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Department of Health
Therapeutic Goods Administration

Method of preparation: Interpretation of minimal manipulation

Australian Regulatory Guidelines for Biologicals (ARGB)

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TGA Health Safety Regulation

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This guide is for sponsors, manufacturers, health practitioners and consumers to explain how the method of preparation of a biological product influences:

- its classification as a Class 2 or 3 biological
- whether autologous HCT products are exempt from specific requirements

Minimal manipulation

The goods have been subjected to minimal manipulation if no process or processes to which the goods have been subjected have altered any of the biological characteristics, physiological functions or structural properties of the original cells or tissues that are relevant to the purpose for which the manufacturer of the goods intends the goods to be used.

Processing that is usually considered minimal manipulation

It is important to consider the properties of the human cell and tissue (HCT) product in the donor when determining whether any processing step(s) have altered the characteristics of the HCT. Processing may not preserve all functions, but the manufacturer must be able to show that selected characteristics related to the intended use are sufficiently maintained. This may require a reasonable understanding of the mechanism(s) of action.

The following list of actions would **usually** be considered minimal manipulation:

- centrifugation
- trimming, cutting or milling
- flushing or washing
- refrigeration
- freezing
- freeze drying
- the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents
- irradiation for the purpose of bioburden reduction

Processing that is usually considered more than minimal manipulation

Where relevant characteristics of the HCT product are altered, the product function in the recipient cannot be predicted and such actions that would generally be considered to be more than minimal manipulation.

These may include:

- cell culture
- mixing demineralised bone with a gelatinous carrier, e.g. glycerol
- mixing demineralised bone with a medicine e.g. recombinant bone morphogenetic proteins (BMPs)
- seeding of cells on to a medical device
- enzymatic dissociation of tissue
- in vitro differentiation of cells or tissues
- genetic modification

Distinguishing between minimal and more than minimal manipulation

Below are examples of how we would distinguish between minimal and more than minimal manipulation.

Adipose tissue

1. Adipose tissue is collected from one area of the patient and used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is **minimal manipulation** because the processing does not alter the cushioning and support of the adipose tissue.

2. A manufacturer processes adipose tissue (enzymatic or physical dissociation) with the aim to dissociate cell-cell contacts and isolate the cellular portion. The resultant product (such as stromal vascular fraction (SVF)) is injected back in to patients for reputed anti-inflammatory uses. In this case the cells responsible for the intended use and to which the determination of minimal manipulation applies (e.g. mesenchymal stem cells) would be considered the autologous HCT product. Such methods used to disrupt adipose tissue would be considered **more than minimal manipulation**. The process applied to isolate the cells is likely to result in changes to their properties, e.g. activation state or surface molecule expression, which could significantly impact the cells' characteristics or functions.

Amniotic membrane

3. A manufacturer processes amniotic membrane to preserve it and package it in sheets, for use in wound covering. This is considered **minimal manipulation** as the barrier function of the membrane is not altered by the processing.

4. A manufacturer processes amnion and then grinds it in to particles for injection into a wound to improve healing. This may be considered to be **minimal manipulation**, as long as the manufacturer can demonstrate to the satisfaction of the TGA that the mechanism of action for the clinical claim is a result of the intrinsic characteristics and functions of amniotic tissue, and that the manufacturing process does not alter these relevant characteristics. Note that although the processing step may be considered minimal manipulation, the intended use may not be considered to be homologous.

Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF)

5. Preparation of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) from a single uninterrupted venepuncture, for injection into damaged tissue. Generally, because the processing involved does not alter the functions of the platelets, this is considered **minimal manipulation**.

Conditioned serum

6. Preparation of conditioned serum from a single uninterrupted venepuncture, for injection into damaged tissue. Generally, because the processing involved does not alter the functions of the serum, this is considered **minimal manipulation**.

Musculoskeletal tissue

7. A manufacturer performs mechanical machining to shape bone during total knee replacement. This would generally be considered to be **minimal manipulation** as the structural element is maintained and is the crucial characteristic of the tissue relating to its intended use.

8. A manufacturer grinds the bone to form morselised chips and particles for filling of bone voids. The structural element of the bone is no longer maintained, but this would still generally be considered to be **minimal manipulation** as the strength and resistance to compression is maintained, which is the crucial characteristic of the tissue relating to its intended use.

9. A manufacturer demineralises morselised bone sufficiently to increase the malleability of the bone, with the intended use restricted to void filing. This is considered **minimal manipulation** as it maintains the utility to support bodily structures.

10. A manufacturer demineralises the bone sufficiently to increase the exposure of the bone morphogenetic proteins, for use in bone grafts where osteoinductive potential is desired. This may still be considered to be minimal manipulation, as osteoinductivity is an inherent property of mineralised bone. However, the manufacturer must be able to demonstrate that the manufacturing process does not substantially diminish the osteoinductive potential (to a clinically relevant level). Note that due to batch variation in osteoinductive potential, presumably due to variation between donors, most demineralised bone matrix (DBM) preparations would require batch testing where an osteoinductive claim is made. Mixing the DBM with a carrier is considered **more than minimal manipulation**.

Skin

11. A manufacturer processes skin to decellularise it and leave the collagen matrix for use in covering burns. The utility of the skin to provide a protective covering is not substantially compromised by the processing, so this is considered **minimal manipulation**.

Version history

Version	Description of change	Authors	Effective date
V1.0	Original publication incorporating new legislative changes and information previously published on the TGA website.	Biological Science Section Regulatory Guidance Team	July 2018
V2.0	Updates to reflect regulatory changes to conditioned serum	Biological Science Section Regulatory Guidance Team	July 2019

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