "if the product is authorized in all Member States".²³ This provision can be contrasted with the situation envisaged in the advanced therapies proposal, whereby EU resources and incentives will be made available for the licensing of advanced therapy medicinal products via the centralized procedure, yet national ethical concerns, as noted above, could result in products remaining beyond the reach of patients across the Union. There could be a contradiction here which Parliament may consider it appropriate to explore further.

²² See http://pharmacos.eudra.org/F2/advtherapies/docs/SEC_2005_1444_EN.pdf, pp. 22-23

²³ Amended proposal on medicines for pediatric use; amendments not accepted by the Commission, pp. 14-15. See: http://pharmacos.eudra.org/F2/Paediatrics/docs/COM_2005_0577_EN.PDF.

Hospitals and tissue banks

55. An important consideration during the development of this proposal was the extent to which it could unintentionally impact hospitals and tissue banks. A limited number of hospitals and tissue banks in the EU are involved in tissue engineering for their own patients or for supply locally. The particular circumstances of small scale manufacture of tissue engineered products in hospital environments need to be recognized. The treatment only of individual patients, or very small numbers of patients, should not be subject to the requirement for marketing authorization via the EMEA.

56. The Commission has sought to define advanced therapy products to include only those “intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process”. One problem is that this clarification appears only in recital 5 of the proposal. It might be appropriate for Parliament to set out in the text of the Regulation itself that its requirements do not apply to products prepared in full and used in a single hospital in accordance with a medical prescription for an individual patient. Directive 2001/83 (as amended) on the Community Code relating to medicinal products contains a similar list of exclusions (eg. magistral formulations), and for the sake of clarity it might be useful to do the same in this case. This would reassure those with concerns about the unintentional impact that this legislation might have on hospitals and other very small scale operations.

57. A very careful balance is needed here. On the one hand, European patients must be able to expect that products with which they are treated are safe, of high quality and efficacious, with appropriate pharmacovigilance requirements. On the other hand, European law must not be too heavy handed or, for that matter, erect too high a barrier to entry to new operators, or deter research and development.

The proposed Committee on Advanced Therapies

58. The Commission proposes to establish a Committee for Advanced Therapies (CAT) within the EMEA. This body would comprise

- five members and five alternates of the EMEA's Committee for Medicinal Products for Human Use (CHMP)
- one member and one alternate appointed by each member state whose national authorities are not represented among the members and alternates appointed by the CHMP
- four members appointed by the Commission – two to represent surgeons and two to represent patients associations.

59. The role of the CAT will be to:

- advise the CHMP on “data generated in the development of an advanced therapy medicinal product, for the formulation of an opinion on its quality, safety and efficacy” (Article 23(a))
- provide expertise to the CHMP and the Commission on scientific issues relevant to advanced therapies
- provide advice at the request of the Executive Director of the Agency or the Commission
- assist scientifically in the elaboration of documents relating to advanced therapy products (eg. guidelines and technical guidance)

60. The CAT will not in its own right adopt scientific opinions leading to the grant of a marketing authorization. This will remain a responsibility of the CHMP. More strangely, the proposal as currently drafted does not require the CAT to be involved in giving advice in cases where this is requested of the Agency under, for example, articles 17 and 18 (scientific advice and scientific recommendations on classification). This may be an oversight and may need to be rectified.

61. Also strangely, it is proposed that the composition of the CAT would be significantly different from that of the Committee on Orphan Medicinal Products, with which it is likely to be compared. The latter comprises one member nominated by each member state, three members (nominated by the Commission) to represent patients' associations and three other members (again nominated by the Commission). The Commission should clarify why it has chosen yet another formulation for the composition of the CAT. In addition, there will no doubt be suggestions that the CAT should count among its members an individual whose background includes bio-ethics.

62. Parliament may also wish to examine with Council and Commission whether it is possible yet to establish the CAT with less than all member states represented on it. This is probably unlikely for the present but there will clearly come a point at which it will no longer be considered necessary for each member state to be represented on such committees. Expertise is, after all, undoubtedly in this case a far more important criteria for membership of the CAT than national origin. The member states are anyway fully represented on the CHMP. Under the proposal all representatives on the CAT are required to be expert in scientific areas covered by advanced therapies (Article 21.2). This is welcome.

63. On potential conflicts of interest, the same provisions will apply to members of the CAT as those that apply to members of the EMEA Management Board, committees, rapporteurs and experts. The Commission additionally proposes that indirect interests relating to the pharmaceutical sector, medical device sector or biotechnology sector be entered in a public register (as established by Regulation 726/2004, Article 63(2)). This is appropriate.

Donor consent

64. The proposal requires that the donation and procurement of human tissues and cells must be done in accordance with directive 2004/23 on human cells and tissues. The procurement of tissues and cells on a voluntary basis and without direct payment was a major point of parliamentary concern during the adoption of directive 2004/23 (Liese report). The eventual compromise arrived at provides for the following:

Article 12

Principles governing tissue and cell donation

1. Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells.

Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted.

Member States shall report to the Commission on these measures before 7 April 2006 and thereafter every three years. On the basis of these reports the Commission shall inform the European Parliament and the Council of any necessary further measures it intends to take at Community level.

2. Member States shall take all necessary measures to ensure that any promotion and publicity activities in support of the donation of human tissues and cells comply with guidelines or legislative provisions laid down by the Member States. Such guidelines or legislative provisions shall include appropriate restrictions or prohibitions on advertising the need for, or availability of, human tissues and cells with a view to offering or seeking financial gain or comparable advantage.

Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non-profit basis.

Article 13 of directive 2004/23 refers further to the legal requirements applicable in member states and sets out in an annex the information which must be provided to donors or their relatives for consent or authorization.

65. In view of the significance of this aspect of the proposal and Parliament's likely concern about it, Parliament may consider it appropriate to review the Commission's assessment of the implementation of these provisions (see paragraph 1, Article 12, directive 2004/23, above) during the legislative scrutiny of the advanced therapies proposal.

ANNEX

Directive 2004/23 setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Traceability and confidentiality

Article 8

Traceability

1. Member States shall ensure that all tissues and cells procured, processed, stored or distributed on their territory can be traced from the donor to the recipient and vice versa. This traceability shall also apply to all relevant data relating to products and materials coming into contact with these tissues and cells.
 2. Member States shall ensure the implementation of a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
 3. All tissues and cells must be identified with a label that contains the information or references allowing a link to the information referred to in Article 28(f) and (h).
 4. Tissue establishments shall keep the data necessary to ensure traceability at all stages. Data required for full traceability shall be kept for a minimum of 30 years after clinical use. Data storage may also be in electronic form.
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5. The traceability requirements for tissues and cells, as well as for products and materials coming into contact with these tissues and cells and having an effect on their quality and safety, shall be established by the Commission in accordance with the procedure referred to in Article 29(2).
 6. The procedures for ensuring traceability at Community level shall be established by the Commission in accordance with the procedure referred to in Article 29(2).
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Article 14

Data protection and confidentiality

1. Member States shall take all necessary measures to ensure that all data, including genetic information, collated within the scope of this Directive and to which third parties have access, have been rendered anonymous so that neither donors nor recipients remain identifiable.
 2. For that purpose, they shall ensure that:
 - (a) data security measures are in place, as well as safeguards against any unauthorised data additions, deletions or modifications to donor files or deferral records, and transfer of information;
 - (b) procedures are in place to resolve data discrepancies; and
 - (c) no unauthorised disclosure of information occurs, whilst guaranteeing the traceability of donations.
 3. Member States shall take all necessary measures to ensure that the identity of the recipient(s) is not disclosed to the donor or his family and vice versa, without prejudice to legislation in force in Member States on the conditions for disclosure, notably in the case of gametes donation.
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