Should autologous cell therapy companies have the right to refuse treatment to patients?

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Problem Statement-1

• Decisions on the appropriateness and suitability of a treatment are made by healthcare professionals taking into consideration the medical condition to be treated, any other medical conditions, available treatments, and any known drug interactions with existing medication.

• Under normal circumstances the manufacturer has no reason to know anything about the patient, they simply supply product upon request.
Problem Statement - 2

• Autologous cell therapy presents a new situation where the manufacturer could be said to have an ‘interest’ in the health of the patient since they will handle tissue or cells from that patient.

• Should the manufacturer have the right to refuse to process tissues and cells from positive patients?
2. **Living donors**

2.1. *Autologous living donor*

2.1.1. If the removed tissues and cells are to be stored or cultured, the same minimum set of biological testing requirements must apply as for an allogeneic living donor. Positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross-contamination with other grafts and/or no risk of contamination with adventitious agents and/or mix-ups.

1. **Biological tests required for donors**

1.1. The following biological tests must be performed for all donors as a minimum requirement:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1 and 2</td>
<td>Anti-HIV-1,2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>HBsAg</td>
</tr>
<tr>
<td></td>
<td>Anti HBc</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-HCV-Ab</td>
</tr>
<tr>
<td>Syphilis</td>
<td>See 1.4 (below)</td>
</tr>
</tbody>
</table>

Consulting on Advanced Biologicals
Sec. 1271.90 Are there exceptions from the requirement of determining donor eligibility, and what labeling requirements apply?

(a) **Donor-eligibility determination not required**. You are not required to make a donor-eligibility determination under 1271.50 or to perform donor screening or testing under 1271.75, 1271.80 and 1271.85 for:

1. Cells and tissues for autologous use; or
2. Reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or
3. Human immunodeficiency virus, Type 2 (e.g., FDA licensed screening test for anti-HIV-2);
4. Hepatitis B (e.g., FDA licensed screening test for HBsAg); and
5. Hepatitis C (e.g., FDA licensed screening test for anti-HCV).

(b) In the case of a neonate, the mother's specimen is acceptable for testing.
4.3 Contraindications

Hypersensitivity to any of the excipients or to bovine serum.
ChondroCelect must not be used in case of advanced osteoarthritis of the knee.
EU: ChondroCelect

European Public Assessment Report

Manufacture

Biopsy procurement

The starting material consists of an autologous articular cartilage biopsy procured arthroscopically from a non weight-bearing area of the femoral condyle of the patient’s knee. The Applicant provides hospitals with biopsy procurement kits, which are stored at the orthopaedic unit. Each kit is labelled with a unique lot number on the outer box and the containers within.

Eligible patients for ChondroCelect treatment are screened for HIV type 1 and 2, HCV, HBV, and syphilis. Only tissue from donors who test negative will be released from quarantine and allowed into the tissue/cell processing area.

Common name: characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins

Procedure No. EMEA/H/C/000878

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
USA: Carticel

FDA Summary of Product Characteristics

4 CONTRAINdications
Carticel should not be used in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides or materials of bovine origin.

5.1.2 Risk of Transmissible Infectious Diseases
The Carticel product is intended solely for autologous use. Patients undergoing the surgical procedures associated with Carticel are not routinely tested for transmissible infectious diseases. Therefore, the cartilage biopsy and the Carticel product may carry the risk of transmitting infectious diseases to the health care provider handling these tissues. Accordingly, healthcare providers should employ universal precautions in handling the biopsy samples and the Carticel product.

Gentamicin is used in the cartilage biopsy transport media and in the culture media used during the processing of Carticel. Residual quantities of gentamicin up to 5 μg/mL are present in the Carticel product.

Fetal bovine serum is a component in the culture medium used to propagate the autologous chondrocytes. Trace quantities of bovine-derived proteins may be present in the Carticel product.
SUMMARY FOR BASIS OF APPROVAL

BLA Ref. No. 96-0372        Drug Licensed Name: Autologous Cultured Chondrocytes
Drug Trade Name: Carticel™

Manufacturer: Genzyme Tissue Repair
64 Sydney Street
Cambridge, Massachusetts 02139-4136

Neither the patient nor the patient's expanded cell culture is tested for infectious viral agents. Therefore, all products are considered to be subject to biohazard precautions and labeling. All biopsy samples and cell cultures are handled separately within biological safety cabinets which are decontaminated between each use.
## EU Incidence Data (2007)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Incidence /100,000</th>
<th>EU Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>6.0</td>
<td>26,029</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.51</td>
<td>6,481</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>6.87</td>
<td>26,840</td>
</tr>
<tr>
<td>Syphilis</td>
<td>4.39</td>
<td>17,603</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td><strong>76,953</strong></td>
</tr>
</tbody>
</table>

Source: *Annual epidemiological report on communicable diseases in Europe 2009*
http://www.ecdc.europa.eu
People Living with HIV

Cumulative total cases in EU
>240,000 (2006)

HIV infections newly diagnosed:
cases reported in 2006 per million population
WHO European Region

HIV cases per million
- 200+
- 100 - 199
- 20 - 99
- < 20
- Not available

North America
1.4 million
[880,000 – 2.2 million]

Caribbean
250,000
[190,000 – 320,000]

Latin America
1.7 million
[1.3 – 2.5 million]

Western &
Central Europe
740,000
[580,000 – 970,000]

Middle East & North Africa
460,000
[270,000 – 760,000]

Sub-Saharan Africa
24.7 million
[21.8 – 27.7 million]

Eastern Europe &
Central Asia
1.7 million
[1.2 – 2.6 million]

East Asia
750,000
[460,000 – 1.2 million]

South & South-East Asia
7.8 million
[5.2 – 12.0 million]

Oceania
81,000
[50,000 – 170,000]

TOTAL: 39.5 (34.1 – 47.1) MILLION

WHO/UNAIDS (?2006)
## EU Prevalence

### EU Population ~500 million

<table>
<thead>
<tr>
<th>Infection</th>
<th>Estimated Prevalence</th>
<th>Approx. EU Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>0.2% (0.1-0.5%)</td>
<td>~1 Million</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0.3%*</td>
<td>~1.5 Million</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>0.5-2%</td>
<td>~2 Million</td>
</tr>
<tr>
<td>Syphilis</td>
<td>??</td>
<td>~0.5 Million</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>~0.8%</td>
<td>~4 Million</td>
</tr>
</tbody>
</table>

*WHO estimate for Chronic Hep B in UK*
Sex diseases soaring due to Facebook romps
Patient’s Position

• If an existing chronic viral infection does not prejudice the success of the treatment why should I be excluded?
• No other medical treatment, including invasive procedures, are withheld.
• Infected blood and tissues are handled in pathology daily.
• The decision to treat should be a clinical one, not decided by a manufacturer.
• Isn’t this an infringement of my human rights?
• I pay my taxes!
It is contrary to the principles of GMP to deliberately introduce adventitious agents into the manufacturing facility.

- Risk of cross contamination
- Duty of care employees: risk to manufacturing staff (esp. manual handling steps)
- May need to take additional measures with known infected samples (increased cost).
- We would need data to show that product manufactured from virally infected tissues behaved the same in the process.
- We pay our taxes too!!
Regulator’s Position

- The manufacturing process must assure that cross contamination cannot occur.
- False negative test results will occur - albeit very infrequently.
  - The ‘status’ of a patient can be complex to determine, especially where vaccination is also possible, e.g. HBV
- However – there is no legal basis to force manufacturer’s to process positive cells and tissues (US or EU).
- We spend your taxes wisely.
Where a manufacturer of a medical product refuses to supply a product to a patient (or their physician), then it is possible that the manufacturer will be exposed to a claim as a result of a failure to comply with Article 8 of the Human Rights Act.

**Article 8: Right to respect for private and family life**

1. Everyone has the right to respect for his private and family life, his home and his correspondence.

2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.
The first autologous cell therapy product to obtain centralised approval in the EU currently allows the manufacturer to exclude patients that test positive for HIV, HBV, HCV and/or syphilis.

There are scientific and safety arguments for and against processing known positive patient tissues and cells.

The EMA and FDA have no legal basis to force manufacturers to process positive samples.

Manufacturers may be at risk of legal action from patients in the EU under the Human Rights Legislation.