

Part C: Therapeutic Use of Tissue

So far this document has focused on the use of tissue for non-therapeutic purposes. Part C looks at the issues that need to be covered when tissue is used as a therapeutic product.

The use of human tissue as a therapeutic product has improved the quality of life for many people, including the recipients of organ and tissue transplants. The increasing success of these types of treatments and the potential offered by new techniques mean that it is timely to examine the current regulatory framework for the therapeutic use of human tissue.

In looking at the regulatory framework the following issues are of primary concern:

- Is the proposed use or therapy acceptable to the community, including different cultural groups?
- What systems are needed for the collection of tissue for tissue-based therapies?
- What type of safety and quality control system needs to be in place to make tissue-based therapies as safe as possible?

C1 What are tissue-based therapies?

The following description is drawn from a discussion paper released by the Australian Therapeutic Goods Administration (2003), which summarises the different types of tissue-based therapies.

Tissue-based therapies can be broadly categorised as:

- human tissue and cells, and cellular and tissue-based therapies
- gene and related therapies
- xenotransplantation.

These are discussed in turn below.

C1.1 Cell and tissue therapies

The transplantation of human tissues has been undertaken successfully for some time. The following types of treatments are now well established practice:

- transplantation of kidney, liver, lung and pancreas
- transplantation of heart valves to replace defective heart valves
- transplantation of corneas to restore eyesight
- skin replacement after severe burns
- transplantation of bone.

Recently, technology has advanced and the potential uses of human tissue have expanded considerably. Improvements in biotechnology have led to new ways in which human tissues can be manipulated to provide therapeutic benefits.

The above list details the use of larger amounts of tissue as a therapeutic product, but it is also possible to use cells as therapeutic products or replacements for cells that are defective or deficient in particular conditions.

There is no clear line between tissue therapy and cell therapy. A therapy may make use of living cells that are organised as tissues, or tissues may be purified to extract certain cells, and cell lines developed for therapeutic benefit.

One of the most significant developments in cell therapy is the identification and use of stem cells. Stem cells are found in different human tissues and are capable of developing into different types of cells with particular characteristics. For example, particular stem cells could grow into bone cells or nerve cells, and be used to replace damaged cells. Stem cells have the potential to be used in a range of therapies and treatment, although much research in this area still needs to be undertaken.

Stem cells from blood have been used for several years to treat people with bone marrow diseases. Recent research suggests, however, that there may be great potential for stem cells from different tissues to be used for a broad range of therapies, such as in treating certain degenerative brain conditions.

C1.2 Gene and related therapies

Gene therapy, simply put, is the genetic modification of cells to produce a therapeutic effect. This means that a number of medical conditions caused by genes that do not work normally could be cured or alleviated by gene therapy. Cystic fibrosis may be amenable to gene therapy, for example. Gene therapy is currently the subject of research and is not a therapeutic treatment at this stage.

One definition of gene and related therapies is:

Somatic gene therapy is defined as the insertion of DNA/RNA into the somatic cells³⁰ of humans. The term 'related therapies' has been used to allow the inclusion of some vaccines containing genetically modified organisms and novel DNA-based strategies or technologies that might be developed and have the potential to modify the human host genome (Therapeutic Goods Administration 2003).

Gene therapy can involve cells being removed from a patient, modified in the laboratory and put back into the patient, or it can involve the genetic modification of cells while they remain in the body.

³⁰ A somatic cell is any cell other than a sperm or egg cell.

Under current regulation, undertaking such processes would require approval under the Hazardous Substances and New Organisms Act (to perform the genetic modification) and the Medicines Act (see section C2 for a description of this legislation).

It is important to note that the process of gene therapy described in this section is not the same as germ-line genetic modification. Germ-line genetic modification generally means the genetic modification of gametes and embryos which, if implanted and allowed to develop, would mean the altered genes are passed on to subsequent generations. The genetic modification of gametes and embryos for reproductive purposes is likely to be prohibited under new human-assisted reproductive technology legislation.

C1.3 Xenotransplantation

Xenotransplantation is the transplantation of live cells, tissues or organs from another species (such as pigs) into humans. Xenotransplantation also includes any procedure where human fluids are exposed through a filtering system to living non-human cells, tissues or organs. The actual tissue transplanted is called a xenograft.

Xenografts are live tissue from another species, which makes them different from, for example, the pig heart valves that are routinely used in cardiac surgery and which contain no living cells.

Xenotransplantation is currently not undertaken in New Zealand, although in the future there may be the potential to use the following types of xenografts:

- clusters of specialised cells, such as pancreatic islet cells to treat diabetes
- other tissues such as skin
- solid organs such as a kidney or heart.

Xenotransplantation is a complex area, which raises significant issues in terms of acceptability and risk.

The current regulation of xenotransplantation is discussed in section C2.1 and the issue of public acceptability of this technology is discussed in section D3.

C2 Current regulation of tissue for therapeutic use

The use of tissue for therapeutic purposes is regulated through the:

- Medicines Act 1981
- Human Tissue Act 1964
- Code of Health and Disability Services Consumers' Rights 1996
- Hazardous Substances and New Organisms Act 1996.

These are discussed below.

C2.1 Medicines Act 1981

The primary concern of the Medicines Act 1981 is the safety of medicines and medical devices. The Act establishes a system of pre-market approval for medicines, an approval mechanism for clinical trials of medicines, and a licensing scheme for manufacturers and wholesalers of medicines. The Act also provides for post-market controls on medicines and medical devices.

Currently, the safety regime in the Medicines Act applies only to tissue that meets the definition of a medicine or medical device. The Medicines Act does not cover whole human organs and other transplantable tissue that have not been subject to a manufacturing process. The safety provisions of the Medicines Act and proposals to amend them are covered in detail later in this Part.

The Medicines Act also contains important provisions about 'specified biotechnical procedures', which includes xenotransplantation. Under part 7A of the Medicines Act no one may undertake xenotransplantation in New Zealand (including clinical trials) without the permission of the Minister of Health. Before permission for xenotransplantation to take place could be given, the Minister must be satisfied that any risk to the health or safety of the public is minimal and will be managed effectively, and that any ethical, cultural and spiritual issues have been adequately addressed. No applications to undertake xenotransplantation have been requested under these provisions. The provisions that limit xenotransplantation are due to expire in June 2005. One of the goals of the Review is to have new legislation in place for xenotransplantation before these provisions expire. This is discussed in section D3.1.

Work is under way to replace the Medicines Act, to implement the joint therapeutic products regulatory scheme and to regulate New Zealand-specific aspects of medicines regulation. The specific vehicle for tissue-based therapies discussed later in this section will be considered at a later date.

C2.2 Human Tissue Act 1964

The Human Tissue Act is contained in Appendix 2. The Act sets out the requirements to be met before tissue may be removed from the body of a deceased person for therapeutic purposes.

With regard to obtaining consent, or, as it is phrased in the Human Tissue Act, establishing a 'lack of objection', the Act distinguishes between when the wishes of the deceased person are known and when they are not known. Table C1 provides a summary of the consent provisions in the Act for therapeutic use of tissue. In each of these cases, the person lawfully in possession of the body of the deceased must be sure that an inquest or coronial post-mortem is not required before the body can be used for therapeutic purposes. If a coronial post-mortem is required, consent must be gained from the coroner before organs or tissue can be retrieved for transplantation. If the coroner gives consent, the coronial post-mortem would take place after the retrieval of organs for therapeutic use. About 50 percent of donors also require a coronial post-mortem.

The person lawfully in possession of the body may be:

- the person in charge of the hospital where the deceased person is lying (a hospital is defined in the Health and Disability Services [Safety] Act 2001 and the Mental Health [Compulsory Assessment and Treatment] Act 1992)
- the superintendent of any penal institution where the deceased inmate is lying.³¹

A discussion about the appropriateness of this definition, and the concept of 'lack of objection', is contained in Part B of this document (see sections B7.2 and B5.2), where it is recommended that the test become one of giving consent and that the concept of the 'person in possession of the body' be updated.

In ascertaining the views of the persons listed in Table C1, the person lawfully in possession of the body is required to make 'such reasonable inquiry as may be practicable' to inform their decisions'. In guidance issued in 1987, the then Department of Health described this phrase as requiring, in most instances, that the matter be discussed with any one relative who has been in close contact with the deceased person. The relative should be asked their views, the views of the deceased, and if there is any reason to believe that any other relative would be likely to object.

The guidance further notes that there is no need to establish a lack of objection from all relatives or to make inquiries that are unreasonable or impractical. For example, if a donor's relatives were found to be young children, inaccessible, or seriously ill, it would be impractical to ask them.

³¹ In practice penal institutions are now under the control of chief executives or general managers as opposed to superintendents.

Table C1: Decision authority for the collection of tissue from deceased persons for therapeutic use under the Human Tissue Act 1964

Person lawfully in possession of the body	May allow this use if there is no known objection from the deceased, surviving partner, or any surviving relative.
Deceased person (the wishes of the deceased may be written, or oral and witnessed by two people)	May request or object to the use. In requesting this use, the person may specify the terms of the request (eg, the body parts to be used, and for what purpose).
Surviving partner	May object to a request by the person lawfully in possession to use the body for this purpose.
Surviving near relative	Not mentioned in relation to therapeutic uses (but mentioned in relation to non-therapeutic uses, see section B2.1.1).
Any surviving relative	Has the same right as a surviving partner to object to a request by the person lawfully in possession to use the body for this purpose.
Summary	<p>If the deceased has requested this use, then the use <u>may</u> be authorised by the person lawfully in possession. Any terms specified by the deceased must be honoured.</p> <p>If the deceased has objected, then the use cannot be authorised.</p> <p>If the deceased hasn't stated an opinion, then the decision rests with the partner and family.</p> <p>If there is no known objection from the deceased or relevant family, then the use may be authorised by the person lawfully in possession.</p>

C2.2.1 Seeking consent for tissue donation in practice

Although not strictly required by the law, in practice, even if a person has stated their wish to be an organ or tissue donor, the whānau or family will always be asked for their agreement to the procedure and much good practice has developed in this area. Some people find this practice unacceptable, however, particularly in light of the gap between the demand for organs and other tissue for donation and the supply. This important issue is discussed further in section C4.

C2.3 Code of Health and Disability Services Consumers' Rights 1996

The Code of Health and Disability Services Consumers' Rights (the Code) is contained in Appendix 3. The Code is in regulations established under the Health and Disability Commissioner Act 1994. It applies to living people and provides a set of rights for people receiving health and disability support services. In terms of the therapeutic use of tissue, the Code relates to those situations where:

- a living person is a donor of tissue (eg, live kidney donation)
- a person is the recipient of a tissue-based therapy.

While all of the rights in the Code are relevant, those relating to information and consent are critical in relation to tissue-based therapies. In summary, services may be provided to a consumer only if that consumer makes an informed choice and gives informed consent.³² For example, a person must give their consent, after being given sufficient information, to living tissue or organ donation, or to receiving a tissue-based therapy.

C2.4 Hazardous Substances and New Organisms Act 1996

The Hazardous Substances and New Organisms Act is primarily concerned with protecting the environment and the health and safety of people and communities. This Act has recently been amended so that the genetic modification of human cells and tissues has been brought within its coverage.

Human cells are defined as follows:

‘Human cells’ –

- (a) means human cells, human cell lines, or human tissues that are being grown or maintained outside the human body; and
- (b) includes human reproductive cells or human embryonic cells that are being grown or maintained outside the human body.³³

The effect of this change is that any proposal to genetically modify human cells and tissues or import genetically modified human cells and tissues will require approval under the Hazardous Substances and New Organisms Act. This will include a risk assessment process that will assess the potential for adverse environmental, health and economic effects.

It is important to note that the Hazardous Substances and New Organisms Act applies to the genetic modification of human cells outside the human body (ie, in test tubes). If these cells were then to be used for other purposes, such as clinical trials in humans, additional processes will apply. In the case of clinical trials the approval processes under the Medicines Act 1981 will apply.³⁴

³² Right 7(1).

³³ Hazardous Substances and New Organisms Act, section 2.

³⁴ Work is under way to replace the Medicines Act, to implement the joint therapeutic products regulatory scheme and to regulate New Zealand-specific aspects of medicines regulation. The approval processes for clinical trials will be carried into the new regulatory environment for therapeutic products.

C3 What are the issues, gaps, or problems?

The Ministry has identified three areas where the current framework for regulating tissue for therapeutic use should be examined:

- whether particular tissue-based therapies are acceptable to New Zealanders, and how therapies that arise in the future can be considered (this is discussed in Part D)
- whether the legislative requirements for organ and tissue donation are the best approach to maximising the organs and tissue available for transplantation while also respecting the wishes and beliefs of the public
- how the safety of tissue-based therapies can be best assured.

C4 Organ and tissue donation

In common with people in other countries, there are more New Zealanders who could benefit from an organ or tissue transplant than there are organs or tissue available for transplantation. The projected increase in the proportion of older people in the population and trends that show an increasing number of people with conditions such as diabetes indicate that the gap between demand and supply is likely to widen.

The Ministry is approaching the issue of organ and tissue donation in two ways, by:

- examining the legislative provisions through this Review, which involves examining the current provisions of the Human Tissue Act that deal with consent and the issue of sale and purchase of organs and tissue
- examining service-level issues relating to organ donation in conjunction with the National Donor Co-ordination Office and District Health Boards, which includes service funding issues, the role of the National Donor Co-ordination Office, the training of health practitioners, and public education.

While it may be possible to make improvements to the current legislative framework for organ and tissue donation, the Ministry considers that changes to practice will have the most impact on rates of donation.

C4.1 Organ and tissue donation in New Zealand

In New Zealand the following organs or tissue may be transplanted:

- heart or heart valves
- pancreas
- lungs
- eyes (corneas, sclera)
- liver
- bone
- kidneys
- skin.

At any one time there are around 350 people on the waiting list for organ transplants, and of these, about 300 are waiting for a kidney transplant. Increased waiting times for patients on transplant waiting lists are associated with increased periods of hospitalisation prior to transplantation, increased morbidity at the time of transplantation, longer rehabilitation following transplantation and, sadly for some, death while waiting for a suitable transplant to become available.

Organs and tissues can be donated following death in the following circumstances.

- Organ donation – those who have suffered severe and irreversible brain damage, most commonly following a brain haemorrhage or trauma, will be admitted to an intensive care unit, will be on artificial ventilation, and brain death will be certified. After brain death has been confirmed the family will be offered the option of organ donation.
- Tissue donation – in Auckland, the donor tissue co-ordinators, employed by the University of Auckland, contact the families of those requiring a coroner's autopsy to offer the option of tissue donation.
- Eye donation – eye donation can be facilitated in a number of circumstances. It can take place in a hospital ward mortuary or funeral home.

The acceptable age and medical criteria for potential donors have been increasing for several years in an attempt to increase donor rates. However, the numbers of organs and tissues available for transplantation in New Zealand has remained relatively unchanged over the past 10 years.

New Zealand has one of the lowest organ donor rates in the world when measured by donors per million population (dpmp). New Zealand's rate of organ donation dpmp for 2002 was 9.6, slightly lower than Australia's rate of 10.4 and well below Italy's rate of 18.1 (Herbertt and Russ 2003). This measure is influenced by people's willingness to donate, as well as factors such as the number of intensive care beds available in each country.

- The number of cadaveric kidneys retrieved for transplantation in the past 10 years has remained unchanged (69 in 2002). Organs are allocated to patients of a compatible blood group and tissue type. Live kidney transplant rates have increased as a result of the low cadaveric kidney donation rate (48 in 2002).
- The number of livers retrieved has increased since the New Zealand Liver Unit has been established due, at least in part, to improved logistics (ie, New Zealand donor co-ordinators will travel within New Zealand to examine livers that may be marginal. This doesn't happen in Australia due to the Australians' increased travel costs). Organs are allocated to patients of a compatible blood group.
- The number of hearts and lungs retrieved is often dependent on the types of recipients on the waiting lists. For hearts and lungs the recipient must not only be of a compatible blood group, but of similar body weight to the donor.

The majority of hospitals in New Zealand that have an intensive care unit or can otherwise support ventilated patients are involved with organ donation. Some patients will have been transferred to a tertiary centre for treatment, whereupon organ donation becomes an option.

Tissue donation, such as eye donation, can take place in a more flexible range of circumstances. Donation can take place several hours after a person has died and the use of technology such as ventilators is not necessary. This means that a person who dies in the community may be able to be a tissue donor where they may not be able to be an organ donor.

C4.2 Increasing the organ and tissue donor rate in New Zealand

Organ and tissue donors are largely deceased persons,³⁵ so there is, therefore, a natural limit to the number of potential donors. Welcome reductions in road traffic deaths and other tragic events have further reduced the number of potential donors. It has been estimated that even with very proactive strategies to recruit donors there will still be a significant gap between the demand for organs and tissue and the supply (Jessamine 2001).

Other factors that influence New Zealand's donor rate are:

- the number of intensive care beds available and whether people are able to be cared for in an intensive care unit
- whether health practitioners identify potential donors and seek consent to organ and tissue donation
- whether people are willing to donate organs or tissue
- whether the surviving relatives consent to donation.

While there are natural limits to the number of organ and tissue donors in New Zealand, the Ministry considers that there is the ability to increase the current donor rates. The Ministry is also very conscious of the highly personal and sensitive nature of organ and tissue donation, and that in seeking to improve the rate of donation, care must be taken to respect the wishes of individuals and families.

These objectives seem to be best balanced by taking an approach that aims to ensure that everyone who is suitable to be an organ donor is offered – or their family/whānau is offered – the opportunity to be a donor. This aim should then result in all organs and tissue that are able to be donated being donated and transplanted.

³⁵ A limited amount of live organ donation occurs in New Zealand. This is discussed in section C4.8.

C4.3 The role of legislation

The Human Tissue Act 1964 sets out who is able to make decisions regarding the use of organs and tissue for therapeutic purposes after a person's death. The provisions are detailed in section C2.2 and Appendix 2, and are summarised as follows.

- A person may, before their death, record their wish to be an organ or tissue donor and they may specify the particular organs or tissue to be used. If this request is made, the person lawfully in possession of the body may authorise the removal of organs or tissue. This is subject to the person lawfully in possession having no reason to believe that the request was withdrawn.
- If a person has not recorded their wishes, the law allows the person lawfully in possession of the body to authorise the use of organs or tissue so long as they have made sure that there is no objection to this from the surviving partner or any surviving relative. In effect this means that the decision rests with the surviving partner or relatives if the deceased person hasn't recorded their wishes.

It is important to note that, in practice, families will always be asked for their consent to organ or tissue donation. Each family is recognised as being unique, is placed under no pressure to make a decision, and is encouraged to take the time they need to make a decision that is right for them. Even if it is known that a deceased person wished to be an organ donor, organ donation will only take place with the agreement of the family. The practice of allowing the family the final say over donation, even when the wishes of the deceased person are known, is contentious for some people.

C4.3.1 What are the problems with the current law?

A recent report (Chen et al 2003) analysing both New Zealand law and the laws of other countries set out the following issues with New Zealand's current law.

- Even though the Human Tissue Act was amended in 1989 to allow for a central computer system to be established recording organ donors, the number of organ donors in New Zealand remains low.
- A person's request to be an organ donor under section 3 of the Act is not required by the law to be mandatory upon that person's death. If that was the intention of the legislation, that is not how the Act is worded and the person lawfully in charge of the body is under no legal obligation to carry out the request of the deceased.
- Even if a person has indicated a preference to become a donor, at the time of their death the family will always be asked for their agreement. This appears to be contrary to the intent of the legislation, which does not require the permission of the donor's relatives where the donor's wishes are known.
- Practically, the most likely way a person will record their wish to be a donor is on their driver's licence. About 43 percent of licence-holders have indicated they wish to be donors. Recording a wish to be a donor on a driver's licence does not equal recording one's wishes under the Human Tissue Act. It does, however, provide an indication of what a person's wishes were. The driver's licence application notes that in the event of the licence-holder's death, family will be asked for their agreement to donate organs even if the licence-holder has ticked the 'yes' box.

- The driver's licence application form does not allow a person to specify what organs or tissue they are comfortable donating. Some people would be happy to donate some organs (eg, their kidneys) but not others, such as their heart, and may be put off ticking 'yes' for this reason.

Public debate about the legislation in New Zealand centres on the ability for the family to override the wishes of the deceased person to donate their tissue for therapeutic purposes. While this does happen in practice when family members find the idea of donating tissue overly distressful, in general people wish to follow through with the wishes of their loved ones.

C4.4 What are the options for changing New Zealand's law regarding consent to organ and tissue donation?

In addition to the system under our current law, there are four other approaches taken in laws around the world that could be considered for New Zealand. Some of these options could be used in combination with each other.

Important: With each of these options it is very important to note that organ and tissue donation is a secondary consideration to the duty of care and treatment of any individual. A person would only ever be considered as a potential organ or tissue donor once it is clear that a person is likely to become brain dead. The aim of saving life, and the best possible quality of life, remains the first consideration. Section C4.5 discusses brain-death.

Given the gap between the demand and supply of organs and tissue, the central issue in considering these options is which of two competing principles should be paramount, and whether the differences between the non-therapeutic and therapeutic uses of tissue justify different principles applying for these different uses.

In the non-therapeutic part of this document it has been proposed that the wishes of deceased persons should be regarded, but that there are situations where the wishes of the living should be able to take precedence. For example, section B5.2.2 proposes that the law should not require the wishes of the deceased to be followed when a person has requested that their body be used for anatomical examination after their death, if at the time of their death this would cause undue distress to the surviving family. In this situation the wishes of the living are allowed to override the wishes of the deceased.

In the case of organ and tissue donation, it could be decided that the benefit to be gained from increasing the availability of transplantable organs and tissue warrants a different approach. This approach could be thought of as based on the principle of maximising all possible health benefit obtainable from transplantation. If this principle were to take priority, the options that limit the ability for individuals to decide about donation of tissue (such as presumed consent) become more acceptable.

These are fundamental matters concerning how individuals, groups and cultures in New Zealand view their bodies, life and death. The Ministry is not proposing that either principle outlined above take priority in relation to organ and tissue donation. The principles are outlined only to illustrate the dilemma that needs to be resolved. Your views on this dilemma are welcomed.

C4.4.1 Option 1: Presumed consent

This system presumes that everyone is an organ or tissue donor unless they have specifically recorded their objection to being a donor. This system operates in a number of countries that have a higher donor rate than New Zealand, such as France, whose donor rate is 17 per million (Chen et al 2003). The system also operates in a partial fashion in Singapore, whose law states that all mentally competent citizens or permanent residents aged between 21 and 60 who are victims of fatal accidents are presumed to be kidney donors when they die unless they opt out by signing a form.

While it is likely that a presumed consent system would increase New Zealand's organ and tissue donation rate, it may not be acceptable to New Zealanders for a number of reasons. In particular, the approach:

- appears inconsistent with the culture of individual informed consent in the health and disability sector
- is likely to impact most on people who are poorly educated or unaware of how to opt out of the system if they do not wish to be donors
- may increase the grief for family members at an already difficult time – family members may feel unhappy at the idea of organs or tissue being retrieved from a loved one, but feel unable to prevent this happening
- may be inconsistent with different cultural views.

On the other hand, a presumed consent system may be the most effective way of increasing the number of organs and tissue available for transplantation. It has also been suggested that it has the advantage of not requiring families to make an important decision when they are grieving. Supporters of presumed consent systems also feel that the system is justified because:

- people can always opt out of the system, and this preserves their autonomy to make an informed choice
- it is a cost-effective system as less money needs to be spent on advertising and awareness, and it may also be more efficient to administer as health practitioners do not need to spend time gaining consent from families.

C4.4.2 Option 2: Requiring donor wishes to be followed (requirement for wishes to be followed)

A second option for New Zealand is to change the current law to require that donor wishes be followed. That is, if a person has recorded that they wish to be an organ donor, this wish *must* be followed if they die in the right circumstances and are suitable to be a donor (eg, they have been assessed as medically suitable to be a donor). Currently, health practitioners, who always seek the consent of the potential donor's family, do not take this approach.

This option would also require that where a person had stated that they did not wish to be a donor that this wish is followed.

If this option were to work in New Zealand it would need to be supported by both the general public and health practitioners. In particular, the public would need to be confident that they would still receive the best of treatment in intensive care units if they agreed to be an organ or tissue donor. Health practitioners would need to be confident that the public supported the system and would need guidance in providing support to bereaved families.

Other conditions that would be important to having this system work successfully are as follows.

- Informed consent – it would be important, if the wishes of the deceased person were required to be followed, that in making their decision during life the deceased person's decision was made with informed consent (ie they had been provided with sufficient information, and had not been subject to coercion – see Box B2)
- Currency of view – it would be important to know that the recorded wish of the deceased person was their view at the time of death. Experience with the driver's licence database is that decisions relating to organ donation do not necessarily remain fixed once they are initially made. When renewing drivers' licences people change their minds about donation in both directions. An analysis shows that about 3.2 percent of people changed their donor status from 'yes' to 'no', and about 7 percent changed from 'no' to 'yes'.³⁶ These changes are significant if the law is changed to require donor wishes to be followed.

Currently there are concerns that the donor rate may fall if this type of approach were taken. This is based on the fact that only about 43 percent of people who hold a driver's licence have indicated their wish to be a donor, although about 55 percent of families consented to donation in an audit of intensive care units.³⁷ In the United States, however, the laws regarding following the wishes of the deceased person are stronger, and the United States has a higher donation rate.

³⁶ This analysis was conducted by the Land Transport Safety Authority and included a sample of licence holders.

³⁷ Chen et al 2003, referring to Streat (in preparation).

C4.4.3 Option 3: Requiring New Zealanders to indicate their wishes (requirement to state wishes)

Another option for New Zealand is that people be required to indicate whether they wish to be a donor or not. This system would mean that people would have to make a decision. This option would then be combined with Option 2 above. That is, if people were required to make a decision, it would then be necessary to require that decision to be followed.

New Zealand already has a variation of this system through the requirement that people state their wishes when they obtain a driver's licence. However, this is not currently associated with a requirement to then follow those wishes. The concerns raised above regarding people changing their wishes have important implications for this option.

C4.4.4 Option 4: Requiring organ and tissue donation to be discussed with all patients entering hospital (requirement to request)

This requirement is part of the Uniform Anatomical Gift Act in the United States and could be an element of a New Zealand system. Such a requirement would mean that organ and tissue donation would have to be discussed with all people who are admitted to hospital. For most people this would mean that they would consider organ and tissue donation and would make a decision to be a donor or not should the situation arise at some time in the future. The acceptability of discussing organ and tissue donation with reasonably, or very, unwell people needs to be considered, however.

For a much smaller group of people this would mean that organ and tissue donation would be discussed with them, they would make a decision, and they may become a donor during that hospital stay.

This option would not capture all New Zealanders, only those entering a hospital. It should also be noted that most hospital patients that become donors are admitted to hospital in an unconscious state and many young donors will never have been in hospital before. This option could, however, be combined with another option already described.

C4.4.5 Status quo

The current system under the Human Tissue Act is explained in section C4.3. In brief, the system is that a person may indicate their willingness to be a donor during their life and if they die in the appropriate circumstances their family will be asked if they wish to donate organs. The Human Tissue Act allows for organs to be collected from a deceased person based on that person's record of their wishes (which may be written or oral and witnessed by two people), however in practice the grieving family is always asked if they know what the deceased person's wishes were and for their consent. The 'flag' of donor wishes on a driver's licence is an indication of a person's wishes only – it does not constitute a record of a person's wishes under the Human Tissue Act. It is also important to note that almost all organ donors are people who die in an intensive care unit.

C4.4.6 Access to information for tissue donation

The Ministry is also aware that there is concern in the tissue donation sector about the need for a timely assessment of medical suitability to be a tissue donor. It is highly preferable to assess whether a person is suitable to be a donor before donation is discussed with the family of the deceased person. Discussing donation before this assessment can be very distressing for families if donation is not then able to proceed. As tissue donors are often people who have died in the community (or in hospital outside an intensive care unit), information about their health status needs to be accessed from other health providers, such as their general practitioner or a hospital where they have previously been treated.

This has been an issue internationally, particularly for eye donation, and the Ministry is interested in the processes and experiences of the tissue donation sector and others in New Zealand in accessing information about the medical suitability of potential donors, including experience of the operation and interpretation of the Health Information Privacy Code in this regard.

We are seeking your views

34. The new legislative framework could consider five options (with combinations) to consent for organ and tissue donation. Of the options below, please tell us which you think may be better and why. The options are:
 - 1) presumed consent
 - 2) requirement for wishes to be followed
 - 3) requirement to state wishes
 - 4) requirement to request
 - 5) status quo.
35. If you think one of the options (other than status quo) would be better for New Zealand, do you think there should be any time when families/whānau should be able to override the wishes of the deceased person? Why or why not? If not, do you have suggestions for managing a situation when the wishes of the deceased person are not the same as those of the family/whānau?
36. The Ministry is interested in the processes and experiences of the tissue donation sector and others in accessing information about the medical suitability of potential donors. Please describe any experiences, difficulties or good practice in this area – including experience of the operation and interpretation of the Health Information Privacy Code.

C4.5 Defining death and determining brain-death

The Human Tissue Act refers to 'death' and a 'deceased person', but it does not provide a definition of these terms or a way of establishing that a person has died. This section seeks your views on whether a definition of death, and a process for establishing death, should be included in new legislation.

Organ donors are usually people who have suffered brain-death. Ventilators (breathing machines) and other medical processes are used to maintain the bodily systems of the brain-dead person until organ retrieval can take place. The use of ventilators and other systems means that organs are kept in good condition for transplantation, but it is not possible to use traditional tests, such as a lack of heart beat, to determine that a person has died.

In these situations, doctors use brain-death tests to determine that a person has died and that it is only machines, such as a ventilator, that are keeping the person's bodily systems working. The Australian and New Zealand Intensive Care Society's (1998) *Recommendations Concerning Brain Death and Organ Donation* use the definition of death contained in most Australian state laws:

a person is dead when there is irreversible cessation of circulation of blood in the body of the person, or irreversible cessation of all function of the brain of the person.

The *Recommendations* also contain detailed guidance about how brain-death tests should be done. The *Recommendations* are used in New Zealand and are contained in the *Guidelines for Organ and Tissue Donation* issued by the National Transplant Donor Co-Ordination Office (1998). For organ donation, two sets of brain-death tests are done by two different doctors at two different times. After the second doctor completes the second test, brain-death can be certified, and this is the time of death that is recorded on the person's death certificate.

The process for determining brain-death has been thoroughly considered by experts in this area and the Ministry does not propose to review it here. The Ministry is also not aware that there is any non-compliance with the recommended practice for determining brain-death. The Ministry is, however, interested in your views on whether the new regulatory framework should require compliance with this type of guidance.

We are seeking your views

37. Do you think that the new regulatory framework should contain a definition of 'death'? Please explain what you think the advantages or disadvantages of including this definition would be.
38. If you think a definition should be included, is the following a suitable definition? If not, please suggest any changes you would make.

'A person is dead when there is irreversible cessation of circulation of blood in the body of the person, or irreversible cessation of all function of the brain of the person.'
39. Do you think that the new regulatory framework should require compliance with the current guidelines for establishing brain-death? Why or why not?

C4.6 Different types of deceased donors

Most deceased persons who donate organs or tissue for transplantation will have had their bodily systems maintained by ventilators and other processes until the organs or tissue are retrieved. This is called 'heartbeating donation'. When transplantation began in the 1960s, organs and tissue were retrieved from 'non-heartbeating donors'. That is, the deceased person was not maintained by medical processes and death was determined by the absence of a heart beat or breathing. Non-heartbeating donation diminished as the development of technology allowed donation from heartbeating donors.

As transplantation medicine has advanced and the gap between the demand for, and supply of, organs has widened it is timely to consider whether the regulatory framework can be improved to support non-heartbeating donation. As there are limitations to the people that will be able to be heartbeating donors (see section C4.2), changes to the regulatory framework may also allow more people to fulfil their wish to be a donor.

C4.6.1 How does non-heartbeating donation work?

A non-heartbeating donor is a person who is declared dead on the basis that breathing and heart beat have ceased. For example, the donor may have suffered a non-recoverable brain injury and has died after the family and health practitioners have discussed and made the decision to withdraw life support systems; or the donor may be in the emergency department following a cardiac arrest and resuscitation efforts are unsuccessful.

If a deceased person's organs are to be in good condition for donation and transplantation it is important that the kidneys, for example, are cooled quickly. This cooling can be performed before the life support machine is withdrawn or before resuscitation is stopped if the family has agreed to donation. The cooling process involves inserting a small tube into the aorta to carry cooling solution to the organs. The detailed processes involved in non-heartbeating donation are sensitive and complex; and currently there is no detailed guidance developed to guide New Zealand practice in this area (Australian and New Zealand Intensive Care Society 1998: 15).

Some of the more complex ethical and practical issues that arise in this area are as follows.

- Is it acceptable to undertake processes to cool the organs of a deceased person, thus preserving the opportunity of donation, while donation is discussed with the family? This difficulty arises when it has not been possible to discuss donation with the family earlier.
- What process should be used for withdrawing life support from a person with a non-recoverable injury who may be a suitable donor? Issues that arise are the clinical evaluation that death is likely to occur and within what time period, the need to ensure that such assessment is thoroughly undertaken and records kept, and that there is a clear separation between the doctor(s) assessing the likelihood of death and the team of people involved in any subsequent transplantation.³⁸

³⁸ In the case of heart beating donation there is currently a clear separation between the doctors involved in assessing brain death and those involved in transplantation.

- Is it acceptable to keep a person who may be able to be a non-heartbeating donor on life-support systems for a longer period to allow arrangements to be made for donation to take place?

These types of issues need to be carefully considered but are beyond the scope of this Review. The issue for the Review is whether the new regulatory framework should make specific provision for non-heartbeating donation to take place, subject to such detailed guidance being developed. Including provisions in the new regulatory framework for non-heartbeating donation provides a degree of ‘future-proofing’ for the framework, and the Ministry considers this may have merit, provided that safeguards are in place. In particular, standards to guide practice should be developed by those expert in this area.³⁹

We are seeking your views

40. Should the new regulatory framework allow for non-heartbeating donation to take place, subject to appropriate standards and guidance being developed in this area? Please explain why you agree or disagree.
41. As well as informed consent, one particular safeguard that needs to be in place is a separation between the health professionals that assess a non-heartbeating donor and those that are involved in transplantation processes. Please describe any other safeguards you think should be considered.

C4.7 Directed donation by deceased donors

Internationally the practice is that organ or tissue donation by deceased donors is an unconditional or anonymous act. That is, a donor is not able to place conditions on the use of their organs or tissue. For example, a donor cannot state that their organs or tissue be given to a person of a particular age, gender, or ethnicity. Direct contact between donor families and recipients is also discouraged (see Box C1).

Donations of organs or tissue are gratefully accepted by the health and disability system and allocated to those who are in the best position to benefit from them. In order to determine who should receive donated organs or tissue, careful matching is undertaken between the donor and the recipient. It is useful to note that ethnicity is a factor in assessing tissue matches as, for example, there is a better clinical match between Māori donors and Māori recipients. This is, however, assessed on clinical grounds only.

Another criterion for determining who receives donated hearts, lungs or livers is how critically ill the recipient is: some people waiting for donated organs to become available are very ill and may die within a short period of time if a suitable organ is not available for transplantation.

³⁹ Note: the Australian and New Zealand Intensive Care Society (1998) have signalled the need for work in this area

Please refer to section D4 for a discussion on payment issues.

Box C1: Organ and tissue donor co-ordinators

There are organ and tissue donor co-ordinators for whole organs, eyes and other tissues. The co-ordinators provide similar services with regard to information and support for the family, with specific expertise in their particular area. Co-ordinators are often health professionals who work to organise the donation processes. One of their main roles is to provide information and ongoing support for families who have agreed to donation.

After donation and transplantation have taken place, the co-ordinators can:

- provide donor families with general information about the recipient (eg, age, sex and how successful the transplant operations were); this can happen days or years after the donation took place
- help recipients and their families express their gratitude. Direct contact is not recommended, but an anonymous letter of thanks from the recipient to the family of the donor can be forwarded through the co-ordinator. The donor family is always contacted to see if they wish to receive such a letter or card (National Transplant Donor Co-ordination Office undated, New Zealand National Eye Bank 2003).

We are seeking your views

42. Should the new legislative framework make it clear that donation of organs or tissue from people who have died should only be on the basis that the organs or tissue are an 'unconditional gift'?
43. Do you think that, if both parties wish to, donor families and recipients should be able to meet? If so, what type of support should be offered for this to happen?

C4.8 Live tissue donation

So far the discussion has focused on the donation of organs and tissue from people who have died. There is also the ability for living people to donate kidneys and parts of the liver for transplantation. The most well-known type of live donation and transplantation is kidney transplantation between relatives.

The National Health and Medical Research Council (1997) identifies two issues that need to be carefully considered in relation to living donors.

- The potential for harm to the donor – undertaking live donation of tissue causes a degree of harm, risk, pain or loss to the donor. This may be relatively short-lived (eg, when a person donates blood, which is quickly replaced by the donor), or it may be permanent, such as when a person donates a kidney. In the latter case, the person suffers a permanent loss from their body. The donation procedure also requires the donor to suffer a degree of pain; this may be minor as in the case of blood donation, or more significant, as in the case of surgery to obtain a kidney.

- The fact that the donation is to benefit another person who may be known to the donor – this situation raises the difficulty that the donor may feel, as a result of coercion or as a result of the gravity of the situation, that they have little option but to be a donor. The donor may also gain great satisfaction from having been able to assist a family member and witness their improved health.

The key to managing the live donation process is ensuring that good informed consent processes are followed. In New Zealand, the Code covers both live tissue donation and transplantation (see section C2.3 and Appendix 3). The Code provides for informed consent to health care procedures, and these requirements cover both the donor and recipient of tissue. The question for your consideration is whether you believe that the provisions of the Code are sufficient coverage for live organ and tissue donation, or whether special provisions are needed.

We are seeking your views

44. Live organ and tissue donation in New Zealand is regulated through the Code of Health and Disability Services Consumers' Code of Rights, in particular the requirement to ensure that informed consent is obtained before such procedures (either donation or transplantation) take place. Do you think the new regulatory framework should include any additional provisions? If so, please explain what these should be and why.

C4.9 Safety of whole organs that are transplanted

The section following this (C5) contains a detailed discussion of a proposed regulatory framework for tissue-based therapies. Section C5.2.6 contains a number of proposed exceptions to the framework. One of the proposed exceptions is whole organs for transplantation. While whole organs for transplant may best be exempt from regulation under therapeutic products regulation, ensuring the safety of these transplants is an important part of a comprehensive framework for therapeutic tissue. This section seeks your views about the current arrangements for ensuring the safety of whole organs for transplant and whether there should be changes.

Currently the safety of whole organs for transplant is governed by the *Guidelines for Organ and Tissue Donation* (National Transplant Donor Co-Ordination Office 1998). The *Guidelines* cover the following factors related to the safety of whole organs that are transplanted:

- criteria to identify a potential donor, and criteria that exclude a potential donor (eg, untreated bacterial, fungal or viral infections, or HIV)
- blood and other tests that need to be done before a person can be confirmed as a donor, and that are needed to match the donor with a recipient (these tests include blood type, HIV antibodies, Hepatitis B, and Hepatitis C)
- guidance for the clinical management of the donor in the intensive care unit once it is decided that donation will proceed (eg, the management of the ventilator and tests to ensure that oxygen levels are appropriate)

- guidance for the clinical management of the donor just before and during the donation operation (eg, anaesthetic requirements)
- special process requirements for when several organs are being donated (including special requirements for cornea donors).

The transplanting team also assesses medical suitability of organs before a transplant takes place.

We are seeking your views

45. Do you think the new regulatory framework should formalise safety guidance for whole organ donation? Please explain why or why not.

C5 Safety of tissue-based therapies

As a result of research, significant advances have been made in the ability to use tissue-based therapies to treat a number of ailments and improve the health of people. Just as legislation is needed to ensure that pharmaceuticals are safe to use, the Ministry considers that legislation is needed to ensure that tissue-based therapies are as safe as possible.

Because tissue-based therapies are a relatively recent treatment option the current regulatory framework under the Medicines Act and the Health and Disability Services (Safety) Act does not provide full coverage of these therapies. The Medicines Act only provides coverage of certain tissue-based products if they have been subject to a 'manufacturing' process, and the Health and Disability Services (Safety) Act has not been extended to cover services that deliver tissue-based therapies.

The regulation of services delivering tissue-based therapies is discussed next (section C5.1), and the regulation of tissue-based products is discussed in section C5.2.

C5.1 Regulating services and entities that deliver tissue-based services

The Health and Disability Services (Safety) Act provides a framework for setting safety standards in the health and disability sector. It also encourages continuous quality improvement by providers of services. The Act enables standards to be set for particular types of services. Providers are then independently audited against those standards and certified by the Director-General of Health to provide the relevant services. The Act also contains strict provisions for providers who do not meet the required standards. Table C2 illustrates how the Health and Disability Services (Safety) Act works.

Table C2: Framework for services safety under the Health and Disability Services (Safety) Act 2001

	Process	Requirements to be met	Sign-off
↓	Service to be covered (eg, hospital, rest homes)	Services not yet anticipated by the Act may be added so long as acceptable standards have been developed or will be developed within 12 months, and providers have at least 12 months to comply with the standard.	Governor-General
	Standard (has the status of regulation)	Standards must be independently developed in consultation with the sector; ⁴⁰ consultation must have been considered, and be in the public interest in terms of safety and compliance costs.	Minister
	Audit and certification	Designated audit agencies must be independent and approved.	Director-General

The Act recognises that providers may need to change their systems and practices in response to any standards put in place, and allows providers at least 12 months to comply with a new standard.

Services across the sector (eg, hospital services, residential disability care and rest home services) are regulated under the Act. The Act does not currently apply specifically to services providing tissue-based therapies (eg, tissue banks). When the Act was developed, however, it was anticipated that these types of services should be regulated in the future and specific provision was made for services that provide tissue-related therapies to be included in the regime.

There are tissue banks in New Zealand for corneas, skin and bone. The Ministry is conscious that, while operating under voluntary codes of practice,⁴¹ tissue banks are not formally regulated in New Zealand and that this is unusual internationally and creates risk in the following areas:

- the potential inability for some people to benefit from tissue grafts
- a recipient of a tissue graft could become ill
- difficulty in controlling costs
- the inability to look back through records to respond to an adverse event if one should arise (Compass Group 1999).

The same report notes that these risks could be created by:

- inadequate storage systems
- donor screening and processing
- inefficient use of resources
- factors such as ethical considerations, business continuity and data control
- inadequate systems for tracking donors to recipients.

⁴⁰ Consultation is required with consumers, representatives of affected providers and a number of providers, funders and consumers.

⁴¹ For example, the American Association of Tissue Banks Standards and the New Zealand Eye Bank Quality Manual.

These types of issues could be addressed by bringing tissue-banking services under the Health and Disability Services (Safety) Act. This would mean that a national standard for tissue banking would need to be developed in consultation with the sector. Tissue banks would then be independently audited against the standard and, pending the outcome of the audit, certified to provide tissue-banking services.

There is also the potential to regulate the collection of tissue for therapeutic purposes under the provisions in the Health Act 1956 that regulate blood and controlled human substances. Currently these provisions have only been given effect for blood, blood products and bone marrow. The detailed provisions of the Health Act are contained in Appendix 5. Using the provisions in the Health Act could:

- give particular entities the authority to collect controlled human substances (eg, corneas or skin)
- prohibit trade in controlled human substances (issues related to the sale and purchase of human tissue are discussed further in section D4).

We are seeking your views

46. Do you think tissue banking services should be regulated under the Health and Disability Services (Safety) Act, noting that this would mean the development of a national standard for tissue banking that was then audited and providers being certified accordingly? Please explain why you agree or disagree.
47. Do you think tissue services should be regulated under the provisions in the Health Act (excluding for the moment the provisions that restrict trade, as these are discussed in a later section)? Please explain why you agree or disagree.

C5.2 Regulating tissue-based therapeutic products

As noted previously, the Medicines Act is currently primarily concerned with medicines and medical devices, and only provides coverage of certain tissue-based therapeutic products. The Ministry proposes that the legislation that regulates medicines and medical devices should be extended to make it clear that it also covers tissue-based therapeutic products. This section discusses how this could work in practice, as tissue-based therapeutic products are different from traditional medicines in a number of important ways.

C5.2.1 What coverage do tissue-based therapeutic products have under current legislation?

The Medicines Act defines a medicine to be:

... any substance or article ... that is manufactured, imported, sold, or supplied wholly or principally:

- a) for administering to one or more human beings for a therapeutic purpose; or
- b) for use as an ingredient in the preparation of any substance or article that is to be administered to one or more human being for a therapeutic purpose, where it is so used
 - i. in a pharmacy or hospital or
 - ii. by a practitioner, or registered midwife, or designated prescriber or in accordance with a standing order or
 - iii. in the course of any business that consists of or includes the retail sale, or the supply in circumstances corresponding to retail sale, or herbal remedies; or
- c) for use as a pregnancy test.⁴²

In practice, this definition has been interpreted to apply to manufactured products such as tablets and capsules, and to blood and blood products, but not to tissue-based therapeutic products that have not been subject to a manufacturing process. For example, skin that has been donated by a person for use in transplantation (eg, after serious burns) and is stored in a skin bank until it is required is currently not subject to the Medicines Act because it has not been manufactured.

In practice, therefore, the following tissue-based therapeutic products are currently not subject to the Medicines Act:

- whole organs for transplantation (eg, kidneys, liver, heart and lungs)
- tissue that has not been significantly altered (eg, skin, tendons, ligaments, heart valves, corneas and bone)
- tissue-based therapeutic products that are custom-manufactured for a particular person.

By not having these types of tissue-based therapies covered by legislation, the government has limited ability to:

- control the safety and quality of tissue-based therapeutic products – the key safety concerns are the transmission of disease and poor tissue processing
- withdraw tissue-based therapeutic products from use
- control the use of clinical trials using tissue-based products.

⁴² Medicines Act 1981, section 3(1).

C5.2.2 What requirements are medicines subject to under the Medicines Act?

For the products covered, the Medicines Act applies a system of pre-market approval of products and licensing of manufacturers. The Act also contains a number of exemptions from these requirements, such as when a clinical trial of a medicine is conducted (although approval of the trial is required), or when a medical practitioner requests that a particular form of a medicine be supplied for the care or treatment of a particular person.

Medsafe, the unit of the Ministry of Health that administers the Medicines Act, gives effect to the Act by:

- ensuring that medicines are assessed and shown to be safe, of high quality, and effective before they are marketed in New Zealand
- monitoring the ongoing safety of medicines once they are on the market, and removing permission to market them in New Zealand if they are proven unsafe at a later time
- licensing and auditing manufacturers, packers and wholesalers of medicines to make sure their premises and practices meet an acceptable standard
- approving clinical trials of medicines in New Zealand (clinical trials are subject to detailed requirements under the Medicines Act, including being independently evaluated by specialist committees of the Health Research Council)
- handling complaints and investigations.

C5.2.3 Tissue-based therapies are different from pharmaceuticals

In designing a regime for the safety of tissue-based therapies, it is useful to note a number of significant differences between pharmaceutical and tissue-based therapies that will need to be accounted for in a new regulatory framework. In contrast to regular pharmaceuticals the following characteristics apply to the safety of tissue-based therapies.

- The product is often a one-off, and therefore more labour intensive to produce. In contrast, pharmaceuticals are produced in large production batches with a high turnover of product.
- The processes for production are less able to be standardised and may be to some degree experimental, whereas pharmaceuticals are produced through highly developed and controlled processes.
- The recipient of the product is often the primary consideration in development, as opposed to pharmaceuticals, which are manufactured for unknown users.
- Products generally have a short shelf-life.
- Those developing and applying the therapy may have limited control over the starting material because it is derived from a human or animal.
- Sterilisation to eliminate pathogens can be more difficult.

Key issues in the use of tissue-based therapies are, therefore:

- the potential for the transmission of infectious disease – an infectious disease may be present in the tissue when it is collected from the donor, or may be caused by contamination during handling or processing
- proving clinical effectiveness and safety – pharmaceuticals must receive approval before they can be marketed to the public. This approval is dependent on proof that the pharmaceutical is both effective and safe. Because many tissue-based therapies are ‘one-off’ products, this type of approach is not practical. It also needs to be recognised that tissue-based products may be offered to people with very serious medical conditions and few other treatment options.

C5.2.4 Designing a new regulatory framework for tissue-based therapeutic products

The New Zealand and Australian governments have agreed to establish a Joint Therapeutic Products Agency. The agency will replace the Australian Therapeutic Goods Administration and New Zealand’s Medsafe from 1 July 2005 (subject to the passage of legislation and ratification of a treaty⁴³), and will regulate therapeutic products such as medicines and medical devices.

Both New Zealand and Australia are undertaking work on the regulation of tissue-based therapies. Once each country has decided on its approach, the Government may decide that the Joint Therapeutic Products Agency should also regulate tissue-based therapeutic products. This is a significant decision to be taken at some time in the future.

Decisions about how New Zealand wants to regulate tissue-based therapeutic products will be made to suit the particular needs of this country. Looking to the future, however, it is useful to examine the approach that Australia is proposing to take to tissue regulation and consider how it may be adapted for New Zealand. Taking this approach means that the two systems will be similar if, in the future, the Government decides that tissue-based therapies should be regulated by the Joint Therapeutic Products Agency.

The following proposal for a regime to regulate tissue-based therapeutic products is, therefore, largely drawn (with amendments as required for the New Zealand context) from a discussion document released by the Australian Therapeutic Goods Administration in 2003 to inform deliberations in Australia.

C5.2.5 What needs to be included in the new legislation?

There are three areas that need to be regulated:

- a) issues relating to safety and quality
- b) issues relating to promotion and labelling
- c) issues relating to the administration of a regulatory system.

⁴³ The Agreement between the Government of Australia and the Government of New Zealand for the establishment of a joint scheme for the regulation of therapeutic products.

Issues relating to safety and quality

There are two main concerns with regard to the safety and quality of tissue-based therapeutic products: the transmission of disease and the way the tissue is processed.

With any use of human tissue there is some risk of diseases being transmitted. This risk is dependent on factors such as whether the donor and the recipient are the same person (autologous use), the tissue has been stored in a tissue bank, what types and what volume of other tissue are processed by the tissue bank, and the degree to which the tissue has been handled or manipulated in preparation for transplantation.

The regulation applied to minimise the risk of disease transmission should be commensurate with the level of risk posed. For example, the autologous use of tissue within a single surgical procedure presents a low risk of disease transmission, whereas tissue that has been transported or stored with other tissue from a range of donors presents a higher risk.

Some of this type of risk can be managed through requiring tissue banks to comply with a standard of practice, such as that proposed under the Health and Disability Services (Safety) Act (see section C5.1).

Other risks to the safety and quality of the therapeutic product are posed by processing tissue. The level of risk presented by processing tissue will depend on:

- the level of manipulation of the original tissue – this impacts on the potential for transmitting disease and the ability of the tissue to function as desired, although increasing levels of manipulation do not always mean increased risk
- whether the tissue is to be used for its normal biological function (homologous use) – non-homologous use of tissue may involve additional risks compared to homologous use, as it may be more difficult to predict accurately how the tissue will behave, but this may also vary with the type of tissue and the non-homologous use to which it is put
- whether the tissue is combined with non-tissue-based components – tissue-based therapeutic products that are combined with non-tissue-based products need to be considered in terms of the type of components added and the action of the added product
- whether the tissue is to be used for a metabolic function – products with a metabolic function will generally rely on viable cells to provide that function (eg, stem cells or islet cells). This is important for the handling of the product, as these types of cells are easily damaged, which will affect their ability to function after transplantation. Which is to say, minimally manipulated stem cells may carry significantly more risk than highly manipulated tendon tissue (which is non-metabolic).

These issues pose real questions with regard to how a regulatory framework should be designed.

Issues relating to promotion and labelling

The medicines legislation contains strict provisions regarding the packaging and labelling of medicines, including the statement of purpose, what it contains, and storage conditions. Similar issues arise with tissue-based therapeutic products.

Promotion and labelling issues for tissue-based therapeutic products include what the tissue is, how it should be used, and what its effects are. Any promotion of a tissue-based therapeutic product needs to be backed by studies that prove its efficacy and safety.

Issues relating to the administration of a regulatory system

The new regulatory framework needs to be focused on safety and quality. However, it also needs to make sure that it does not place unnecessary restrictions on practice and treatment, and barriers to innovation. In particular the system needs to:

- be able to respond to the development of new tissue-based therapeutic products and to new information about the risks posed by existing products
- allow for exceptional circumstances when a person's life may be seriously and immediately at risk and the only option is to use tissue that has not completed screening processes
- be focused on improving outcomes and continuous quality improvement and not simply on process issues
- be clear and unambiguous about the coverage of tissue-based therapeutic products and be well integrated with current processes for therapeutic products regulation
- be mindful of the international context of tissue-based therapeutic products and not place unnecessary barriers to New Zealanders accessing tissue-based therapeutic products
- distinguish between medical procedures and manufacturing processes. As noted earlier, there are important differences between tissue-based therapeutic products and pharmaceuticals; there are also current exemptions for health practitioners in certain areas. The place of these types of one-off innovative treatment needs to be considered in the new regulatory framework.

C5.2.6 A new legislative framework for tissue-based therapeutic products

Defining the product to be covered

In an environment where technology and science are developing rapidly it is useful to develop quite a broad definition of tissue to allow for future uses of tissue as a therapeutic product. A broad definition can then be narrowed with specific exemptions. A potential definition (based on material from the United States) is:

Human cells, tissue and cellular and tissue-based products are articles containing or consisting of, or derived from, human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

If a broad definition, such as that above, is used it will be necessary to provide a number of exceptions. The following are proposed as exceptions:

- blood and blood products – the use of blood is currently regulated through the Health Act and the Medicines Act and the system is working well, and it is proposed that New Zealand follow international practice and continue to regulate blood separately
- secreted or extracted human substances (eg, breast milk)
- products used in the manufacture of tissue-based therapeutic products such as antibiotic solutions – these products would continue to be regulated as medicines
- reproductive cells (ie, in-vitro gametes and embryos), which will be regulated under the proposed human assisted reproductive technology legislation (see section B2.5)
- cells, tissues and organs derived from animals (a proposed approach to xenotransplantation is discussed in section D3.1)
- non-viable tissues, such as heart valves, which are currently regulated as medical devices
- whole human organs for transplantation (see C4.9).

We are seeking your views

48. Do you think the definition of human cells, tissue and cellular and tissue-based products adequately describes the 'subject' of the proposed new regulatory framework for tissue-based therapeutic products? Please explain any changes you would make.
49. Do you agree that the products listed above should be exempt from the regulatory framework? Please explain your views.

Defining the activity to be regulated

Developing an appropriate description of the activity to be regulated is a key part of the new regulatory regime. Currently the Medicines Act uses the term 'manufacture' to describe:

any process carried out in the course of making the medicine; but does not include –

- a) dissolving or dispersing the medicine in, or diluting or mixing it with, some other substance used as a medium for the purpose of administering the medicine to another person;
- b) incorporating the medicine in any animal food.

Consideration has been given to whether the term 'manufacture' can appropriately be applied to tissue-based therapeutic products. Other terms that may more accurately reflect the actual processes are 'handle' or 'process'. This discussion has been conducted internationally, and it has been concluded that terms other than 'manufacture' are too narrow and that 'manufacture' should continue to be used as the umbrella term to capture the actions and organisations that are involved in the preparation of tissue-based therapeutic products.

If the term 'manufacture' is used in New Zealand for tissue-based therapeutic products, it may need to be tailored specifically for these products. The definition of manufacture proposed in the United States is 'any or all steps in the recovery, processing, storage, labelling, packaging or distribution of any human cell or tissue, and the screening or testing on the cell or tissue donor'.

A further issue that needs to be resolved is whether there are any activities that should not be considered as part of the manufacturing process. In the Medicines Act definition of manufacture for medicines, activities such as the dissolving of the medicine in water for administration to a person are excluded. Similarly, it is proposed that the definition of manufacture of tissue-based therapies could exclude the following activity:

- the removal of tissue and its implantation in a single surgical procedure – this may be autologous or non-autologous use.

We are seeking your views

50. Do you think the term 'manufacture' and the definition proposed for that term is appropriate for tissue-based therapeutic products? If not, please share your suggestions for a better term or definition.
51. Is the proposed exemption from the definition of 'manufacture' appropriate? Are there other activities you think should be exempt from the definition? Please explain your suggestions.

Defining the people to be regulated

The third branch of the proposed regulatory framework is defining the people who should be regulated with regard to tissue-based therapeutic products. Currently the Medicines Act provides exemptions from licensing requirements for a number of people.

- An authorised prescriber may manufacture, pack and label medicines that are specially prepared for administration to a patient under that prescriber's care.⁴⁴
- Pharmacists working in a hospital or registered retail pharmacy do not need a licence to manufacture, pack, label, sell and supply a medicine to a patient that has requested that medicine (these provisions do not, however, give pharmacists the right to prescribe medicines).⁴⁵

In deciding whether there should be exemptions from licensing for particular people involved in manufacturing tissue-based therapeutic products, the following factors need to be considered.

- Most 'manufacture' of tissue-based therapeutic products occurs in hospital settings that are already subject to safety standards. However, the safety risks associated with the manufacture of tissue-based therapeutic products may be the same regardless of whether the manufacturing occurs in a hospital or in another setting. For this reason it may be inappropriate to exempt medical practitioners and others from the regulatory regime where they are manufacturing tissue-based therapeutic products for the benefit of an individual patient.
- Should the ongoing use of a 'one-off' tissue-based therapeutic product be exempt from the regulatory regime on an ongoing basis? That is, at what point is a product no longer a 'one-off' manufacture for a specific patient? The issue at the heart of this question is whether the types of tissue-based therapies being developed pose any special risks that should distinguish them from other custom-made medicines or medical devices; and if so, what level of regulation is appropriate? This question is related to definitions of innovative treatment and international moves to license hospitals for all 'manufacture'.
- How should the distinction be made between supply and manufacture on the one hand, and medical practice on the other? This is a particularly complex issue and we are interested in your views on this.

⁴⁴ Medicines Act, section 25.

⁴⁵ Medicines Act, section 26.

We are seeking your views

52. Your suggestions on potential exemptions from licensing requirements for particular people are sought. Consideration of this issue needs to be in the context of:
- other exemptions proposed for particular products or manufacturing activities
 - any differences in the risks posed by the processing of tissue in a hospital setting compared to other settings
 - whether exemptions for custom-made products are appropriate
 - how we distinguish between medical practice and supply and manufacture of tissue-based therapeutic products, and the impact of any regulation on clinical decision-making.

A risk-based approach to regulating tissue-based therapeutic products

As described previously, the risk to safety posed by any tissue-based therapeutic product is a complex combination of the type of product, the use proposed for the product, and the degree of manipulation of the product. Table C3 provides a summary of the degree of risk posed by different tissue-based products, which could form the basis of the degree of regulation applied to each type of tissue.

Table C3: Summary of the degree of risk posed by different tissue-based therapeutic products

Low risk	Medium risk	High risk
Tissue that has not been altered at all, or subject only to flushing, trimming and cutting	Any tissue that has been banked, including tissue that has been subject to only flushing, trimming or cutting processes (or their equivalent); except where that tissue would fall under 'high risk'	Tissue that has been manipulated using chemical or genetic processes that alter the natural properties of the tissue
Tissue that has been subject to processes equivalent to flushing, trimming or cutting that does not deliberately alter the biological or mechanical characteristics of the tissue		Tissue that, by its action, produces a pharmacological or chemical effect in the recipient
Tissue that is removed and re-implanted in a single surgical procedure – either autologous or non-autologous use		Tissue manufactured using biological reagents such as monoclonal antibody sequestering, or cell expansion techniques
Tissue used for a homologous or a metabolic purpose in the person from whom it was obtained, or in a close blood relation of the donor – provided that the tissue is also minimally manipulated and used without non-tissue components		Tissue used for either non-homologous use or for a metabolic purpose where the patient is not a close blood relative of the donor

We are seeking your views

53. What do you think of the categorisation of tissue contained in Table C3? Would you assign any activities differently? Please explain your comments.

What level of regulation should apply to the different categories of risk?

The level of regulation applied to tissue-based therapeutic products needs to be commensurate with the level of risk posed and other arrangements that are in place, or are proposed to be put in place. The Ministry proposes that:

- low-risk tissue-based therapeutic products could be exempt from regulation under new therapeutic products regulation – these products are largely covered by safety standards for whole organs discussed in section C4.9
- medium-risk tissue-based therapeutic products could be exempt from regulation under new therapeutic products regulation, but that tissue banks be regulated as described in section C5.1
- high-risk tissue-based therapeutic products be subject to regulation under new therapeutic products regulation.

This would mean that high-risk products would be:

- assessed to ensure they are safe, of high quality, and effective before they are used in New Zealand
- subject to ongoing monitoring once they are in use, and would be removed from use if proven unsafe at a later time.

The process of collection, manufacture, packing and distribution of these products would also be licensed and audited to ensure that acceptable standards were met.

Clinical trials of such products would be subject to the approval processes through the medicines regulator and an ethics committee. The committees currently involved in such approvals are described in Appendix 4.

In giving effect to this type of regulatory system, the medicines regulator would require information about:

- the product, any sub-products and the method by which it has been manufactured
- important steps in manufacture, such as the source and criteria for acceptance of raw materials, the tests applied to raw materials to ensure they are free of infectious diseases, the tests and criteria for acceptance applied to the final product, and other quality control systems
- the uses for the product and how it is to be administered to people
- robust evidence that validates the critical steps in the manufacture, storage, freedom from infectious agents, quality and safety of the product.

The classification of a product as high-, medium- or low-risk would be made by the medicines regulator on an ongoing basis, as is currently the case for pharmaceuticals.

We are seeking your views

54. Your comments are sought on the proposed regulatory approach to tissue-based therapeutic products and any concerns you have about how it may impact on the practice of health care.