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Tissue engineered medical products (TEMPs): A prelude to risk management

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Abstract

In medical practice products containing cultured cells have emerged. These products could be labelled Tissue Engineered Medical Products (TEMPs). A literature review covering the past ten years was carried out to collect information useful for the assessment of risks associated with these products and to provide suggestions on developing regulatory strategies. The information was structured according to the EN-ISO 14971 standard for risk management. Regulations and standards for other medical products, such as medicinal products, blood and blood products and medical devices were discussed as to their applicability for TEMPs. Products that contain cells of animal origin were excluded. In view of the large amount of research currently being carried out, the number of available products is expected to increase in the coming years. Due to the novelty of TEMPs, their risks have not been clearly identified yet. Experiences with other medical products indicate the most important risks as being related to transmission of disease, bio-compatibility and efficacy. All parties involved in the life cycle of TEMPs will take decisions on the acceptability of risks. These decisions are preferably based on pre-defined standards. Although these are not available for TEMPs at the moment, they can be expected in the (near) future. Most measures for risk control included in current regulations and standards covering products like medicinal products, blood and blood products and medical devices were found to be applicable in generic form to TEMPs. Control measures for TEMPs should be combined into a regulatory framework which is complementary to current European regulation on medical products and attuned to it.

Preface

This report describes risk management strategies for the application of Tissue Engineered Medical Products (TEMPs) in medical practice. This review was performed on the joint request of the Health Care Inspectorate and the Pharmaceutical Affairs Department, both part of the ministry of Health, Welfare and Sport of the Netherlands. The information gathered here is presented as basic information to staff of these departments who contribute to the design of a Dutch act on human tissues, but it may also be useful for other parties involved in the life cycle of TEMPs.

The chosen approach starts by labelling TEMPs as neither being a medicine nor a medical device. This in itself may be disputable, but it was considered essential for a 'de novo' approach to discuss an optimal set of risk management strategies for TEMPs. This set of strategies obviously refers to elements from existing strategies for medicines or medical devices and combines these in a free fashion. Readers having affinity with the world of medicines and/or medical devices are invited to follow the approach as described and for a moment step aside the(ir) well-trodden regulatory paths.

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Samenvatting

Zeer veel wetenschappelijk onderzoek is en wordt verricht op het gebied van de vervaardiging van biologische substituten die weefselfuncties kunnen herstellen, handhaven of verbeteren. Een groep van deze substituten die levende cellen bevatten is te benoemen als 'Tissue Engineered Medical Products' (TEMPs). Het is te verwachten dat in de komende jaren een toenemend aantal producten ter beschikking komt voor patiënten, waarbij ervaringen met gerelateerde medische producten suggereren dat de belangrijkste risico's liggen op het gebied van overdracht van ziekten, biocompatibiliteit en werkzaamheid. Europese regelgeving die de kwaliteit en veiligheid van deze producten bewaakt ontbreekt op dit moment, maar maatregelen ter beheersing van risico's uit bestaande regelgeving voor medische producten zoals geneesmiddelen en medische hulpmiddelen lijken in generieke zin toepasbaar voor TEMPs.

Dit is van belang voor alle partijen die betrokken zijn bij de fabricage van TEMPs. Zij zullen besluiten moeten nemen t.a.v. de acceptatie van risico's en zich moeten voegen naar de nader vast te stellen regelgeving voor deze producten. Specifieke standaarden die besluiten ten aanzien van de acceptatie van de risico's kunnen ondersteunen ontbreken momenteel, maar zijn in de nabije toekomst te verwachten.

Alle betrokken partijen verlangen de vaststelling van specifieke Europese en nationale regelgeving. Ter ondersteuning van de ontwikkeling van specifieke strategieën voor risicomanagement en regelgeving zijn de risico's die samengaan met TEMPs geïdentificeerd met behulp van een overzicht van de relevante literatuur van de laatste 10 jaar, waarbij gebruik gemaakt is van de structuur van de EN-ISO 14971 standaard voor risicomanagement. TEMPs die cellen van dierlijke oorsprong bevatten zijn buiten beschouwing gelaten. Verder zijn de risicobeheersmaatregelen voor andere medische producten gewogen op hun toepasbaarheid voor TEMPs. Deze beheersmaatregelen zouden opgenomen kunnen worden in een structuur voor wet- en regelgeving die de bestaande Europese productregelgeving aanvult.

Het systematisch evalueren van de diverse opties tot beheersen van risico's van TEMPs draagt uiteindelijk bij aan bescherming van patiënten tegen onveilige of onwerkzame medische producten.

Summary

A large body of research has been directed at the creation of biological substitutes, which can restore, maintain or improve tissue functions. A certain group of these substitutes contain living cells and could be labelled as 'Tissue Engineered Medical Products' (TEMPs). It can be anticipated that an increasing number of products will become available for patients in the coming years. Experiences with related medical products indicate that the most important risks will relate to transmission of disease, biocompatibility and efficacy. European regulation that guards the quality and safety of these products is absent at the moment, but elements of current regulation on medical products like medicines and medical devices seem applicable in generic form to TEMPs.

These findings are relevant to all parties that are involved throughout the life-cycle of TEMPs. They will have to decide on acceptability of risks and will have to conform to the regulation that will be developed for these products. Specific standards that support the decisions on risk acceptability are not available at the moment, but can be expected in the near future.

Several parties have indicated their desire for European and national regulation for TEMPs. In order to support the development of risk management and regulatory strategies risks associated with TEMPs were identified by means of a review of the relevant literature of the past 10 years. This review was structured following the EN-ISO 14971 standard for risk management. TEMPs that contain cells of animal origin were excluded. Reference was made to regulations and standards for other medical products. Furthermore, risk management strategies were discussed with respect to their applicability for TEMPs. Control measures like those discussed are to be combined into a regulatory framework that is complementary to and connects with current European regulation on medical products.

The systematic evaluation of the various measures for risk control contributes to the protection of patients from unsafe or ineffective medical products.

1. Introduction

Health care technology is facilitated and supported by developments in various fields of natural sciences. In the last decade the combination of techniques that are derived from fields like (bio)material science, biochemistry, pharmacology and cellular physiology has produced new solutions for clinical problems and presents a promise for future products. One cluster of techniques is known as 'tissue engineering' and has been defined as *'the application of principles and methods of engineering and life sciences towards fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function'* [Skalak 1988]. The products that arise from these techniques may provide an alternative to available therapies to replace damaged, injured or missing body tissues. Conventional therapies either face a limitation of supply and necessitate immunosuppression (in case of transplantation) or do not completely replace all functions of a lost organ or tissue and often fail in the long-term (when using surgical reconstruction, drugs, mechanical devices). The theoretical possibilities of the concept of tissue engineering drives a large number of research and development programs that have resulted in an increase of knowledge relating to the control of cellular functions. These developments are expected to result in an increasing number of clinical applications in the coming decade.

From the wide range of innovative health care products that combine cellular elements with the traditional materials of construction we have defined a group, which we have labelled as 'tissue engineered medical products' (TEMPs) as subject of this review. We have confined the scope of this report to products that contain human cells or tissues. Consequently, TEMPs that contain xenogenic sources of cells are excluded from this report. Some of the products under consideration are already available and some are being evaluated in clinical trials. Other products that are merely theoretical possibilities at this moment have also been included. It is emphasised that TEMPs as such is not a widely (European) recognised acronym, but it is used for the purpose of this report.

The combination of living cells with biomaterials in TEMPs creates products for which presently no European regulation is in force [Jong 2000]. It may be anticipated that many of the risks associated with TEMPs will be similar to those associated with medicines and medical devices, although new risks will emerge. Therefore, a review of the strategies for management of risks is deemed necessary for TEMPs. Before specific risk management measures can be determined, specific risks must be identified and evaluated. This report reviews risk management strategies for TEMPs.

2. Methods

Various literature databases (e.g. Medline, Current Contents) were searched for relevant literature that was published during 1989-1999. The Internet was searched for additional information.
The resulting data were used for risk management purposes following the structure of EN-ISO 14971 'Medical-Devices- Risk Management - Application of risk management to medical devices'. Given the generic nature of the strategies described in this standard, it was deemed appropriate not only for the risks that can be related to the application of medical devices, but also of TEMPs. In EN-ISO 14971 the process of risk management is defined as the systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk. Risk management is described as a set of repeatable steps throughout the entire life cycle of medical devices, re-evaluation of all steps in the process being an essential part of the process. Subsequent steps include (see Figure 1):

- description of the intended use/purpose of the device, identification of known and foreseeable hazards and estimation of their risks
- evaluation of the identified risks
- analysis of control options, implementation of the selected control options and evaluation of residual risks
- a risk benefit analysis incorporating the results of the previous steps
- periodical re-evaluation of all previous steps, which incorporates all information available (including post-marketing information)

The primary user of risk management is the manufacturer, because it is this party that is placing the product on the market and therefore has the obligation to ensure quality, including safety. EN-ISO 14971 was designed as a framework to be applied by manufacturers for effective management of the risks associated with the application of medical devices. However, a systematic approach to analysis, evaluation and control of safety problems may also be of use to other parties like health care facilities, regulatory authorities and researchers.

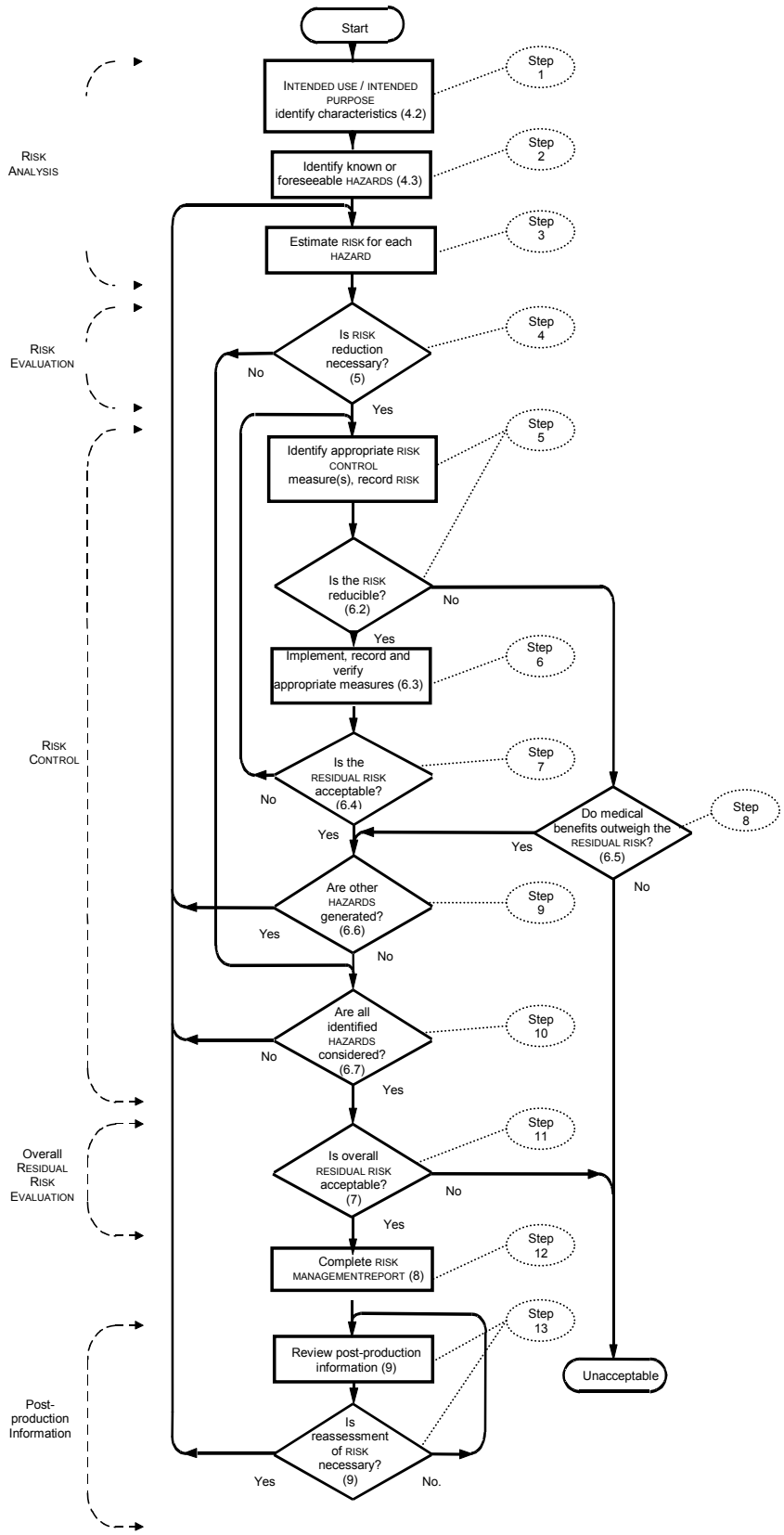

Figure 1. Overview of risk management process, EN-ISO 14971

3. Results

3.1 Risk analysis

3.1.1 Intended use/purpose of TEMPs

3.1.1.1 Basic product characterisation

TEMPs typically are a combination of three entities, i.e. isolated cells, an extracellular matrix (ECM) and signal molecules, such as growth factors.
The cells can be derived from autologous or allogenic sources. Theoretically, every cell of the body can serve as a source, but at this moment not every cell can be processed (e.g. kept in culture) to become part of a tissue-engineered product. Cells can be harvested from individuals ranging from embryo's in their early stages of development up to adults. Evidently, the role of the cells is to form a new tissue. The expression of the appropriate genes to develop and maintain the tissue-specific functions must be guaranteed in the final product.
The ECM serves three primary roles. Firstly, it facilitates the localisation and delivery of cells in the body. Secondly, it defines and maintains a three-dimensional space for the formation of new tissues with appropriate structure. Thirdly, it guides the development of new tissues with appropriate function. The ECM can consist of biodegradable, or non-degradable material, usually polymers. These materials can be synthetic, like poly-lactic acid, poly-glycolic acid, hydroxy apatite or isolated from natural sources, like collagen, hyaluronic acid, alginate. The interaction of cells and the ECM is of great importance for the intended function of the final product.
Signal molecules serve as additional and essential stimuli in order to guide the cells towards their intended function. These signal molecules can be synthesised by the cells during their interaction with the ECM. They can also be isolated or synthesised and attached to the ECM before having contact with cells, or they can be added to the product in a final stage. Examples of signal molecules are Epidermal Growth Factor [Pollok 1996], Angiogenic Factors, Bone Morphogenetic Proteins, Transforming Growth Factor-ß, Nerve Growth Factor and Fibroblast Growth Factor [Baldwin 1998].

3.1.1.2 Intended use

The intended use of TEMPs is the treatment of the loss or malfunction of a tissue or an organ. TEMPs are intended to be used as implants or as extra-corporeal devices to be connected to the blood circulation of the patient. While extra-corporeal connection is usually for temporary support (e.g. liver support), the longevity of TEMPs after implantation can vary and will partly depend on the degradation characteristics (possibility and speed) of the matrix and the persistence of viable cells.
TEMPs are supposed to support or replace the functions of diseased tissues. Generally, two specific cell/tissue functions can be discerned: structural (skin, bone, cartilage, blood vessels) and metabolic (e.g. insulin synthesis and secretion). The level of interaction between the product and the tissue of the recipient can be local (providing a scaffold for cells) and/or systemic. Within the group of systemic TEMPs, a subset can be discerned of which the cells are encapsulated. This capsule not only functions as a means to deliver and localise the cells in the body but also as a semi-permeable barrier. The object of this strategy is to prevent

immunological recognition and subsequent rejection phenomena while nutrients and cell products can be exchanged with the surrounding recipient tissues.

3.1.1.3 Current products

Several skin and cartilage TEMPs are available on the market [Eaglstein 1997, Eaglstein 1998].
Dermagraft® (neonatal human dermal fibroblasts, including collagen, growth factors, matrix proteins on resorbable poly-G-lactin, additional pre-marketing studies required by the FDA); Dermagraft TC® (avital human neonatal dermal fibroblasts, including collagen, growth factors, matrix proteins on nylon mesh covered by a silicone membrane, FDA approved); Apligraf® (neonatal human keratinocytes on neonatal dermal fibroblasts, including collagen, growth factors, matrix proteins on bovine collagen, FDA approved); Epicel® ASAProgram (vital autologous keratinocytes on petrazolum mesh) [Eaglstein 1998].
Carticel® is a product consisting of autologous chondrocytes, which have been cultured and stimulated to proliferate after harvesting in order to be returned to the donor for repair of traumatic damage of knee cartilage[1].
A review of the current state of the art of research on tissue engineering indicates that almost every kind of tissue of the human body is the focus of study. Several tissues are only studied in vitro, but an increasing number of products is being evaluated in animal studies or clinical studies. In Appendix 1 a summary is given of the various tissue types that have been studied. In case of successful animal studies, these tissues can be expected to be evaluated in clinical studies in the near future. Table 4 in Appendix 1 lists examples of innovative health care products that are either in development or already on the market. For all kinds of tissues it may be expected that eventually the powerful combination of tissue engineering and gene technology will be used to construct superior products.

3.1.1.4 Life cycle of products and involved parties

Throughout the life cycle of medical products one can discern several phases such as research and development, selection of source materials, manufacturing, product review, application, follow-up. Inherent to 'high tech' medical products is the diversity of parties involved in customer-supplier relationships during these phases and the various roles they fulfil (see Table 1). Risk evaluation at any phase of lifecycle is the responsibility of the manufacturer.

Briefly, the quality of the TEMP throughout its life cycle depends on the quality of and the interactions between the components, which are obtained from various establishments. The quality of processing and of the agreements between these parties are also relevant to the quality of the final product. The manufacturer should ensure the quality of the product throughout its lifecycle.

Human cells can be derived from living donors, brain-dead donors, deceased donors (shortly after circulatory arrest), foetal donors and embryos. Ethical aspects will play an important role in this phase of tissue engineering. Harvesting of cells/tissues can be organised by health care providers (in a hospital ward/morgue, at home), or by specially designed laboratories (e.g. blood/cell bank). After harvesting, cells/tissues can be stored in commercial or non-commercial banks, either before processing (e.g. isolation/selection of various cell types), or following processing, enabling storage of e.g. separate cell lines in a bank (e.g. frozen stem cells). In order to prepare cells/tissues for further processing, manipulation ranges in complexity from minimal (e.g. freezing) to extensive (e.g. influencing division and development of cells). These

[1] See http://www.fda.gov/medwatch/safety/2000/cartic1.pdf (Rev. G 2/2000), july 2001

manipulations can be performed by hospitals, universities, companies, or in sequence by these various institutions. The same parties, on their own or in various forms of co-operation, can be involved in the actual construction of a TEMP.

Given the diversity of components of TEMPs suppliers will probably specialise in the production of components and/or half-products (cells, matrix materials, signal molecules). It can be foreseen that matrix materials with various characteristics (e.g. degradation speed, structural strength) tailored to specific applications will be manufactured in bulk quantities and become available for other parties as 'half-product' for inclusion in a TEMP. The same development is expected for the signal molecules. Specialised companies are already manufacturing growth factors, e.g. angiogenic factors. This situationcan theoretically be further expanded to a scenario in which specialised cell banks can offer any cell line by manipulation of human stem cells.

Review of results of pre-clinical testing is mandatory to optimise production processes and to assess acceptability for subsequent clinical evaluation. Review of results of pre-clinical as well as clinical evaluation contributes to assessment of acceptability of marketing. As regulatory authorities are involved in the protection of the public health, it can be expected that this phase will be subject to their control. The follow-up of patients carrying TEMPs can be performed by health care providers. Both health care providers and patients are the parties most likely to become aware of adverse events and report these through the appropriate channels.

Table 1. Parties possibly involved and their roles during the life cycle of TEMPs

Role	**Party**
Sourcing	
Source of cellular components/tissues	Donor
Source of non-cellular components (signal molecules/matrix materials)	Supplier
Harvesting of cellular components/tissues	Manufacturer, laboratory, hospital
Processing	
Manipulation/storage of cells	Laboratory, bank, manufacturer
Construction of TEMPs	Manufacturer
Testing/Evaluation	
Pre-clinical evaluation	Manufacturer/Test house
Clinical evaluation	Manufacturer/CRO/Health care provider/ recipient/Ethical review commission
Marketing authorisation	Competent Authority or designated body
Clinical application	
Application of TEMPs	Health care provider
Follow-up of TEMP-patient combination	Health care provider/recipient
Reporting adverse events	Health care provider, manufacturer, recipient

3.1.2 Hazard identification

Publications and reports on adverse events with TEMPs are scarce, mainly because of limited clinical experience. Only a small number of products have been available for a few years. An other explanation can be the absence of regulation for this class of products, which means absence of the obligation to report. The Manufacturer and User facility Device Experience database (MAUDE) of the FDA has only a limited number of records that relate to TEMPs. A

search (August 1999) resulted in no reports concerning Carticel® and 22 reports (20 adverse events and 2 other) on Dermagraft® and Dermagraft-TC®. All cases described infectious complications in fourteen burn patients and eight patients with ulcers. As an infection is a very common complication in burn and ulcer patients it is not surprising that the classification of the relation between the product and the complication varied between 'unknown', 'remote' and 'possible'.
A number of hazards that are related to TEMPs are listed in Table 2, Part A. Most of them are either theoretical or derived from experiences with transplantation of human tissues and organs [Gottesdiener 1989, Patel 1997]. Additional, but more generally applicable (public health) hazards are, for example: absence of regulation on the safety of hazardous products, control measures themselves (e.g. false-negative HIV test results, virus inactivation steps introducing chemical residues).

3.1.3 Risk estimation

Several forms of 'potential harm' that are associated with the hazards in Table 2, Part A are listed in Table 2, Part B. As previously discussed, the clinical experience with adverse events of TEMPs in terms of frequency and severity of outcome is limited. Consequently, quantification of the magnitude of the various risks is not possible at this moment. However, considering the (clinical) experience with related product groups like organ transplantation and biomaterials, it is foreseen that the most important risks are related to transmission of disease, biocompatibility and efficacy.
Transmission of disease is a significant risk carried by products containing living cells and tissues. Conventional sterilisation procedures cannot be used because they compromise the viability of cells and therefore the efficacy of the product. Biocompatibility relates to the dynamic interaction between the TEMP and the recipient: TEMP cells react to their (micro-) environment and the recipient's immune system reacts to the implant. These mechanisms will also affect efficacy. Efficacy can also be compromised by inconsistent quality of the final product. Manufacturing of TEMPs requires considerable control of cell culturing and processing techniques in order to produce TEMPs of consistent and high quality. An additional risk lies in the unfamiliarity of users with (these) new products, the indications/contraindications for use, clinical handling and complications.

3.2 Risk evaluation

It should be decided for each identified hazard whether the magnitude of estimated risk(s) is acceptable, or requires the pursuit of risk reduction. However, while probabilities on the occurrence of adverse events can often be extremely remote, it is universally accepted that in all cases, zero risk is an unattainable goal. For instance, when using TEMPs in allogenic applications, the risk of transmission of disease cannot be fully eliminated without damage to the cellular functions. Therefore, the level of safety to be expected and achieved must be defined.

As with safety, the acceptability of risks is not an absolute concept. No fixed level of risk has been identified as acceptable in all cases and under every regulatory program. The acceptability of the risks depends on [Fischhoff 1993]:

- the probability of the occurrence of the hazard and the severity of the harm,
- the reversibility of the health effect,
- the (im)possibility of further risk reduction,
- the knowledge or familiarity of the risk,

- the fact whether the risk is voluntarily accepted or involuntarily imposed,
- the benefits of the risk imposing activity,
- risks and benefits of any alternative.

Additionally, possible compensation for the exposure to the risk may also play a role when a decision has to be made on the acceptability of risk. Deciding on risk acceptability is an iterative process. Once new information becomes available, for example in the post-marketing phase, the acceptability of risk should be re-evaluated.

Risk evaluation can be based on predefined safety standards. Standards should specify requirements which, if implemented, will indicate achievement of acceptability concerning particular kinds of TEMPs or particular risks [EN-ISO 14971, 1999]. A brief review of the development of safety standards in general and for specific product groups like medicinal products, medical devices, IVD's and blood (products) is given in Appendix 2. Specific standards for TEMPs are not available at this moment. The American Society for Testing and Materials has set up a division to formulate mostly product-specific standards for TEMPs, which are expected to be finalised in the next few years (see Appendix 3). The European Committee for Standardization (CEN) has set up a task group to determine the need for development of European standards related to tissue engineering. This group recommends the start of standardisation on horizontal subjects related to the field of TEMPs. Specifically the following subjects are mentioned: risk management, quality systems, biological safety, microbiological safety, and terminology. It is to be expected that a number of existing safety standards for medicinal products, medical devices and blood products can be used for TEMPs, or for their components after validation with respect to their applicability for TEMPs. For a non-exhaustive list of standards and documents (for related products) that can be of interest also for TEMPs, see Appendix 4. An important issue in combining standards is whether it is allowed to add the results of separate safety evaluations of each of the different components of a product. The combination of components should also be safe. It is well known, also for risks, that the combination can be more than the sum of the parts, which means that at least additional testing would be required.

3.3 Risk control

A pan European regulatory framework for health care products arising from tissue engineering is not yet in place. In order to limit the probability that the hazards identified in Table 2, Part A might cause harm and to reduce the (severity of) possible consequences as described in Table 2, Part B, control measures can be considered, as listed in Table 2, Part C. These risk control measures should be considered throughout the life cycle of TEMPs. Control measures, although very diverse in nature, can be characterised by three aspects: 1) *When* (phase of life cycle) are they applied; 2) *What* measure is applied; 3) *Who* is (responsible for) applying the control measure.

When

Control measures can be applied in any phase of the life-cycle of the product. However, the production and pre-marketing phases may deserve special attention, as prevention still is the mainstay of risk management. The borderline between pre-marketing and post-marketing is an important time point, because it involves decisions to be made as to which products are considered safe enough to be used in the general patient population. The post-marketing phase is important because the product is then used in daily practice, which generates useful experience.

Table 2. Hazards, potential harm and control measures related to TEMPs.*

	Part A **Hazard**	***Part B*** **Potential Harm**	***Part C*** **Control measures**
1	Microbial contamination of cells and/or matrix	• local/systemic infection/disease transmission, possibly also leading to malfunction	• selection/screening of sources • decontaminating measures • sterility testing
2	Contamination of cells and/or matrix with viruses, parasites, TSE's	• local/systemic infection/disease transmission	• selection/screening of sources • inactivation/elimination processes • product quarantine procedures
3	Natural variation in cell characteristics (e.g. production of insulin)	• desired effect not achieved (under-/overtreatment)	• quality control of source materials
4	Variation in natural source materials (e.g. ratio's of types of collagen)	• desired effect not achieved	• quality control of source materials
5	Contamination of cells/tissues for autologous use with allogenic cells	• disease transmission • immune-response/rejection leading to malfunction	• quality control of processing steps
6	Contamination with unwanted cell types	• desired effect not achieved • adverse effects	• cell-type specific culturing conditions
7	Endotoxin contamination	• pyrogenic reaction	• endotoxin testing
8	Reduced viability of cells	• desired effect not achieved	• viability testing
9	Altered gene expression by cells affecting intended synthesis	• desired effect not achieved • adverse effects	• RNA-testing
10	Tumourogenicity	• uncontrolled cell growth in product	• process monitoring
11	Processing residues	• toxic/immunologic effects	• processing/final product testing
12	Processing/manipulation: minimal vs. complex	• alteration of cellular function	• increasing level of quality control of processing and products from minimal to complex processing
13	Production time of (autologous) TEMPs	• deterioration of condition of patient	• criteria for application
14	Inadequate function of active/metabolic TEMP (e.g. releasing insulin)	• potential systemic effects	• follow-up
15	Heterologous intended use (e.g. cartilage cells around ureter), incompatibility of TEMP source cells and target tissue	• desired effect not achieved • adverse effects due to local tissue reaction	• increasing level of control as compared to homologous intended use
16	Altered structural strength of ECM (e.g. membrane failure of encapsulated TEMPs)	• desired effect not achieved • overdose by massive release of entrapped substances • immune phenomena	• mechanical testing • testing of resorption speed
17	Histoincompatibility	• rejection, possibly leading to malfunction	• HLA matching • immunosuppression
18	Bio-incompatibility of (metabolites/components of) the biomaterial	• adverse effects • cross reactions/auto-immune phenomena	• biocompatibility testing (e.g. cytotoxicity, mutagenicity, hemocompatibility)
19	Tumourogenicity	• neoplasm formation in recipient tissue	• follow-up
20	Altered resorption/diffusion	• desired effect not achieved • adverse effects due to accumulation of substances	• follow-up
21	Unanticipated hazards	• ?	• follow-up
22	Use-related hazards	• diverse	• labelling • training

* nr. 1-4: sourcing phase; nr. 5-13: processing phase; nr. 14-22: post-marketing phase

What
The methods of risk control are obviously closely related to the subject of control. One can for instance focus on the people that provide the safety-critical services, on critical manufacturing processes, on source materials. An integrated approach would be to require parties to implement a full Quality Assurance system. This would include control measures during the research & development and manufacturing stages such as performing in-process controls, review of product design, of the results of in-vitro testing, or animal and clinical studies. Additionally, specific systems (to be developed) that are unique to address the generic issues related to tissue engineering can be applied.

Who
The party that is responsible for the application of control measures, most often being the manufacturer, should be clearly identified. Depending on the timing of the application and the instruments used any party mentioned in Table 1 (or others) can be involved. In addition, it needs to be assured that the control measures are applied as intended and that the results conform to applicable standards. This involves an other party, which often is the regulatory authority. Their instruments in this situation are usually a formal review of documentation, inspection of facilities, etc.

It is clear that all these aspects are closely interrelated and can be combined in various ways. Furthermore, different review strategies can be applied for products in different groups that are classified according to the estimated magnitude of risk. This has been included for instance in the European regulation for medical devices and in the US in the FDA program "Proposed approach to regulation of cellular and tissue-based products" [FDA 1997]. Several criteria for risk classification of medical products that include cells have already been proposed [FDA 1997, Omstead 1998]. These criteria and additional ones are summarised in Table 3.

Table 3. TEMP parameters relevant to risk classification.

	Low Risk	High Risk
Cell Donor – Recipient combination	Autologous	Allogenic
Immuno-isolation potential	High	Low
Manipulation of cells	Minimal	More than minimal
Natural cellular function vs. intended function	Homologous use	Non-homologous use
Action	Structural (local)	Metabolic (systemic)
Contact site*	Ext./s.c./i.m.	i.p./i.v./i.t.
Potential for recovery	Yes	No
Duration of exposure	Short	Long
Information regarding indications for use	Adequate	Insufficient
User (medical staff) skill/experience	High	Low

*ext.: external; s.c.: subcutaneously; i.m.: intramuscularly; i.p.: intraperitoneally (in the abdominal cavity); i.v.: intravenously; i.t.: intrathecally (in the central nervous system)

The immuno-isolation potential applies to encapsulated TEMPs. Manipulation refers to a variety of techniques of handling cells, ranging from simple to complex, such as trimming, packing, controlled rate freezing, selection, culturing, stimulation, and incorporation of new genes. Homologous use refers to similarity in function between the source tissue of the cells and the tissue location after implantation. The potential for recovery applies to e.g. products

containing biodegradable materials. Such a classification scheme has resulted in control measures of the FDA focusing on: source selection (donor screening); processing; clinical safety/efficacy; promotion/labelling and monitoring (e.g. PMS-systems)/education. Certain subgroups of these products (e.g. having metabolic function, combined with a device) will be subject to US regulation for either biologicals or medical devices (see above) [FDA 2001b]. TEMPs with a structural function (e.g. bone, cartilage) can be considered to raise other safety issues than TEMPs with a metabolic function (e.g. insulin secreting Langerhans cells).

Complying with the EN-ISO 14971 we will follow the phases of product life cycle. In this paragraph we focus on the pre-marketing phase. The phase between pre-marketing and post marketing is dealt with in paragraph 3.4. The post-marketing phase is discussed in more detail in paragraph 3.5. In absence of specific control measures for TEMPs, measures for other medical products are frequently used as examples.

3.3.1 Quality systems

It is now generally accepted that quality assurance systems (e.g. ISO 9000 series) are a prerequisite to assure that handling, processing and manufacturing result in products that meet applicable requirements and specifications. In the field of medicinal products, manufacturers, suppliers, blood banks and test laboratories have to comply with quality system requirements like GMP, Good Laboratory Practices (GLP) and other more general quality assurance standards. Reference to these standards is included in recommendations for blood and blood products [R(95)15], and in regulation for medical devices [90/385/EEC, 93/42/EEC, 98/79/EEC] and medicinal products [65/65/EEC]. For medicinal products regulatory authorities ensure that the manufacture of the product is subject to the holding of an authorisation. To this end the regulatory authorities are allowed to inspect the facilities of the manufacturer. National law may require health care providers to formulate annual reports on plans and outcome of their quality management efforts.
With respect to the “products” that are processed by tissue banks, several organisations such as the European Association of Tissue Banks (EATB) have described their general standards, which can be appreciated as a form of Good Tissue Practices (GTP).
The American Association of Tissue Banks (AATB), similar to it’s European counterpart EATB, has also described guidelines. These guidelines have been reviewed in the developing of proposed new FDA rules for Current Good Tissue Practice (CGTP) to be used for the manufacture of all human cellular and tissue-based products [FDA 2001a].
An important element addressed by these quality assurance systems is the qualification and skills of staff, the ‘human factor’. General quality systems like ISO 9000 require that personnel are competent, trained, qualified, skilled and experienced. It should be realised that the educational requirements for personnel apply to all who are somehow involved in the life cycle of a product, e.g. regulatory authorities, notified bodies, distributors, (hospital) purchasers and clinicians who apply the product. All these requirements can be expected also to be applicable for TEMPs.
The requirement that personnel involved in the development and manufacturing of medicines is appropriately qualified is laid down in the EU in directives [75/319/EEC].
No formal regulation exists which specifies the educational requirements for personnel in medical device and in vitro diagnostic industry. However, the existence of a quality system is often a requirement in the EU regulation for medical devices and in vitro diagnostics.
For blood and blood products, the requirements for personnel involved in processing are described in Recommendations of the European Council [R(95)15], which rely on Good Manufacturing Practice (GMP). Also the proposed CGTP of the FDA includes this aspect.

Directives describe minimal requirements for the qualification of personnel involved in the authorisation process of medicinal products [(EEC) No 2309/93], medical devices [90/385/EEC, Annex 8, 93/42/EEC, Annex XI] and in-vitro diagnostics [98/79/EEC, Annex IX].

3.3.2 Product testing

During the pre-marketing phase the safety aspects of any medical product can be evaluated by reviewing the results from pre-clinical studies as well as results from clinical investigations. Pre-clinical safety testing (in vitro/in vivo) generally focuses on physical and biological characteristics of the product and the interaction between (components of) the product and biological systems like cells or animals. Clinical testing focuses on performance and/or efficacy evaluation and safety evaluation in humans. In dealing with the phasing between pre-clinical and clinical studies, two issues need to be distinguished: 1) safety information from pre-clinical studies must warrant the start of clinical investigations in humans); 2) safety information from clinical and pre-clinical studies must warrant marketing of the product. For medicinal products and medical devices the contents and phasing aspects of pre-clinical and clinical testing have been formulated in various standards.

3.3.2.1 Pre-clinical studies

Pre-clinical safety studies with medicinal products focus on the pharmacological, toxicological and immunological effects. For some product groups viral safety aspects are also relevant. Requirements have been formulated in several documents (see Appendix 3). The topic of phasing of pre-clinical studies in relation to clinical studies is dealt with in several ICH documents [ICH1 1997].

For medical devices, guidance for evaluation with respect to the performance or efficacy is defined in several standards (see Appendix 4). Parts of these are horizontal standards, which are applicable to all medical devices. Additional vertical standards have been developed for specific (groups of) products or processes. Standards refer to aspects such as electrical safety, biocompatibility, risk management and viral safety (relating to the use of animal tissues). At present no horizontal guidance document deals specifically with the phasing of pre-clinical studies with medical devices in relation to clinical studies. This topic is part of the risk management process, and is dealt with in the standard on risk management for medical devices (EN-ISO 14971) and the draft guidance of the FDA on the contents of product development protocol (PDP) applications. Several vertical (product specific) US guidance documents deal with the phasing of pre-clinical studies in relation to clinical studies.

For blood and blood derived products the required characteristics have been described in various Recommendations of the Council of Europe [98/463/EC, R(95)15, R(86)6]. These recommendations are additional to European Agreements (e.g. on the exchange of therapeutic substances of human origin, 1958). A large part of these standards consider the selection and testing of donors. This aspect has also been included in proposed US regulation on human cellular and tissue-based products [FDA 1999c].

3.3.2.2 Clinical studies

By adopting the European directives [65/65/EC, 75/318/EEC] in national laws, clinical evidence on safety and efficacy of medicinal products needs to be provided pre-marketing by clinical trials. There are several standards and guidance documents that apply to clinical trials. The worldwide recognised ICH/GCP guidance documents have been developed for clinical trials involving medicinal products. The ICH/GCP guidance documents address among other things organisational, design and statistical considerations for clinical trials. The

regulatory status of ICH/GCP will gain with the adoption of the Clinical Trial Directive which regulates the implementation of ICH/GCP in the conduct of clinical trials on medical products for human use.
The provision for clinical evidence of safety and performance of medical devices is not as strictly regulated as that of medicines. While a considerable body of scientific literature and guidance documents is available on methodology of clinical trials with medicinal products, less can be found on methodology of clinical studies with medical devices and related products. To ensure device functionality, monitor safety, and gain experience in using the device prior to commencement of a full size clinical study, a pilot or feasibility study may be performed. Furthermore, the quality of the safety information derived from clinical studies depends highly on the scientific value of the clinical investigation. Two horizontal standards apply to clinical studies with medical devices: EN 540 and ISO 14155. Both standards (which are currently being harmonised) only address the organisational requirements and responsibilities for the parties involved in clinical studies. Currently an EN standard is being developed which deals with clinical investigation plans (protocols). Design and statistical issues are not addressed in this standard. The organisational requirements and responsibilities in relation to clinical investigation of medical devices in the US are described in the Investigational Device Exemptions Manual [FDA 1996a]. The issue of scientific evidence is dealt with in a FDA statistical guidance for clinical trials of non-diagnostic medical devices [FDA 1996b].
Clinical trials involving the use of components and fractionated products derived from human blood or plasma have been described in a Recommendation [R(93)4]. An other recommendation in this field addresses medical research on human beings [R(90)3].

3.3.3 Residual risks

Earlier (3.2) it was stated that a zero risk is not achievable. Standardised control measures cannot prohibit that the reduction of risks below certain limits may be hampered by technical constraints. An example is the technical impossibility to select organ donors with 100% freedom of viruses. Processing activities to reduce the risk of infection may also introduce new risks, for example the adverse effects of residues from sterilants.
Furthermore, some potential (residual) risks may not be identified during the pre-marketing process. This can be a result of the limitations of the safety standards themselves. During clinical studies, for example, only a limited group of people is exposed to a product, and often only a limited number of physicians participate. The patients form a highly selected and carefully screened group of people, which are closely monitored. Furthermore, participating physicians often have special interest in the therapy under study and may receive extensive training for the purpose of the study. Because of these selection mechanisms the clinical study does not fully represent the clinical situation after market introduction of a therapy.
Finally, even the flawless and comprehensive application of standard control measures cannot prevent previously unknown risks to emerge after market introduction. An example is the discovery that the CJD agent was transmitted by human pituitary derived growth hormone.

3.4 Overall risk evaluation

During the process defined in the previous paragraphs, stakeholders identify each hazard, evaluate the risks, and implement and verify risk control measures one at a time. Subsequently, there is a need to step back, add up all the individual residual risks, and decide on the acceptability of risks and the need and possibility for further risk reduction: the overall risk evaluation. It is possible that the overall residual risk can exceed the stakeholders'

criteria for acceptable risk, even though individual risks do not. If a manufacturer judges the overall residual risk to be acceptable, the marketing phase can be entered. According to current regulation for most medical products tregulatory authorities or designated independent bodies (e.g. Notified Bodies) decide on the acceptability of the overall residual risk of the product by assessing the scientific evidence on safety and performance/efficacy as provided by the manufacturer. If the safety and performance/efficacy is deemed acceptible, market authorisation can be granted.

The existing regulatory frameworks for marketing authorisation of blood, medicinal products, medical devices and in-vitro diagnostics show differences. Authorisation schemes for these product groups also differ between EU and US.

For medicinal products marketing authorisation is granted by regulatory authorities. Extensive files addressing quality, safety and efficacy of the product need to be submitted by the manufacturer to these bodies. In the United States this task is carried out by the FDA (CDER and CBER). In Europe different procedures can be followed depending on the nature of the product. In these procedures, the EMEA (European Agency for the Evaluation of Medicines), national Competent Authorities and Official Medicines Control Laboratories (OMCL) play active roles [75/319/EC]. Biotech products are considered as high-risk products and are allowed only to go via a centralised procedure. If marketing authorisation is obtained through a national procedure in one Member State, the manufacturer can apply for marketing authorisation in other member states by a mutual recognition procedure. For certain medicinal products (e.g. derived from blood or human plasma) a batch release procedure is required [89/381/EC]. Samples of each batch of the product need to be sent to an OMCL, where product specific safety and potency parameters are tested. Only after approval of the test results by the competent authority the manufacturer is allowed to place the batch on the market.

For medical devices the USA-approach and the EU-approach differ considerably. In the USA a pre-marketing approval has to be obtained from the FDA (mostly CDRH, some products by CBER), very much like the system for medicinal products. In the EU manufacturers are required to place a CE-mark on the medical device thereby claiming that the device complies with the Essential Requirements of the Medical Device Directive [93/42/EEC]. This Directive classifies products in 4 risk groups and requires the manufacturer to follow certain CE-conformity assessment procedures depending on the risk class. These procedures are combinations of requirements for the product and the manufacturer. Depending on the classification of the product, more detailed information has to be provided. Most of these procedures require the involvement of a so-called Notified Body (NB). NB's are commercial organisations, accredited by a competent authority, which test and/or review data with respect to the CE-conformity assessment. Specific NB's are designated for specific product groups. When medical devices form intrinsic combinations with medicinal products or stable derivates of human blood or human plasma, the non-device constituents should be reviewed according to regulations for medicinal products [93/42/EEC, 2000/70/EC]. CE-marked products are allowed to be marketed throughout the EEA.
In Europe IVD's have to be CE-marked and the conformity assessment may require the involvement of a NB (specialised in IVD's), similar to the system for medical devices. Depending on the risk classification of the products a batch release procedure may be required. In contrast with the batch release procedure for certain medicines, for IVD's a NB instead of a Competent Authority is allowed to release batches.

For blood and blood products marketing authorisation is regulated at a national level in the various European countries.
New US regulation requires all manufacturers of human cellular and tissue-based products to register and list their products with the FDA [FDA 2001b]. It is proposed that they meet the standard regarding determination of donor suitability, and conform to GTP. To this end the FDA may inspect facilities. Certain product groups (like having metabolic function, combining with devices) will be subject to current US regulation for medicines or medical devices. These manufacturers are required to apply for marketing authorisation and are subjected to licensing [FDA 1997].

3.5 Post-marketing issues

When deciding on the optimal strategy for post-marketing risk management of TEMPs, lessons can be learned from pitfalls encountered with other medical products.

3.5.1 Post-marketing risk assessment

Given the intended purpose of medical products reliability is often a key issue. However, it is a theoretical entity rather than an estimate based on long-term (large-scale) field experience. Pre-marketing clinical studies only evaluate short-term safety issues and almost never detect rare (but serious) adverse events. Other problems that relate to product labelling (including instructions), user technique and skill and safety issues (durability, biocompatibility, toxicology and disease transmission) will often only be detected during the post-marketing phase. In addition, under normal conditions of long-term use the frequency of risks may be higher than expected. Hence, information that emerges during the post-marketing phase has to be fed back into the risk management cycle so it can be evaluated whether earlier decisions on risk acceptability need to be reconsidered.
Post-marketing surveillance is the key to post-marketing risk assessment. Surveillance has been defined as ‘the ongoing, systematic collection, analysis and interpretation of health data essential to the planning, implementation and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know’ [Thacker 1988]. Surveillance is manufacturers’ but also public health officials' most important tool for monitoring the safety of products. Surveillance systems form the basis for recognising emerging (public health) problems that may require intervention.
Two types of surveillance methods can be distinguished: passive and active surveillance. Passive surveillance means that parties (hospital staff, laboratories, physicians and manufacturers) that might report essential data are provided with the appropriate instructions, while the collector awaits their reports and hopes that all reportable conditions will be reported. The information is evaluated as it comes in. Active surveillance means that public health officials, manufacturers or researchers actively contact other stakeholders directly to gather data and actively search for information, often on a periodic basis.

3.5.1.1 Methods of passive surveillance

For medical products mandatory and voluntary reporting systems may provide data to be used for passive surveillance. By law EU member states are obliged to have vigilance systems in place for medical products [93/39/EEC, 93/42/EEC]. Vigilance is the process of; (a) monitoring of medical products as used in everyday practice to identify previously unrecognised adverse events or changes in the patterns of reporting; (b) assessing the risks and benefits of medical products in order to determine what action, if any, is necessary to

improve their safe use; (c) providing information to users to optimise safe and effective use of medical products; (d) monitoring the impact of any action taken.

Most data on adverse events with medicinal products comes from voluntary reporting systems. At EU level no obligations exist for individual consumers or health care professionals to report adverse events. However, at a national level reporting by health care professionals may be required. EU Member States should have a system for the collection of spontaneous reports of suspected adverse reactions with medicinal products from health care providers. No such obligation for EU member states exists for medical devices.
With respect to mandatory reporting manufacturers and/or distributors in the EU are obliged to report to the regulatory authorities on product recalls and product related incidents which come to their attention and which led or might have led to serious adverse events (see Appendix 5). Regulatory authorities have an obligation to inform manufacturers about reportable incidents that are brought to their attention through other channels [93/39/EEC, 93/42/EEC]. These requirements apply to all regulated medical products. Other than for blood (products) no requirement exists for products containing human tissue.

In the US, consumers and health care professionals can submit reports of serious events suspected to be caused by products regulated by the FDA to FDA's MedWatch program. Furthermore, under US law a representative sample of so-called user-facilities (e.g. hospitals) is obliged to report on adverse events related to medical products in their institution. The arrangements for mandatory reporting by manufacturers in the US more or less like that in the EU.

3.5.1.2 Methods of active surveillance
There are several approaches to perform active surveillance, but none of them are part of current regulation for medical products. One approach, currently piloted for medical devices in the US by the FDA, is that of so-called sentinel sites [FDA 1999a]. By contracting representative sites where specific (kinds of) medical products are used it is hoped that surveillance can be optimised. By supporting these centres in their efforts to extensively monitor patients a full and accurate reporting system on the use of (those) medical products and the related adverse events can be maintained.
Another approach can be the extension of data collection on patients who participated during pre-marketing clinical investigation. Collection of this information (also for purposes of marketing) is often organised by pharmaceutical sponsors by conducting additional trials (so-called Phase 4 trials) within the first years of marketing [Friedman 1999].
The use of existing health care databases, like for example implant registries (see below), that combine usage data and event data may be helpful to explore potential serious problems as well. Record linkage of health care and/or demographic databases may be another option. Furthermore, epidemiological studies (e.g. cohort or case-control studies) may be used to investigate specific safety issues in depth. Finally, as an additional method explant evaluation studies of TEMPs may give insight in safety matters like durability, biocompatibility, etc.

3.5.1.3 Quality of surveillance methods
The efficacy and quality of the post-marketing surveillance can be described by three characteristics: 1) who has to report; 2) what needs to be reported where; 3) which methods are used to gather and analyse information and to evaluate risks.

Who

The Achilles heel of all passive surveillance systems is the total reliance on the alertness, willingness, and co-operation of users and health care professionals, the first to encounter adverse events. Nevertheless, differential reporting and underreporting, especially by physicians, are well-recognised phenomena [Brewer 1999, Scott 1990]. In an attempt to overcome these problems, the awareness and co-operation of health care professionals has been enhanced by campaigns of active dissemination of general information and adverse event experience, facilitating adverse event reporting but also by training and education of organisations. [MDA 2001; FDA 1999a] Moreover, it has been suggested that the confidentiality of reports should be ensured to counter the fear for liability [IOM 1999].

What and where

It should be transparent for all parties what needs to be reported where. This is clear both in the EU and in the USA for serious adverse events that are related to medicinal products and medical devices. The FDA intends to restrict adverse event reporting of cellular and tissue-based products to the transmission of communicable diseases [FDA 1997, FDA 2001]. Because use-related serious adverse events are a substantial part of problems with medical products, it is being debated whether they should also be reported [GHTF 1999, IOM 1999].

Which methods

By using standard forms, like for example the MedWatch and MEDDEV forms the quality and usability of gathered information could be enhanced. Furthermore, reporting can be facilitated and enhanced by offering multiple ways to report, for example by phone, regular mail, fax and the Internet [ECRI 1998].

The objectives of post-marketing surveillance are to identify rare or novel adverse events, estimate their rate of occurrence and distinguish those that are causally related to the product. Because evidence of causality is based on a statistically significant excess of events in the post-marketing period and/or biological plausibility supported by laboratory evidence, long-term follow-up of products is usually necessary.

The surveillance method chosen has implications for completeness of the data and the validity of risk estimates. Most surveillance done on a routine basis is passive surveillance. Passive surveillance methods are especially useful for identifying rare events and for generating signals that can be used to create hypotheses to be tested in epidemiological studies. Partly because of privacy legislation, complete information on actual use and duration of use will hardly ever become available. This hampers the calculation of incidence rates and confirmation of causation. Given these drawbacks, long-term follow-up of TEMPs through active surveillance seems to be the preferred surveillance method of choice, although it is far more costly, time consuming and labour-intensive than passive surveillance. Gathering of information on adverse events and consumption is useless if there is no systematic program for evaluation and, if necessary, dissemination. Several directives on medicinal products have included such a system. Moreover, ad-hoc evaluations, systematic periodic evaluations, review of published reports and ongoing review of experience with products in other jurisdictions (US, Japan, EU) are ways to assess the post-marketing safety of a TEMP and respond in a timely matter to emerging problems. Given the diversity and complexity of possible problems for TEMPs, evaluation of possible safety problems not only calls for a systematic, but also a multidisciplinary approach.

3.5.2 Post-marketing risk control

The process of risk analysis and evaluation as described in the previous paragraphs is not only intended to assess risks in the post-marketing situation but also to control the risks. In this paragraph some additional control measures are discussed.

3.5.2.1 Traceability

Traceability of medical products from the manufacturer to the ultimate user, the patient, is needed in case a potentially dangerous product has to be recalled. Traceability is an important issue for safety critical (i.e. when failure would likely cause death or a serious deterioration in health) TEMPs. Several methods to organise traceability of medical products have been established, one of the simplest being handing out implant cards, which are filled out after implantation of a device and returned to the manufacturer. The ultimate method would be to have registries. In the US registries have been established not only for marketed products but also for investigational products with unknown, but potentially serious, risks [FDA 1999b]. The need has been expressed to continue these databases even after these products are marketed. Whatever method is chosen – the crucial aspect is that a specific product (unique ID) can be linked to a specific patient and vice versa. This requires a certain level of quality assurance of documentation (preferably centrally, but at least in the patient records) of patient management in institutions that "hand out" a product to a patient.

3.5.2.2 Registries

Registries keep databases identifying products, recipients and treatments. If prerequisites for completeness and the validity of the data are met, these databases can be used to assess the long-term risks of TEMPs. Because they seek 100% ascertainment implant registries are usually expensive to maintain. The usability of registries in relation to risk assessment depends on the information registered (e.g. implant/product-, patient- and procedure characteristics) and availability of follow-up information on registered patients. In case of mandatory registries it appears important to clearly designate the holder(s).

3.5.2.3 Periodic safety update reports

In the EU a so-called Periodic Safety Updates Report (PSUR) is required for each authorised medicinal product [EMEA 1996]. PSURs are a summary of the worldwide safety information available on a product like for example: adverse event reports, clinical studies, literature and other sources of data i.e. epidemiological databases. The objective of a PSUR is 'to establish whether information recorded during the reporting period is in accordance with previous knowledge on drug safety, and to indicate whether changes should be made to the product information' [EMEA 1996].

3.5.2.4 Restrictions on use

The use of new high-risk technologies is often restricted by regulatory authorities to specific health care facilities/providers (like the transplantation of lungs and livers). However, the initiative to restrict the use of a certain product may also be taken by health care professionals. A recent example is the initiative of the Dutch Society for Vascular Surgery to restrict the use of vascular endoprostheses. Likewise, the availability of TEMPs could be restricted to situations were they are applied and monitored by appropriately trained health care professionals.

3.5.2.5 Post-marketing product testing

At random testing of products that are already on the market, e.g. on the shelf of hospitals can give information on the consistent quality of these products.

3.5.2.6 Licenses, product recall and withdrawal

The periodical renewal of licenses for manufacturers, based on the safety information gathered in the earlier years of marketing may also be a way to control safety problems. Suspension of licenses, voluntary or non-voluntary recalls and voluntary or non-voluntary product withdrawals are ways to control risks post-marketing once they have emerged.

4. Discussion

New techniques like tissue engineering hold promise for medical therapy. In this report we reviewed the risks that are known or foreseen to be associated with tissue engineered medical products and discussed the options for risk control. This report may serve as background information for any regulatory structure.
At present, knowledge about the risks is fragmented and incomplete. Therefore, quantification of the risks is often impossible. However, it is possible to devise measures to control the identified risks. Products manufactured by tissue engineering are largely unregulated in the EU at this moment. The ideal way forward would be to negotiate for a suitable pan European framework to address the development of a firm and fair structure to ensure the quality and safety of health care products from tissue engineering. Since it takes many years for such an ideal world to develop EU member states have formulated, or will formulate national regulations.

In describing the management of risks, the EN-ISO 14971 standard relies heavily on Deming's quality circle: the iteration of Plan, Do, Check and Act. According to this circle one has to: plan activities on relevant information, perform these activities according to the plan, take care of appropriate checks afterwards, evaluate the results of these checks and react to the findings by adapting the plan. In theory this strategy will result in a cycle of continuous improvement and elimination of ineffective activities. This concept is also relevant to all parties with regard to improving their strategies to control the safety of all (groups of) products available on the market.
Although reference is often made to 'quality and safety', these are not separate issues. In fact, safety refers to a subgroup of safety-related quality characteristics, e.g. durability and biocompatibility. Therefore, quality requirements for TEMPs should include reference to these safety-related quality characteristics, which are subject of this review.

The most important risks that can be foreseen at this moment (see Table 2) seem to be related to the transmission of disease, biocompatibility and efficacy. Control measures should therefore focus at these aspects. Given the diversity in tissues, matrix materials and signal-molecules, different TEMPs will certainly carry various combinations of risks, each varying in character and magnitude. Classification of products into risk groups can help in designing efficient control measures. Parameters relevant to this classification have already been put forward (Table 3) and may serve as a starting point for the development of a European system.

In addition to the development of a regulatory system, the development of standards should be encouraged, preferably on a world-wide scale. It is the "language" that enables discussion on and interpretation of product and process performance. The need for standards is increasing because some products are already available for clinical application and a large number is under development. Quality and safety standards should also describe the specifications that processes and/or products have to conform with. At this moment the ASTM has instituted specific workgroups for development of TEMP standards. Also CEN has taken formal interest in TEMP developments. It is advisable for European, US and other international parties to communicate in order to establish widespread acceptance of new standards. Given the large diversity of possible products, a horizontal approach (standards applicable to a large number of products) is preferred over a vertical approach (standards for specific product groups). Guided by the identified major risks, the topics of standardisation

should include donor selection criteria and methods for evaluation of safety and efficacy. With respect to donor selection criteria, guidelines from blood and tissue banks may serve as a starting point.
Already before the development of technical standards, new technologies will be discussed by the general public with regard to ethical aspects and perceived risks. The current discussion on xenotransplantation illustrates this process and reveals the strong commitment of several parties against and in support of this technique. The information that becomes apparent from these discussions is relevant to the determination of the level of safety that is expected by the general public. A structured study (interview/questionnaire) among the general public on the limits of acceptance for certain risks may generate additional information.
Standards for professional skills and conduct as well as for specific quality systems (e.g. Good Laboratory Practice) for laboratories or certain area's of industrial activity are just as important as product standards. Manufacturing TEMPs will be based upon highly sophisticated techniques, for which validated processing steps are mandatory to guarantee the safety of products. The capacity and skills of the organisations may be regulated by requiring implementation of general Quality Systems like ISO 9000 and/or systems and standards more specific for the field of tissue engineering. These systems should address e.g. staff skills (training), manufacturing/handling processes and products. Products and processing techniques should be characterised and documented. The regulatory authorities should conduct formal reviews to assure that these requirements (being in itself control measures) are implemented, are used as intended and that the results conform to relevant standards. The results of such reviews can be linked to granting licences for facilities for manufacturing, for marketing authorisation of products or, in case of health care providers, for the application of products.

In view of the complexity of TEMPs and the lack of experience in applying these products in humans it is advisable to conduct a careful, formal and centralised review of the product characteristics before clinical testing as well as before introduction on the market. The results of these investigations should be documented in product files.
A formal review should focus on the results of the pre-clinical studies consisting of *in vitro* tests and animal tests of the new TEMP and/or its components. The contents of the file describing the product characteristics and performance need to be assessed according to pre-defined procedures. This review should lead to a decision on the suitability for clinical evaluation.
Aspects relating to a formal review as discussed for pre-clinical studies are also relevant for clinical studies. The results of these studies should indicate both the clinical safety and the efficacy of the product. Review of both pre-clinical and clinical results is needed to obtain marketing authorisation. For certain high-risk products, an additional batch release procedure (like for certain IVD's, vaccines and blood products) can be considered.
An international review board could perhaps be organised to carry out the formal reviews. Such a review board should be independent of commercial and political influences. It can vary in its character (e.g. EMEA versus Notified Bodies) depending on its mandate and representation of various involved parties like government and academia. Because of the different qualifications required for pre-clinical and clinical reviewers, it is advisable to organise within this review board separate expert groups for pre-clinical and clinical review. Apart from the general desire for a harmonised European approach in regulation, the difficulty of finding a sufficient number of experts for this new topic in a single country can also be an incentive for a (centralised) European approach. Although the organisation of multiple (national) boards would initially favour the logistic aspects of review procedures, it

has the potential drawback of introducing problems in mutual recognition between different boards regarding product approval decisions.
Given the differences in risk between TEMPs with structural versus TEMPs with metabolic functions, the evaluation of TEMPs with a structural function could be consistent with that of devices, while the evaluation of TEMPs with a metabolic function may be more like that of products from blood/plasma. In absence of specific standards for TEMPs, the standards for blood, medicinal products (including those derived from human blood or plasma) and medical devices could be applied.

Once a product is on the market, an additional set of risks, namely use-related, also needs to be taken into account. When the Regulatory Authorities limit the number of centres that use TEMPs risks could be controlled more easily. An alternative approach could be to let the professional organisations decide where clinical experience on new techniques/products will be collected. A limited number of staff is easier to train and because the frequency of application of TEMPs can be kept high, their expertise will remain on an adequate level more easily. Expertise and skills are not only relevant to first-time application, but also to handling of complications and adverse events. To support structural review of experiences, these centres could be required to incorporate their experiences with the new products in an Annual Quality Report. In any case, the review procedure of these reports should be transparent to all parties involved.

Postmarketing clinical experience is valuable in assessing the, mostly long-term, safety of TEMPs. Pre-marketing clinical studies involve only a limited number of patients over a limited period of time. Cells in TEMPs may maintain their function and interact with the recipient for a long time. It is therefore important to monitor the experience with TEMPS after marketing, preferably through long-term active surveillance, including a structured system of (mandatory) adverse event reporting, accumulation of both the adverse events and use data, analysis and (periodic) review. The accumulation, analysis and review of the results of this system should preferably be centralised and performed by an independent party, i.e. neither manufacturer nor health care provider.

As a means to control and limit the consequences of possible adverse events caused by malfunctioning TEMPs, it is advisable to maintain a database system that registers the combination of TEMPs and recipient. This can be a central national system or a local (e.g. hospital, manufacturer) one, by documentation of a minimum set of data by health care professionals and manufacturers. The archive duration of these data should exceed 10 years, as long-term effects may emerge after this period. An independent party should preferably keep the database (or the linking key), as the institutions involved (manufacturer and clinical centre) may have opposing interests. Privacy legislation will prohibit direct and full access by manufacturers and third parties to these databases.

5. Conclusions & Recommendations

- At present, the knowledge about risks related to TEMPs is fragmented and incomplete.
- The most important risks seem to be related to disease transmission, biocompatibility and efficacy.
- Given the risks of products that are produced by tissue engineering techniques it is necessary to develop a system of regulation in Europe.
- This system should be tailored to the specific risks of TEMPs and should be complementary to and connect to existing European regulation for medical products.
- Control measures could be specified for TEMP subgroups that are stratified according to increasing risk.
- Evaluation of acceptability of individual risks should ideally be based on predefined standards. These should be formulated for tissue engineered products and should first aim at generic aspects of products (horizontal approach).
- General quality systems and GMP/GLP with additional specific requirements should be implemented by involved parties.
- Manufacturers should be subjected to a licensing system.
- Results of pre-clinical evaluation should be subject to formal review by an independent body before the onset of clinical evaluation.
- Marketing authorisation should be applied and should be based on a formal review of product/process characteristics (results of pre-clinical and clinical evaluation).
- Additional measures like licensing of manufacturers, batch release procedures or designated clinical centres could be considered.
- Some form of post-marketing surveillance should be installed, preferably including a structured system of (mandatory) adverse event reporting, accumulation of both the adverse events and use data, analysis and (periodic) review.
- Traceability of products to patients should be warranted.

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Appendix 1 Future products

The summary given here is a more-or-less crude indication of the diversity of target tissues and does not pretend completeness.

Nervous tissue

Afflictions to the neural system are generally divided into central and peripheral location. Central location refers to all neural tissues inside the skull and spinal cord, peripheral location refers to all nerves that run outside the skull and spinal cord and innervate muscles and organs, including the sensory system in the skin.

Central neural system:

In the field of TEMPs and disorders of the CNS, the strategy has been directed at the delivery of substances. By encapsulation techniques substances can be delivered locally in the CNS. Moreover, with the right design, these TEMPs are recoverable. These TEMPs usually consist of human cells or xenogenic cells that have been engineered to secrete for instance human growth factors in case of degenerative disorders. In animal models the effect of TEMPs has been studied in relation to Altzheimer's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease and chronic pain states [Gentile 1998]. Already some studies have been performed in humans with TEMPs containing xenogenic cells for treatment of ALS or chronic pain [Gentile 1998]. Although it is known that CNS tissue has poor regenerating capabilities, some ideas are currently being evaluated to try and restore damaged contacts between parts of the CNS (e.g. spinal cord lesions) [Feijen, pers. comm.].

Peripheral neural system:

Tissue engineering may help the regeneration of nerves that are damaged for instance by traumatic transection or during surgical procedures against malignancies. In-vitro and animal studies have resulted in an increase in knowledge on critical parameters for nerve regeneration, like porosity, internal surface texture, electrical properties, additional intraluminal support matrices, additional soluble neurotropic factors and seeding of cells (that secrete neurotropic factors). In the animal model nerve defects up to 5 mm can be bridged by application of guiding tubes composed of natural polymers in combination with Schwann cells and growth factors [Furnish 1998]. These guides prevent ingrowth of scar tissue and direct the regenerating nerve in the proper direction. They can also control the local micro-environment by blocking the entry of macromolecules in the path of regeneration or by release of growth factors. A clinical applicable alternative to neural autografts or vein grafts for nerve repair has not been offered yet [Furnish 1998].

Cornea

In the field of eye surgery TEMPs may offer an alternative for damaged corneas. Current treatment is transplantation of a donor cornea. Corneal epithelial cells that were seeded on a polyvinyl alcohol hydrogel have been tested in rabbits [Kobayashi 1991]. Also human cornea cells have been successfully used for ex vivo construction of corneas [Germain 1999].

Skin

Very briefly stated, tissue engineering of skin substitutes is aiming at controlling the repopulation of fibroblasts and of organised collagen formation instead of scar formation. To this end TEMPs can be designed to offer growth factor delivery by cells and/or a 'natural' scaffolding, or combinations of these. Skin substitutes have evolved from matrix material only,

via matrix material seeded with a single cell type, to bi-cellular substitutes. It appears that for optimal clinical results cell types from both layers of the skin (dermis/epidermis) should be incorporated in a skin substitute [Eaglstein 1997]. These cells are exclusively of human origin. Some of these products have been granted marketing authorisation by the FDA [Eaglstein 1998] and in the very near future (next year clinical studies) more promising products can be expected [Blitterwijk, pers. comm.]. However, the golden standard skin autograft has not yet met its superior alternative in terms of consistent graft take, quality of dermal repair and cosmetic outcome [Teumer 1998]. The engineered skin can be used for treatment of burn wounds, venous ulcers, diabetic ulcers and for reconstructive surgery.

Liver

One strategy for liver support is treatment with an extracorporeal bioartificial liver (BAL) composed of cells on a synthetic network. Hepatocytes from humans or pigs can be seeded on a polymer carrier that is connected to the vascular system of a patient, similar to the renal dialysis process. By using hollow fibres or micro-encapsulation techniques the cells of the BAL and blood of the patient can be kept separated, thus diminishing immunologic reactions. Some of these systems have been evaluated in animals [Dixit 1996]. Current problems are size/scaling (as about 20% of the patient's liver mass is necessary for support) and maintaining the viability of the cells [Friend 1989]. Furthermore, device storage has not been solved yet. The BALs that contain human hepatoblastoma (liver tumour) cell lines carry the risk of transmission of tumourigenic factors; the ones that contain xenogenic (porcine) cells carry the risk of sensitising the patient against porcine proteins [Friend 1989]. A limited number of devices have been tested in controlled clinical settings and have shown hopeful results [Friend 1989].

Pancreas

The TEMPs that have been put forward against diabetes are composed of encapsulated pancreas β-cells in either extracorporeal or implantable devices, the latter being usually implanted subcutaneously or in the abdominal cavity [Lanza 1996]. The implantable TEMPs consist of small tubes or microcapsules (biodegradable or permanent) and have been evaluated in both animals for a limited duration and in two human subjects [Lanza 1996, Monaco 1996]. The most important problems at this stage of development are the fibrotic encapsulation of these implants and the inability to implant the proper amount of cells that is needed for reversal of the diabetic state.

Tissues of the urinary tract

Modern cell culturing techniques allow also in vitro expansion of cells derived from ureters and urinary bladder, i.e. urothelial cells and smooth muscle cells. When these cells were seeded on biodegradable matrices tubular structures appeared and subsequent implantation in animals resulted in the formation of artificial ureters. If these cells were seeded on sheets of biodegradable matrices urinary bladders could be formed in dogs [Atala 1998]. Further evaluation of the functional characteristics of these constructs is needed.

The creation of a bioartificial kidney is much more complex than the formation of structural elements such as ureters and urinary bladders. Apart from filtration, a kidney holds multiple and complex functions, e.g. secretion of hormones related to the formation of red blood cells. Study on the creation of a bioartificial kidney has progressed to the stage where separate kidney cells seeded on degradable polymer and implanted subcutaneously in animals rearranged and organised into renal tubules [Marler 1998]. Gene therapy is thought to replace the other renal functions [Humes 1998].

Tissues of the gastro-intestinal tract

Tubes composed of several polymers have been used as a replacement of canine oesophagus [Langer 1993]. Sections as long as 10 cm could be replaced in dogs and showed repopulation with normal appearing oesophageal mucosa [Ikada 1998].

The TEMPs intended for replacement of bowel segments are yet still in the laboratory phase. The microscopic architecture of intestine is much more complicated than their tube-like appearance suggests. However, basic studies on the creation of an internal bowel lining that is comparable to the natural situation have been pursued in rats by implantation of polymers seeded with fetal intestinal cells [Marler 1998, Langer 1993]. These studies show hopeful results.

Cartilage, bone

A hypothesis that supports the construction of TEMPs is one based on the principles that mesenchymal stem cells (present in e.g. bone marrow) can differentiate into bone, cartilage, or tendon cells if exposed to the right environment, i.e. to mechanical stimuli or cell signalling cues from nearby cells (e.g. growth factors). They limit the repair process and initiate the development of 'new' tissue [Caplan 1998]. This hypothesis has been confirmed in successful animal studies.

It has been shown that cartilage cells (chondrocytes) that were seeded on polymers can lead to cartilage formation after implantation in animals [Marler 1998]. This has led to the development of a clinically available autologous engineered cartilage TEMP. A major future application may be the replacement of cartilage at the articulation surfaces in joints suffering from arthrosis in an early stage. This may prevent the need for total joint replacements in a lot of patients (currently the number of total joint replacements - in particular hip and knee - is still rapidly growing). First generation cartilage TEMPs (cells without carrier) are already on the market. In the very near future (within the next 3 years) second generation cartilage TEMPs (cells or even tissue with carrier) will be evaluated in clinical studies [Blitterswijk, pers. comm.]. Seeding chrondrocytes on pre-formed polymers resulted in cartilage tissue in desired shapes. Shapes like an ear, nasuseptal implants and a temperomandibular (jaw) joint disk could be realised [Marler 1998].

Studies on bone TEMPs are also very successful. Bone has a great regeneration capacity. Constructs consisting of a biodegradable ECM with autologous cells and signal molecules, which are able to integrate completely with existing bone structures, have been developed. Clinical studies have recently been started. Possible applications include bone defects that result from trauma after accidents or removal of malignancies. It may also be possible in the future to build larger structures, which could be used in total joint reconstruction. A recent publication showed the results of a study in which phalanges and small joints were constructed [Isogai 1999]. Three cell types (cartilage, bone and tendon) were seeded on pieces of biodegradable polymer shaped into the form of a human phalanx, including a joint. After being implanted subcutaneously in a mouse for about 40 weeks, this construct showed histological features of a normal phalanx and joint. Clinical application of joint replacement may not yet be within reach in the near future, but these results illustrate the impressive theoretical possibilities of tissue engineering.

Dental tissues

Laboratory studies have been directed at the formation of dental pulp tissue [Bohl 1998] as a first step towards the creation of teeth. Also the effects of growth factors on dental tissues has been studied, aiming at the stimulation of periodontal attachment structures, namely alveolar bone, periodontal ligament and tooth root cementum [Giannobile 1996].

Adipose tissue

Tissue engineered fat can primarily be used in reconstructive surgery for the treatment of e.g. congenital malformations, post-traumatic deformations, defects caused by malignancies. In a laboratory setting the precursor cells of mature adipocytes could be cultured. After implantation in mice they showed differentiation into adipose tissue creating soft tissue augmentation [Patrick 1998].

Cardiac tissues

Cardiac tissue engineering has been focussing on repopulation of cardiac muscle and the creation of valves. In the process of myocardial infarction, cardiomyocytes are lost resulting in a, sometimes, considerable reduction of the contractile capacity of the heart. Studies have been conducted on the implantation of autologous muscle cells (via surgical procedures and via the coronary arteries) in order to repair the myocardial damage [Atkins 1999]. In animal models replacement of the infarcted tissue by new cells has been shown. Problems that need to be solved before restoration of functional cardiac performance include the timing of the administration of cells relative to the infarction, and dosage. In vitro studies demonstrating that three-dimensional cardiac muscle constructs can be engineered with cardiac-specific structural [Luyn 1999] and electrophysiological properties show promising future possibilities [Carrier 1999].

Studies on the tissue engineering of heart valves have shown that it is possible to decellularise porcine valves and seed them with human vascular endothelial cells [Bader 1997]. Other studies in lambs showed the construction of engineered valve leaflets from two cell types (endothelium, myofibroblast) on a biodegradable matrix [Mayer 1997]. The performance of the leaflet (microscopic appearance, short time valve function) depended on the cell source: autologous cells performed better than allogenic ones and cells derived from the arterial wall performed better than from the subdermis. The studies were confined to single leaflet replacement, as the matrix material was too stiff to allow construction of a competent three-leaflet valve.

Blood vessels and cells

Possible applications of tissue engineered blood vessels in the near future are mainly the small diameter vessels. One of the reasons for this observation is the fact that synthetic prostheses for larger vessels made from Dacron or Teflon are mostly functioning quite satisfactorily. Another reason is the fact that larger vessels are more difficult to construct, in particular because of pressures that can occur insides these vessels.

A lot of work has been dedicated to the seeding of endothelial cells on synthetic vascular substitutes [Bos 1998, Nerem 1998] in order to reduce obstruction by blood coagulation. Other techniques aim at construction of complete vascular conduits. By several techniques, the three cell types of blood vessels (smooth muscle cells, endothelial cells and fibroblasts) have been seeded sequentially on biodegradable polymers in tubular shapes yielding actually complete vessels in vitro. Some of these constructs have already been evaluated in dogs or pigs. A lot of studies are in a phase of selection of the optimal culturing and construction techniques [Nerem 1998, Niklason 1999]. Clinical studies with this kind of TEMPs may be expected perhaps in 5 years [Feijen, pers. comm.].

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Table 4. Examples of innovative health care products that are in development or on the market[1].

Tissues	Descriptive text of illustrative products	Technol.	Product
Bone	Bovine bone matrix for load bearing applications		MD
	Hydroxyapatite/tricalcium phosphate matrix for bone ingrowth		MD
	Coralline porous scaffold structure for bone grafts		MD
	Osteoblast* seeded scaffold matrix for bone repair	TE	
	Human DMB matrix for bone remodelling		MP/MD
	HA/TCP/Growth Factor as substitute for bone repair		MP/MD
	Bone Morphogenic Proteins in HA three dimensional matrix		MP/MD
	Chondrocytes* on 3Dform of UHMWPE	TE	
	Bone marrow stromal cells on titanium mesh discs	TE	
	Primary osteoblasts on biodegradable polymer/glass-ceramic composite	TE	
Skin	Keratinocytes/Fibroblasts* on matrix scaffold	TE	
	ECM/Growth Factors on PGA scaffold for dermal replacement	TE	
	Collagen/GAG dermal matrix template for fibroblast infiltration		MD
	Hyaluronate system with biodegradable matrix for burns/ulcers		MD
	Fibroblasts* on modified PGA scaffold for dermal regeneration	TE	
	Autologous keratinocytes* coapplied with fibrin matrix spray	TE	
	Novel porcine collagen seeded with autologous fibroblasts/keratinocytes*	TE	
	Shark collagen matrix with keratinocytes & fibroblasts	TE	
	Collagen matrix with keratinocytes, fibroblasts & endothelial cells (umbilical)	TE	
Cartilage	Chondrocytes* on PGA mesh framework	TE	
	Injectable hyaluronate derivative (microbial) as synovial replacement system		MD
	Injectable hyaluronate derivative (avian) as synovial replacement system		MP
	Autologous chondrocyte* culture systems	TE	
	Culture of autologous chondrocytes with chondral cores	TE	
	Chondrocytes on alginate beads	TE	
	Polyglycolide membrane and osteochondral plugs	TE	
	Collagen three dimensional scaffold with chondrocyte culture system	TE	
	Fibrochondrocytes* cultured on meniscal shaped biosorbable PLA scaffolds	TE	
Blood Vessels	Endothelial cells* on vessel scaffolds for vascular graft	TE	
	PGLA sponge releasing Endothelial Cell Growth Factor ECGF for transplantation site		MP/MD
	Porcine collagen matrix seeded with autologous endothelial cells*	TE	
	Autologous smooth muscle cells* seeded in collagen matrix	TE	
Heart	Human recellularised* porcine valve leaflets	TE	
	Whole porcine heart for organ transplantation (i.e. xenotransplantation)		Xenotranspl.
	Fibroblast* repopulation after decellularisation methods on porcine valves	TE	
Nerve	Cylindrical tubule scaffold of polyhydroxybutyrate for nerve guide regeneration		MD
	Microtubule of human collagen for nerve regeneration		MD
	Schwann cells* in three dimensional suspension complex of alginate	TE	
Spinal Cord	Encapsulated chromaffin cells + for treatment of pain relief		MP
	Alginate microencapsulation of primary fibroblasts		MP
Dental	Collagen sponge with bone morphogenic proteins		MP/MD
	Tricalcium phosphate matrix scaffold with mesenchymal stem cells	TE	
Kidney	Renal tubular cells* on polymer matrix	TE	
Ear	Chondrocytes * for cartilage formation on resorbable matrix	TE	
Oesophagus	Transforming Growth Factor TGF on collagen based cylindrical scaffold		MP/MD
Liver	Hepatic cell system + in delivery system of medical device		#
Pancreas	Encapsulated islet cells* for insulin therapy		MP
Brain	Injectable system of porcine cells + for treatment of Parkinson's disease		MP
Muscle	Myocytes & Chondrocytes* in a PEO/PBT copolymer matrix	TE	
Cornea	Epithelial* cells cultured on amniotic membrane	TE	
Bladder	Urothelial cells* cultured on polyglactin mesh framework	TE	

[1] Table by courtesy of Mike Cox, Medical Devices Agency, London

Notes: *: viable human cells; +: viable animal cells. MD: Medical Device; MP: Medicinal Product. #: Combination of Regulations. Descriptive text of illustrative products in research/development or existing commercial products was obtained from conferences, published literature and websites.

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Appendix 2 Development of Safety Standards

The initiative to develop safety standards is often a combined result of history, public and political and sometimes commercial pressures [HM Treasury 1996]. Three broad approaches from which practical standards emerge have been identified [HM Treasury 1996].

1. 'Traditional approach'
A (popular) traditional approach to safety standard setting is the demand that an activity, product, component should be made 'wholly safe' or 'as safe as possible'. This is an approach which is often used after serious accidents, and is driven by the demand that 'it must never happen again' [HM Treasury 1996] (For example the famous HIV blood scandals). Another traditional approach is the so-called 'rule of thumb' approach, where, as a policy, risks are not allowed to increase even if the balance of costs and benefits changes.

2. 'Tolerability limits, working limits and targets'
Another approach from which practical standards emerge is the development of standards which set (rigid) maximum tolerability limits such as the requirement for sterility that the bioburden is reduced to 10^{-6}. Working limits, which are more flexible, are used to define good practice. These working limits can change due to a development of technology, such as a desired maximum to the rate of death due to transplant rejection after organ transplantation. Finally, (aspired) targets can be set; for example, if it is the aim to improve the general health condition in order to improve the outcome of surgery, the target might be to promote the cessation of smoking among candidates for surgery. One of the drawbacks of each of these methods is that they can be based on historical precedents, for which there is no (longer) scientific evidence. Another problem is that if valid scientific data is lacking or insufficient, limits and targets may be hard to set.

3. 'Cost-benefit trade-off'
A third approach to safety standard setting is the so-called cost-benefit trade off, or - possibly more appropriate in the context of this report - risk-benefit trade-off. This may constitute of formal 'cost'/risk-benefit analyses in the few situations where risks are explicitly valued. More often a less formal approach is used, like the ALARP (As Low As Reasonably Practicable) principle (EN-ISO 14971). The ALARP principle states that above a certain level, known as the upper level of tolerability, risks are unacceptable. If on the other hand risks are already broadly acceptable, then no further precautions are required. Where the risk lies between these two extremes, risk reduction measures must be considered and discussed on the grounds of reasonableness and cost-benefit.

Safety standards are often the result of a hybrid combination of the three aforementioned approaches. Depending on the type of risk to regulate, its quality, severity, predictability and controllability, an approach may be chosen. Herein the perception of the risk by those affected and the societal concern the risks may cause need to be taken into account. The chosen (combined) approach also reflects cultural differences between countries and between professional disciplines. For example, in the US more often maximum tolerability limits are set. In the UK, on the other hand, there is now a preference for the cost-benefit approach. This is reflected in the TOR (tolerability of risk) framework which was developed by the Health and Safety Executive (HSE) in the UK [HSE 1992]. The TOR framework applies a cost-benefit approach (like ALARP) to risks but also imposes maximum absolute levels of

risk and broadly acceptable lower limits, above and below which cost-benefit analyses are not appropriate or required.
The chosen approach will also reflect the interest of those involved in the development of the safety standard. In light of the emerging regulation on human tissues it would be interesting to compare the approaches chosen in the fields of medicinal products and medical devices and in-vitro diagnostics. In each of these fields different parties have been involved in the setting of safety standards.

In the field of medicinal products the development of safety standards and the process of safety standard setting is under control of (inter)national regulatory authorities. At a certain stage in this development there is a consultation stage during which industry can give input. The most important of these regulatory authorities are CPMP (Committee for Proprietary Medicinal Products) in the EU; CBER (Center for Biologics Evaluation and Research, FDA) and CDER (Center for Drug Evaluation and Research, FDA) in the USA; PMSB (Pharmaceutical and Medical Safety Bureau) in Japan. Harmonisation of the interpretation and application of technical guidelines and of the requirements for product registration is mediated through ICH (International Conference on Harmonization) conferences. Apart from that also technical guidelines are being developed by ICH.

In the field of blood and blood products (inter-)national regulatory authorities (European Council, WHO) control the formulation of safety standards.

In the field of medical devices, safety standard setting in the EU is being co-ordinated by CEN (European Committee for Standardisation) and CENELEC (European Committee for Electrical Standardisation). Under the EU Directives, compliance with the harmonised standards, which have been prepared by CEN and CENELEC under a mandate from the European Commission, is a designated means of complying with the EU legal requirements. The European EN standards will rely in some cases on safety standards written by other standardisation bodies like ISO (International Standardisation Organisation) and IEC (International Electrotechnical Committee). Under the Vienna Agreement, CEN/CENELEC and ISO/IEC are not to duplicate each others work but should consult each other in view of adopting each other's standards. The emerging safety standards are a result of consensus of all the parties that join technical committees of these organisations. CEN and CENELEC use weighted voting, with larger countries having a heavier vote than smaller ones. Although the members of the technical committees ought to be a proper representation of industry, government, academia and health care, usually industry is overly represented and there are only very few members of academia and health care. In the USA the setting of safety standards is under control of regulatory authorities (mainly CDRH (Center for Devices and Radiological Health, FDA)). The CDRH participates in the development of national and international consensus standards and voluntary guidelines through interaction with appropriate national and international standards committees. One of the national societies which is involved in developing standards, the ASTM (American Society for Testing and Materials) has focused an interest on developing standards for TEMPs for the past two years (see Appendix 4). In the field of in-vitro diagnostic devices safety standard setting is under the control of regulatory authorities (Common Technical Specifications) as well as CEN and ISO.

References

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Appendix 3 ASTM activities

Table 5. Task groups in ASTM Division F04.4 TEMPs

Task group	Subject
F04.40	Terminology
F04.41	Normal biological function
F04.42	Structural characterisation
F04.43	Tissue-engineered biomaterials
F04.44	Biomolecules
F04.45	Cells
F04.46	Delivery systems
F04.47	Assessment
F04.48	Clinical trials
F04.49	Microbiological safety and adventitious agents

Table 6: ASTM - TEMPS Standards List

Nr.	Title
1	Standard Guide for the Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage
2	Assessment of Heart Valve TEMPS
3	Characterization of biomaterials used for articular cartilage repair
4	Assessment of skin TEMPS
5	Assessment of Islet TEMPS
6	Assessment of Liver TEMPS
7	Assessment of Bone TEMPS
8	Standard Guide for the Assessment of Bone Inductive Materials
9	Assessment Framework and template for Guidance Standards
10	Assessment of Meniscus TEMPS
11	Assessment of Pancreas TEMPS
12	Use of Animal Models in Assessment of TEMPS
13	Standard Test Method for In Vitro Biological Activity of recombinant human bone Morphogenetic Protein-2 (rhBMP-2) Using the W-20 Mouse Stromal Cell Line
14	Guidelines for Surrogate Endpoint Analyses in TEMP Clinical Trials
15	Key Characterization Parameters of Alginate for Use in Biomedical and Pharmaceutical Applications
16	Key Characterization Parameters of Chitosan for Use in Biomedical and TEMPs
17	Guide for Fabricated Biomaterials used in TEMPs that substitute for, repair or regenerate bone
18	Classification of biomaterials used in TEMPS for skin
19	Classification of Methods to Characterize Tissue Engineered tissues
20	Synthetic and Naturally-derived bone void fillers
21	Gel and Putty Devices for TEMPS
22	Classification of Delivery Systems used in TEMPS
23	General Classification of TEMPS
24	Terminology for TEMPS: 6 terms
25	Terminology for TEMPS: Tissue Engineering and TEMPS
26	Normal Biology of Islets
27	Normal Biology of Liver
28	Normal Biology of Skin
29	Normal Biology of Aortic Heart Valves
30	Standards of Analysis for Mechanical Testing for TEMPS
31	Substrates Guide for Materials used for TEMPS
32	Guide for Scaffolds used for TEMPS
33	Guide for Characterization of Collagen used for TEMPS
34	Guide for Proteins used in TEMPS
35	Guide for TEMPS containing Living Cells
36	Guide for Preservation of Cells for TEMPS
37	Test Method for Cell counting and characteriation using the Coulter Counter
38	Designation of Practises for Viability Determinations for Cells for TEMPS
39	Standard Guide for Cell Encapsulation Technology

Appendix 4 Relevant Documents

Documents that may be applicable to TEMPs (not exhaustive).

Blood

Council of the European Communities. Recommendation No. R(79) 5 on the transport and international exchange of substances of human origin.

Council of the European Communities. Recommendation No. R(80) 5 on blood products for the treatment of haemophiliacs.

Council of the European Communities. Recommendation No. R(86) 6 on the guidelines for the preparation, quality control and use of fresh frozen plasma (FFP).

Council of the European Communities. Recommendation No. R(90) 3 on medical research on human beings.

Council of the European Communities. Recommendation No. R(93) 4 on clinical trials involving the use of components and fractionated products derived from human blood or plasma.

Council of the European Communities. Recommendation No. R(95) 15 on the preparation, use and quality assurance of blood components.

Council of the European Communities. Recommendation No. R(96) 11 on documentation and record keeping to guarantee the traceability of blood and blood products especially in hospital.

Council of the European Communities. 98/463/EC. Recommendation on the Suitability of blood and blood plasma donors and the screening of donated blood in the EC.

Medicines

Rules and Guidance for Pharmaceutical Manufacturers 1997.

CPMP/BWP/268/95 NfG on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses

CPMP/BWP/1230/98 NfG on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products

CPMP/BWP/269/95 NfG for plasma derived medicinal products.

Medical Devices

EN 1441 Medical devices - Risk analysis

EN-ISO 14971 Medical devices – Risk management – Part 1, 2001.

EN-ISO 10993 Biological evaluation of medical devices

EN 540/ISO 14155 Clinical Evaluation

EN 12442 Animal tissues and their derivatives utilised in the manufacture of medical devices

Cells/Tissues

Common Standards for Musculoskeletal Tissue Banking, European Association of Tissue Banks/European Association of Musculo-Skeletal Transplantation, 1997.

Standards for Blood and Marrow Progenitor Cell Processing, Collection and Transplantation JCIE/EBMT, 1998.

Guidelines on the organisation and ethical use of human tissue in research, Medical Research Council

Council of Europe. Recommendation on Human Tissue Banking, 1994

Council of Europe. Convention of Human Rights with regard to the application of Biology and Medicine; Bioethics Convention, 1996.

Council of Europe. Guide on safety and quality assurance for organs, tissues and cells. jan 2001.

CPMP/BWP/41450/98 Points to consider on human somatic cell therapy (draft), march 2001.

FDA 1997. Proposed approach to the regulation of cellular and tissue-based products. Rockville, MD, USA. 1997.

FDA 1999c. Suitability determination for donors of human cellular and tissue-based products (proposed rule). FDA, 21 CFR 210, 211, 820 and 1271. Federal Register 1999;64(189):52696-723.

FDA 2001a. Current Good Tissue Practice for manufacturers of human cellular and tissue-based products. Inspection and Enforcement (proposed rule). FDA, 21 CFR 1271. Federal Register 2001;66(5):1508-59.FDA 2001b. Human cells, tissues, and cellular and tissue-based products; Establishment registration and listing (final rule). FDA, 21 CFR 207, 807, 1271. Federal Register 2001;66(13):5447-69.

Appendix 5 EU regulation of adverse events

Table 7: Overview of EU regulation with regard to mandatory reporting of adverse events with medicinal products versus medical devices[*]

EU Medicinal products	**EU Medical Devices**
Responsibilities of marketing authorisation holder	*Responsibilities of legal manufacturer*
Collect, assess and report adverse drug events (ADE)/adverse drug reactions (ADR)	Maintain an efficient system of monitoring and reporting any adverse incidents or near incidents
Have standard operating procedures (SOP) in place to ensure the above	Extend this system from initial development throughout the marketing lifetime of the device
Drug safety officer has to see to the above	Have complaint/recall handling procedures and a comprehensive quality assurance system
Build and maintain a database on ADE's/ADR's	Document any corrective actions
Report according to the requirements	Report according to the requirements
Respond in an adequate way to questions of authorities	Respond in an adequate way to questions of authorities
Report requirements	*Report requirements*
Expedited reporting in 15 days Complex reporting (CIOMS I form) Electronic reporting	Expedited reporting10 days or 30 days Simple reporting (MEDDEV form) no electronic reporting
Periodic reporting	*Periodic reporting*
Periodic safety update reports (PSURs) according to ICH E2C	No periodic reporting
Systems and procedures	*Systems and procedures*
SOP's Access to database from single point within the EU	SOP's Paper file acceptable and no further instructions

* The information in this table is derived from a presentation by Dr. M.C. Koster, Director Product Surveillance for Industries (PSI).