Autologous Cell Therapies Manufactured in the Hospital: ATMPs or Not?

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Cytori Therapeutics

EMA ATMP Workshop - September 11, 2014
Dresden, Germany

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Risks with Autologous Cells

- Same Surgical Procedure
  - Transplantations
  - Same environmental risks as the patient
- Same Surgical Procedure with Point of Care Device
  - CE Marked Device / Reagents
  - Same environmental risks as the patient
- Multiple Day Procedures
  - Culturing Cells
  - Unknown additives and environmental factors

Autologous in Same Surgical Procedure

Harvest adipose tissue (liposuction)

Isolate adipose regenerative cells

Return cells to same patient in about an hour

- Adult ADRC's cells
- Endothelial progenitor cells
- Other key cell types

Autologous Same Surgical Procedure Exemptions

Directive 2004/23/EC

- EUTCD
  - "Tissues and cells used as an autologous graft within the same surgical procedure" are exempt per Article 2 section 2(a).

2004/23/EC

(8) This Directive excludes blood and blood products (other than haematopoietic progenitor cells) and human organs, as well as organs, tissues, or cells of animal origin. Blood and blood products are currently regulated by

Directives 2001/83/EC and 2000/70/EC (1), Recommendation 98/463/EC (2) and Directive 2002/98/EC (3). Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process, are also excluded from this Directive. The quality and safety considerations associated with this process are completely different.

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Existing HTA Decisions on Point of Care Devices

HTA
Human Tissue Authority

HTA position statement

Reference	HTA-POL-067b	**Date approved**	
Author(s)	Josephine Hughes	**Next review due**	
Reviewed by		**Owner**	Imogen Swann
Approved by		**Distribution**	HTA Staff /Stakeholders

Position statement on the regulation of processing and distribution when carried out as part of a single surgical procedure

Existing HTA Decisions on Point of Care Devices

Examples of licensing scenarios:

1. An establishment removes adipose tissue which contains stem cells. Once removed the tissue is processed in the adjoining preparation room, where the patient was anaesthetised. The preparation room has the same environmental controls and aseptic standard as the room in which the tissue/ cells were collected and the staff involved in the procurement also oversee the processing.

   This procedure does not require a HTA licence.

Existing EU Decisions on Point of Care Devices

Ref. Ares(2011)1032941 - 29/09/2011

COMMISSION OF THE EUROPEAN COMMUNITIES
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Directorate D - Health Systems and Products
D4 – Substances of Human Origin and Tobacco Control

Brussels,
SANCO D4/IS/hp ARES(2011)

Meeting of the Competent Authorities for Tissues and Cells

23 - 24 June 2011

Summary Report

Existing EU Decisions on Point of Care Device

can then be redelivered to the same individual within the same surgery process in the same operating room (cells/tissues never leave the operating room).

Several Competent Authorities have expressed their opinions on the procedure (CZ, DK, SK, PT, IT).

Conclusively, the group of Competent Authorities for Tissues and Cells considered that that procurement of stem cells from adipose tissue using the above mentioned procedure, when used to the same individual within the same surgery process, in the same operating room, when cells used with the same essential function ((e.g. adipose-derived regenerative cells restoring the adipose mass of the breast following mastectomy for breast cancer), should be exempted from the Cell & Tissue Directive 2004/23/EC, based on Article 2.a.

How are 2004/23/EC and 1394/2007 Linked?

- Autologous in the same surgical procedure is equivalent to 'not placed on the market'?
- US FDA exempts autologous same surgical procedure cells and tissues in 21 CFR 1271.15(b)
- 1394/2007 and 2004/23/EC work in harmony
  - Recital 14 of 1394/2007
  - Recital 22 of 1394/2007
  - Article 2 of 1394/2007

1394/2007

(14) Directive 2004/23/EC of the European Parliament and of the Council (2) sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This Regulation should not derogate from the basic principles laid down in Directive 2004/23/EC, but should supplement them with additional requirements, where appropriate. Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.

1394/2007

(22) A system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of advanced therapy medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells, and in Directive 2002/98/EC of the European Parlia-

1394/2007

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

Relationship Between 1394/2007 and 2004/23/EC

- Both work in harmony and share definitions
- A basic principle of 2004/23/EC is that autologous same surgical procedure are not regulated (Article 2).
  - Not bringing this 'basic principles' forward into 1394/2007 violates the spirit of Recital 14
  - 'this Regulation [1394/2007] should not derogate from the basic principles laid down in Directive 2004/23/EC'

CAT December 2013 Meeting

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16th January 2014
EMA/CAT/30564/2014
Procedure Management and Business Support Division

Committee for Advanced Therapies (CAT)

Minutes of the 12th – 13th December 2013 meeting

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CAT December 2013 Meeting

4.11. CAT consideration on classification : fat-extracted stem cells, for erectile dysfunction in men after prostectomy: **for discussion**	Most CAT members would consider this product as an ATMP on basis of non-homologous use. A general discussion took place on the classification of ATMPs made 'at-the-bedside' using CE-marked separation devices. It is noted that some of these CE-mark certificates make reference to a clinical use / indication of the cells prepared with these devices. This puts the NCA in difficult position to impose further regulatory oversight for such ATMPs (e.g. via clinical trials, hospital exemption or marketing authorisation). CAT suggested a further discussion with the Notified Bodies, e.g. via the EMA/CAT/Notified Bodies collaboration group. CAT members also discussed if cells/tissues that are excluded from the scope of Directive 2004/23/EC (i.e. tissues and cells used as an autologous graft within the same surgical procedure) are automatically excluded from the ATMP Regulation.

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Establishing Jurisdiction in EU for ATMPs

2001/83/EEC (Medical Device Directive)

- Scope- Article 2: The provisions of this directive shall apply to industrially produced medicinal products for human use intended to be **placed on the market** in member states.

93/42/EEC (Medical Device Directive)

- Definitions- Article 1 (2)h: 'Placing on the market' means the first making available in the return for payment…with a view to distribution and or use in the community market.

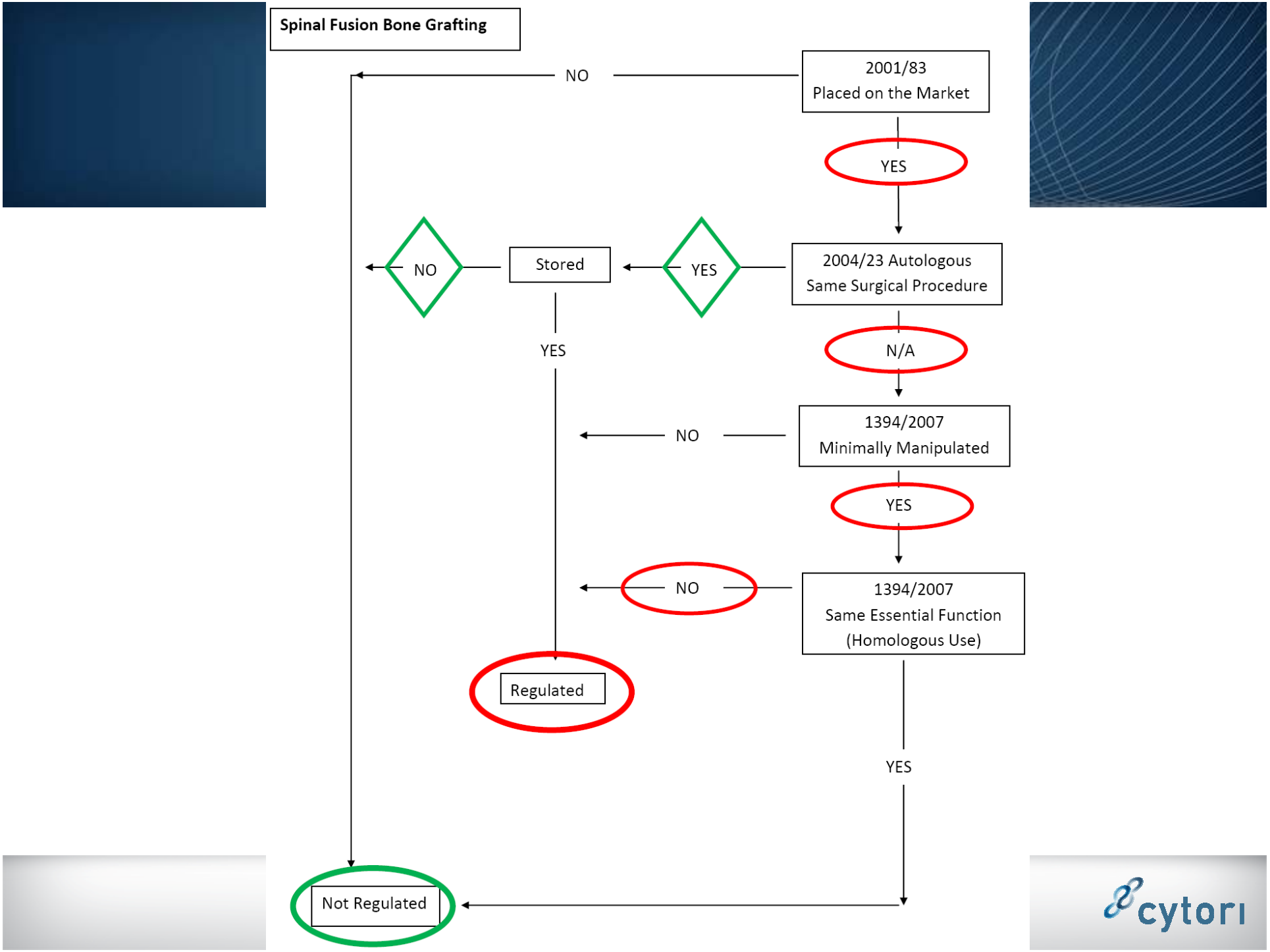
Engineered Cells – 1394/2007

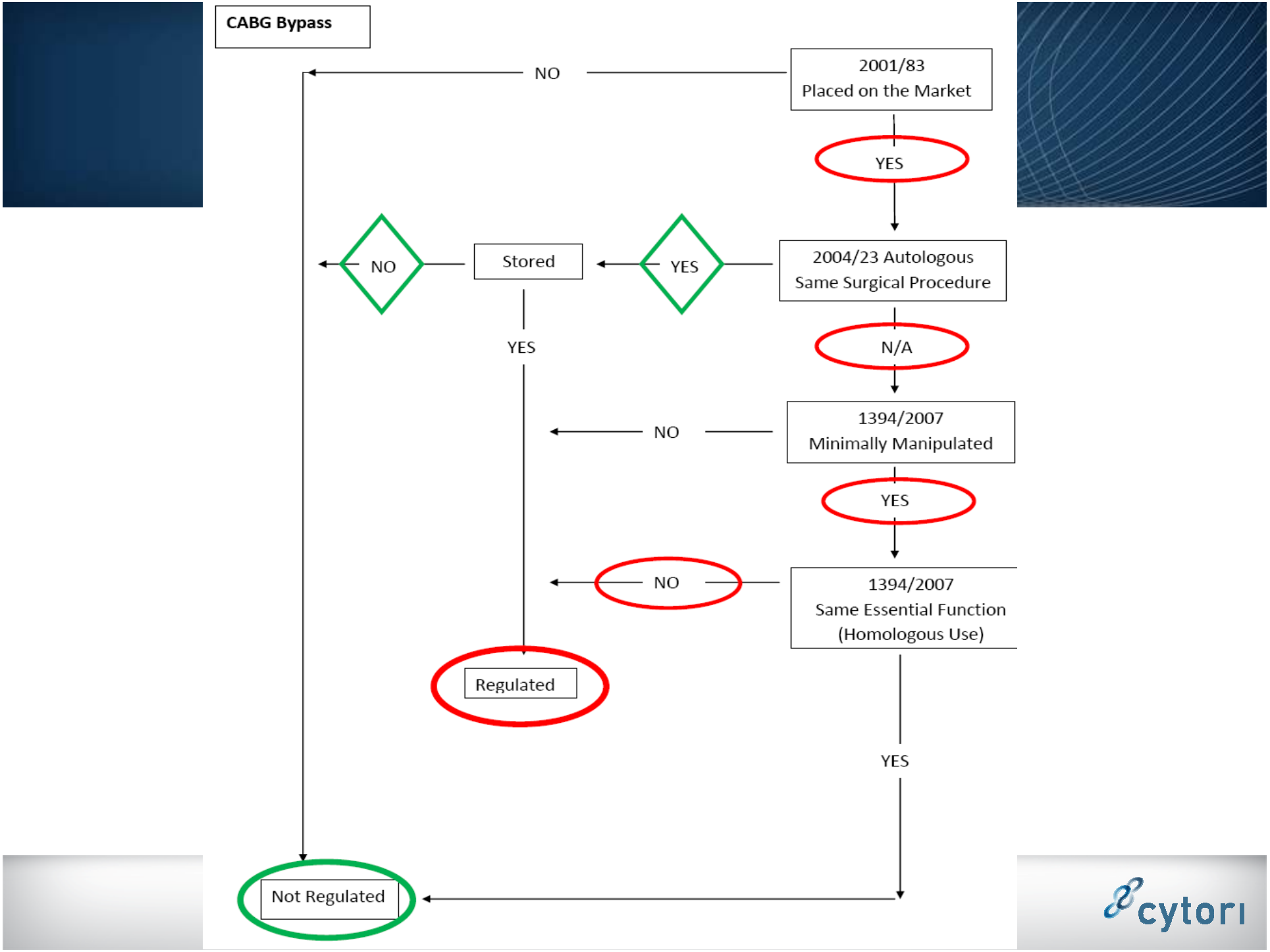
- 1 (C)- Cells or tissues shall be considered "engineered" if they fulfill *at least one* of the following points:
  - 1).Cells or tissues have been subjected to **substantial manipulation**, so that the biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement, are achieved. The manipulations listed in Annex I in particular, shall not be considered as substantial manipulations.

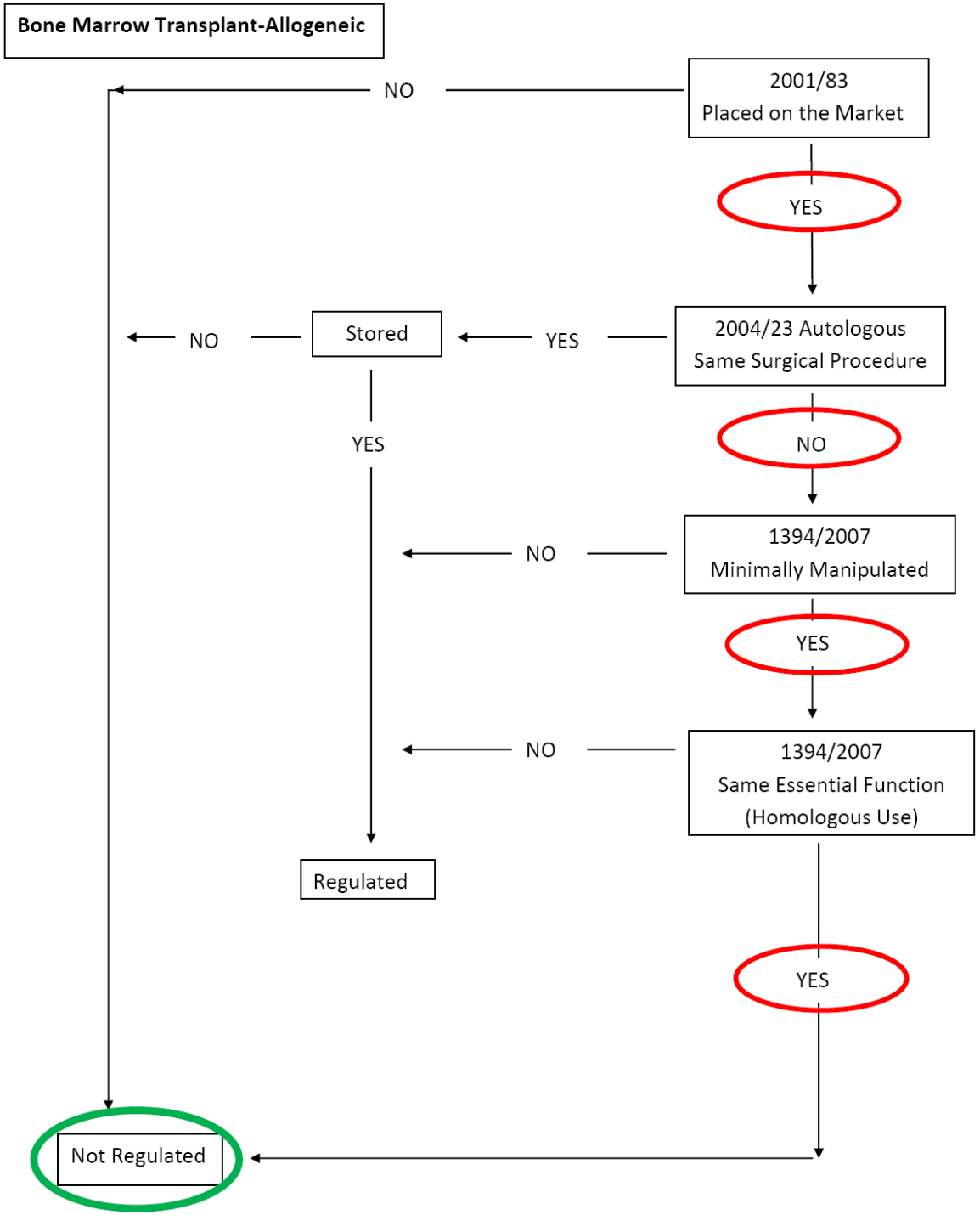
  OR

  - 2). The cells or tissues are not intended to be used for the **same essential function** in the **recipient** as in the donor.

Spinal Fusion Bone Grafting



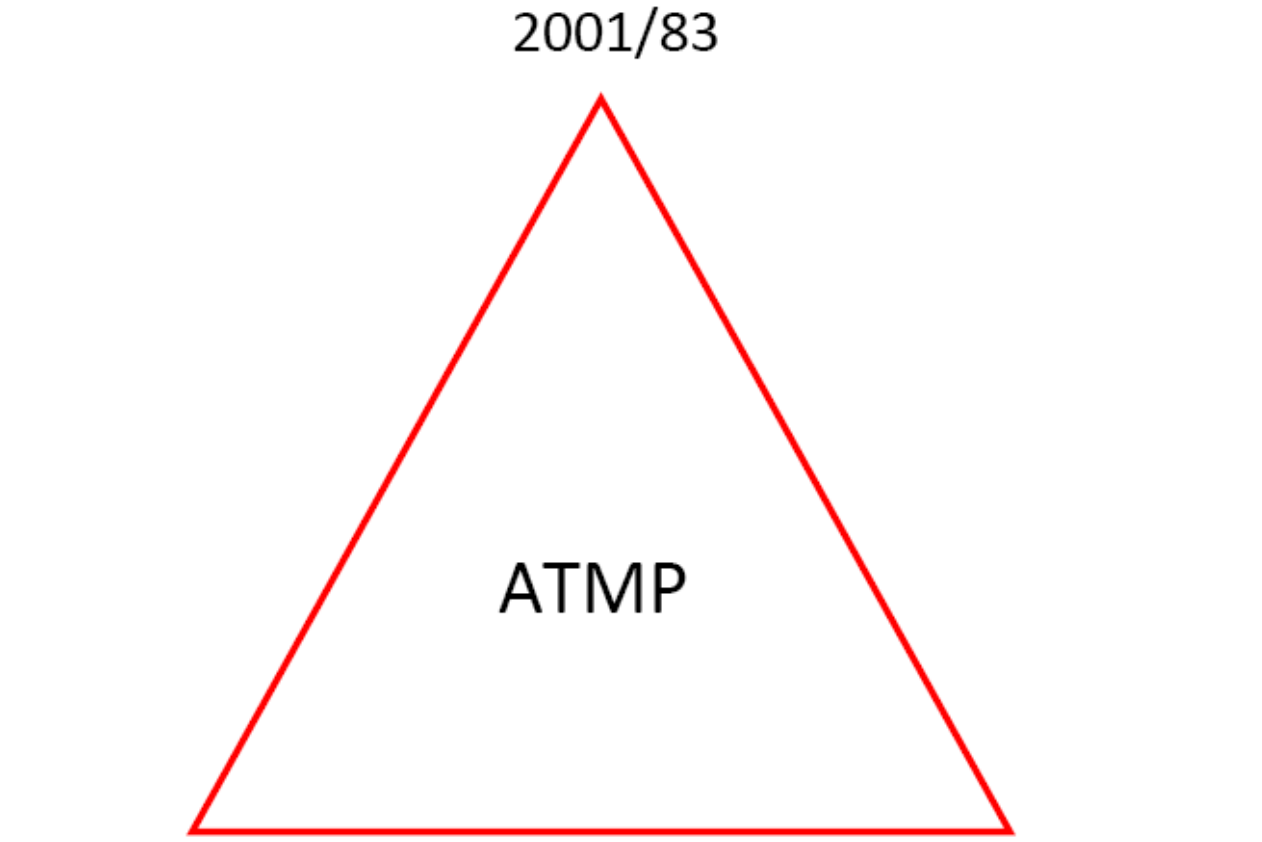

CABG Bypass
2001/83
Placed on the Market
NO
YES
2004/23 Autologous
Same Surgical Procedure
YES
Stored
NO
YES
N/A
1394/2007
Minimally Manipulated
NO
YES
1394/2007
Same Essential Function
(Homologous Use)
NO
Regulated
YES
Not Regulated


Bone Marrow Transplant-Allogeneic
2001/83
Placed on the Market
NO
YES
2004/23 Autologous
Same Surgical Procedure
YES
Stored
NO
YES
NO
1394/2007
Minimally Manipulated
NO
YES
1394/2007
Same Essential Function
(Homologous Use)
NO
Regulated
YES
Not Regulated

Non-Homologous Use Procedures

- Gram's Procedure – performed with a Class I Scalpel Device
  - Use of adipose to patch a stomach ulcer
  - Use of adipose to patch/seal an intestinal re-anastomosis
- Translocation of Colon – performed with Class I Surgical Scissors Device
  - Use of large intestine to build a bladder
  - Use of large intestine to repair esophagus
- CABG Bypass Procedure – performed with Class I Vein Stripper Device
  - Use of a peripheral vein to replace a coronary artery
- Spinal Fusion Procedure – performed with Class I Device bone chisel
  - Replacement of an articulating joint (spinal disc) with a bony fusion

ATMP



Placed on the Market EU Document

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Consumer Affairs
Cosmetics and Medical devices

Brussels, 16 November 2010
SANCO/B/2/PBE/pdw Ares(2010) 332016

INTERPRETATIVE DOCUMENT OF THE COMMISSION'S SERVICES[1]

PLACING ON THE MARKET OF MEDICAL DEVICES

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Placed on the Market EU Document

(9) According to the legal definitions, a product must be "made available" (*mis à disposition*, *überlassen*) with a view to distribution or use whilst making available is to be understood as the supply of a product (*fourniture*, *Abgabe*). The interpretation of these terms indicates that the mere termination of the manufacture is not sufficient for a product to be placed on the market. In addition, it must have entered into the distribution chain.

(10) The *Guide to the implementation of directives based on the New Approach and the Global Approach* ("Blue Guide")[8] states that the placing on the market takes place when the product is **transferred** from the stage of manufacture with the intention of distribution or use on the Community market. Even though the term "transfer" is not used in the legal definition, the German term "Überlassung" in the definition of *Inverkehrbringen* as well as the term "supply" in the definition of *making available* (like "Abgabe" in *Bereitstellung* or "fourniture" in *mise à disposition*) underline that a certain type of transfer needs to take place.

European Commission

The 'Blue Guide'

on the implementation of EU product rules

2014

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Placed on the Market

2.3. PLACING ON THE MARKET

- *A product is placed on the market when it is made available for the first time on the Union market.*
- *Products made available on the market must comply with the applicable Union harmonisation legislation at the moment of placing on the market.*

A product is placed on the market when it is made available for the first time on the Union market. The operation is reserved either for a manufacturer or an importer i.e. the manufacturer and the importer are the only economic operators who place products on the market[46]. When a manufacturer or an importer supplies a product to a distributor[47] or an end-user for the first time, the operation is always labelled in legal terms as "placing on the market". Any subsequent operation, for instance, from a distributor to distributor or from a distributor to an end-user is defined as making available.

As for "making available", the concept of placing on the market refers to each individual product, not to a type of product, and whether it was manufactured as an individual unit or in series. Consequently, even though a product model or type has been supplied before new Union harmonisation legislation laying down new mandatory requirements entered into force, individual units of the same model or type, which are placed on the market after the new requirements have become applicable, must comply with these new requirements.

Placing a product on the market requires an offer or an agreement (written or verbal) between two or more legal or natural persons for the transfer of ownership, possession or any other property right concerning the product in question. This transfer could be for payment or free of charge. It does not require the physical handover of the product.

Placing on the market is considered not to take place where a product is:

- manufactured for one's own use. Some Union harmonisation legislation however covers products manufactured for own use in its scope[48];

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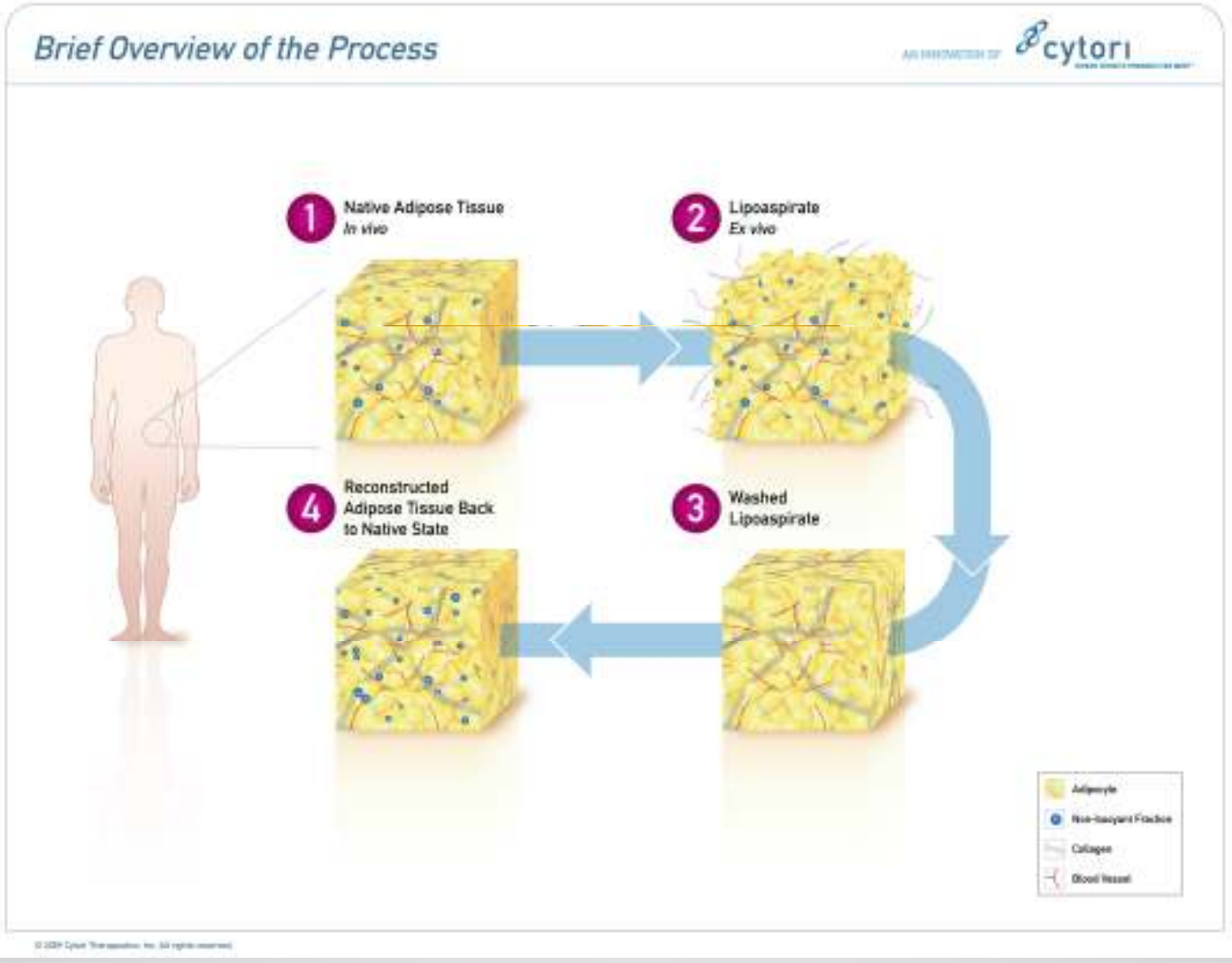
Placed on the Market Starts the Regulatory Process

The placing on the market is the most decisive point in time concerning the application of the Union harmonised legislation[53]. When made available on the market, products must be in compliance with the Union harmonisation legislation applicable at the time of placing on the market. Accordingly, new products manufactured in the Union and all products imported from third countries – whether new or used – must meet the provisions of the applicable Union harmonisation legislation when placed on the market i.e. when made available for the first time on the Union market. Compliant products once they have been placed on the market may subsequently be made available along the delivery chain without additional considerations, even in case of revisions to the applicable legislation or the relevant harmonised standards.

Member States have an obligation in the framework of market surveillance to ensure that only safe and compliant products are on the market[54]. Used products, which are on the Union market, are subject to free movement according to the principles laid down by Articles 34 and 36 TFEU. It must be noted that used products made available to consumers in the course of a commercial activity are subject to the GPSD.

Patient's Cells Never Entered O.R. Suite



So What is Placed on the Market in an Autologous Point of Care Procedure

- Devices and Reagents
  - Placed on the market
  - Must be CE Marked against MDD 93/42/EC
- Cell output from device
  - Not placed on the market
  - ‘manufactured for one’s own use’ is exempt per 2014 EU Blue Guide
  - ‘mere termination of the manufacture is not sufficient for a product to be placed on the market’ per 2010 Commission Report on Placing on the Market of Medical Devices

ATMP Cells and Point of Care Devices Are Regulated Appropriately

Criteria	ATMP Cell Therapy Cultured Autologous Cells	Point of Care Device and Reagents
Article Placed on the Market	Cells	Device and Reagents
Regulatory Oversight	YES	YES
Regulatory Body	EMA	Notified Body with Competent Authority Oversight
Clinical Data	YES	YES – MDD Annex X and Medev 2.71
Drug Device Combinations	ATMP Regulation	MDD Rule 13 (liable to act)
Animal Components	EMA Regulations	MDD Rule 17
Incident Reporting	YES – CA Reporting	YES – Vigilance Reporting
Follow Up Clinical Data	YES – phase IV data	YES - PMS

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Is Placed on the Market a Fundamental Question?

2001/83/EC (ATMP Directive)

- Scope- Article 2: The provisions of this directive shall apply to industrially produced medicinal products for human use intended to be **placed on the market** in member states.

2014 EU Commission Report on ATMPs

EUROPEAN
COMMISSION

Brussels, 28.3.2014
COM(2014) 188 final

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

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2014 EU Commission Report on ATMPs

4.3. Scope of the Regulation and classification of ATMPs

4.3.1. Scope of the ATMP Regulation

Three types of medicinal products are considered ATMPs: gene therapies, somatic cell therapies, and tissue engineered products. The assessment whether a product falls under any of these categories may involve complex scientific judgements. Specifically, the question whether a manipulation of a living material is to be considered as substantial may be difficult to answer. Even the question whether the cells or tissues are intended to fulfil the same function in the donor and in the recipient can be challenging in some cases (*e.g.* bone marrow material).

Experience in the application of the definitions of the various categories of ATMPs by the CAT shows that some aspects of the definition could be further clarified to ensure a better match of the legal definitions with the underlying scientific reality.

Additionally, advanced therapies being a field subject to rapid scientific progress, it is necessary to keep the definitions of gene therapies, somatic cell therapies, and tissue engineered products under continuous review. New innovative products, which are not clearly captured by existing provisions, are emerging. For instance, the development of devices which allow the collection of cells or tissues, the processing thereof in a closed environment and its reinjection into the donor within the same procedure raises questions as to how these treatments should be regulated (particularly in case of non-homologous use).

2014 EU Commission Report on ATMPs

4.3.2. Classification

An increasing number of innovative biological products exhibits characteristics that could potentially fall under various regulatory regimes (*e.g.* medicines, medical devices, cosmetics, or tissues and cells). Clarity on the regime that is applicable to new products is essential to achieve an adequate level of public health protection. Moreover, developers also need a clear understanding of the regulatory framework that will apply to their products so that the development process can be adapted to the relevant requirements.

However, cases have been reported where the competent authorities of the Member States had reached divergent conclusions as to whether a product should be considered as ATMP or not. The disparities that exist across the EU regarding the classification of ATMPs have also been identified as a concern in the public consultation undertaken by the Commission services in preparation of this report.

The possibility that the same product may be subject to different requirements across the EU implies that the level of public health protection is different according to the place of residence of the patient. That the same product can be marketed under different regulatory regimes is not only undesirable from a public health standpoint but it also undermines the incentives to develop ATMPs. First, the uncertainty as to the market potential for a product discourages investments. Secondly, divergent classification of the same product distorts competition between developers. Finally, the application of different regulatory requirements across the EU hinders the free movement of these products.

2014 EU Commission Report on ATMPs

4.4.2. The case of autologous ATMPs

In the case of autologous products the cells/tissues are harvested from a patient, then treated or expanded, and finally they are introduced back into the same patient. The starting material (*i.e.* the cells/tissues) is different for each patient and, as a consequence, the manufacturing process of these products has specific features as compared with other medicinal products.

However, it is important that the requirements that apply to autologous products are proportionate and adapted to the specific characteristics thereof. Requiring autologous products that are manufactured at the hospital prior to the administration to the patient to comply with the quality controls and manufacturing requirements of standardised chemical-based medicinal products would prevent the development of these treatments in practice as a batch release certification would be required per treatment and a manufacturing license would be required per hospital.

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17 Aug 2011 CAT Decision

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 August 2011
EMA/681354/2011
Patient Health Protection

Scientific recommendation on classification of advanced therapy medicinal products

Article 17 – Regulation (EC) No 1394/2007

Disclaimer: This document is a summary for public release of a scientific recommendation on classification of advanced therapy medicinal products. The original text adopted by the Committee for Advanced Therapies (CAT) has been redacted to delete commercially confidential information.

The present scientific recommendation refers exclusively to the case as presented to the European Medicines Agency (EMA) without prejudice to future evaluations by the Agency.

This scientific recommendation is not binding and is without prejudice to any decision taken by Member State competent authorities on matters falling within their own remits.

Short descriptor (or name when available) of the proposed active substance

Autologous mesenchymal stem cells (MSC) committed to cardiovascular lineage.

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17 Aug 2011 CAT Decision

Fulfilment of Article 2(1) of Regulation (EC) No 1394/2007 (definition of advanced therapy medicinal product – see Annex A)

- The product is intended to be placed on the market in the Member States. It will be manufactured under GMP methodologies at an external facility and is therefore regarded as manufacturing by a method involving an industrial process.

- The product can be considered as a not combined ATMP and a tissue engineered product according to the definition in Article 2(1)(b) of Regulation (EC) No 1394/2007 as:

    - it contains engineered cells according to the definition of Article 2(1)(c) second paragraph of Regulation (EC) No 1394/2007, and;
    - it is administered to human beings with a view of regenerating a human tissue;
    - it does not contain medical devices as an integral part of the product and its cellular part contains viable cells.

Based on the above considerations, it is considered that the product falls within the definition of a tissue engineered product as provided in Article 2(1)(a) of Regulation (EC) No 1394/2007.

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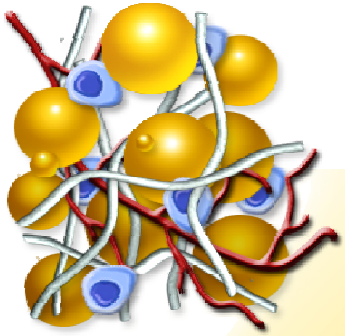
When Does 2001/83/EC Apply to Autologous Cells and Tissues?

- Only applies if the cells and tissues are 'placed on the market'
  - Enter into commerce
  - Made available for sale or distribution
  - Not the same surgical procedure
- Cultured cells or cells and tissues processed in a centralized manufacturing facility
  - Outside of the operating suite / hospital
  - GMP requirements for 'manufacturing activities'

Point-of-Care ADRC Therapy
(Autologous/Same Surgical Procedure)

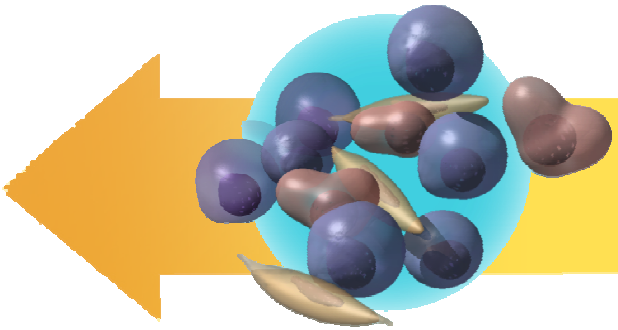


Collect donor tissue

Separate and process ADRCs

1.

Autologous tissue, returned to the same patient during the *same* hospitalization



Return cells to the same patient

1½ - 2 hours

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ATMP – GMP Manufacturing Site

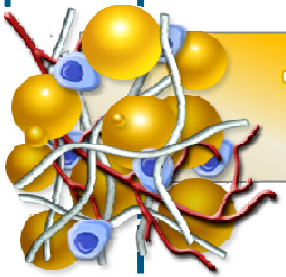
(Autologous - Different Surgical Procedure)

HOSPITAL

GMP FACILITY

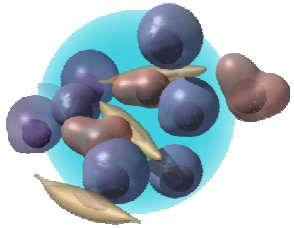
1.

Collect donor tissue



TISSUE

Separate and process ADRCs



2.

Return cells to the same patient

Different procedure

CELLS

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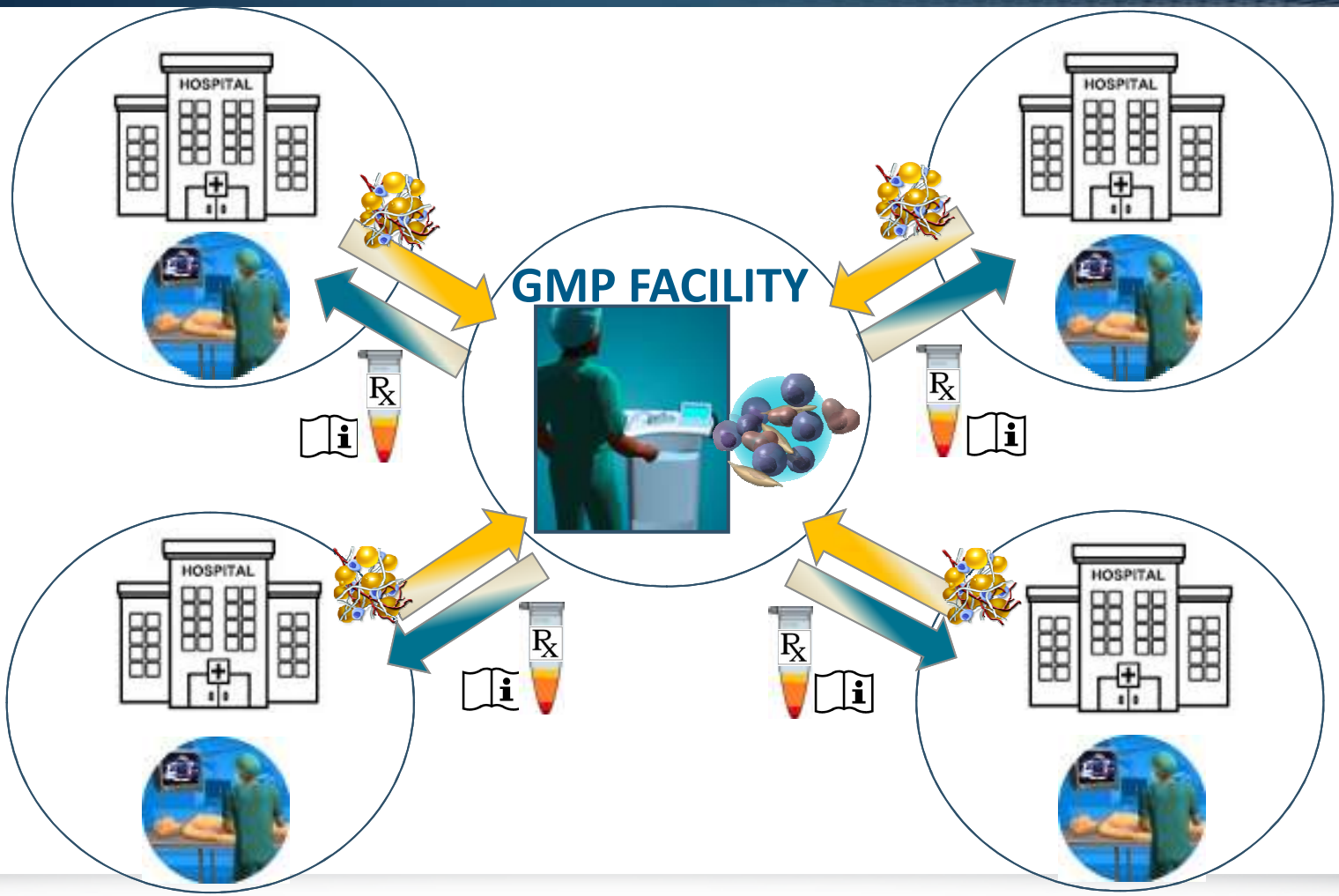
ATMP – GMP Manufacturing Site Overview



Conclusions

- 'Placed on the market' is the first regulatory test in determining if a product is an ATMP
- 'Placed on the market' does not occur when cells and tissues are autologous and in the same surgical procedure
  - 2014 Blue Guide
  - 2010 Commission Guidance Documents
  - Article 2 of 2004/23/EC (EUTCD)
  - Recital 14 of 1394/2007

Conclusions

- Autologous and same surgical procedure are exempt from homologous use and minimum manipulation tests
  - Criminalization of many existing medical procedures (spinal fusion, Graham's procedure, CABG procedure, etc.)
  - 2001/83/EC Article 2 'placed on the market is not fulfilled
  - 1394/2007 Recital 14 'should not derogate from the basic principles [autologous same surgical procedure exemption] laid down in Directive 2004/23/EC'
- Autologous point of care devices and cell output are:
  - Regulated solely under MDD and Notified Bodies
  - Require clinical data, CA reporting, and post market follow up
  - Only become ATMPs when structure function claims are made

THANK YOU!

EMA ATMP Workshop - September 11, 2014

Dresden, Germany

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