



VICTORIAN
COMPREHENSIVE
CANCER CENTRE
PROJECT

Ethical, Commercial and Professional Perspectives on Unproven Therapies

Dominic Wall PhD FFSc (RCPA)

Regional Vice President, Australia and
New Zealand, 2012-2014

Chief Scientific Officer
Cell Therapies Pty Ltd

Operations Director– Pathology & CBCT
Peter MacCallum Cancer Centre



Cell Therapies

- A commercial therapeutics manufacturer
- Majority owned/controlled by Peter Mac
- 4 x Manufacturing TGA licences
 - 149827 Stem Cells –2001
 - 162398 Orthogen Australia– chondrocytes– 2003
 - MI-2009-LI-05411-3 Mesoblast– Mesenchymal Precursor Cells– July 2010
 - Prima Biomed Immunotherapy trial licence
- Trial CMO and other commercial & academic activity
- Consulting, trial and product approvals
- Product and process development
- Major focus on Asian market collaboration
- 15 TGA OMQ audits over 11 years

ute – Centre for Blood Cell Therapies

on and Release of Peripheral Blood
SC) – Learning Module

Patient Identification

Generated by: Peter..... 1
 admission or request
 versions)..... 2
 Placed onto:..... 2

- Pathology: R..... 2
- PBSC: Produ
- L3-001: (large
- Packs: (large
- Tubes: (small
- BacT/Alert: (l

WOOLLARD MR DUMMY PATIENT
 127 UPPER FERNTREE GULLY
 EAST MELBOURNE 3002
 PH: 57232 233 26Jan1945
 LUNG /S SLM Repa 04Dec2002
 79/11/05555
 WOOLLARD, DUMMY
 26Jan1945 DATE :
 TIME : WARD :

CBC102372
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STEP 8

001)
 • Product-Packs
 • Sample-Tubes
 • BacT/Alert

TGA THERAPEUTIC GOODS ADMINISTRATION

Licence to Manufacture Therapeutic Goods

Manufacturer: CENTRE FOR BLOOD CELL THERAPIES
 LICENCE NO: 149827

Manufacturing site for which the licence applies:
 PETER MACCALLUM CANCER INST.
 ST ANDREW'S PLACE
 EAST MELBOURNE VIC 3002

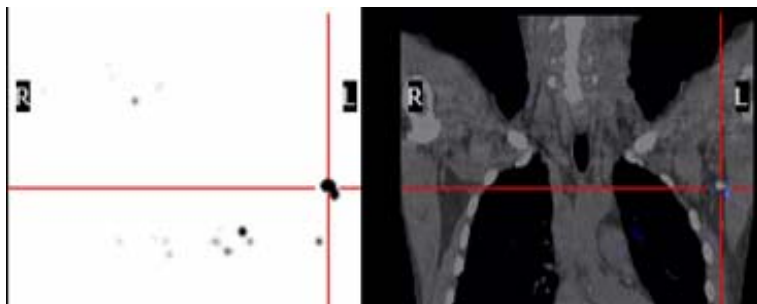
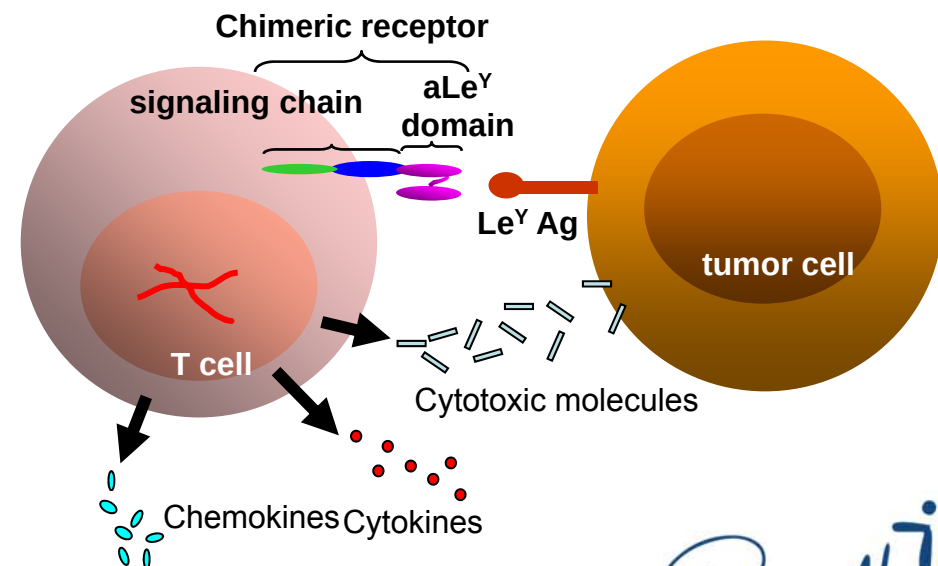
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Product expertise

- Regenerative Medicine



- Immunotherapy



Inherent challenges for cell & tissue products

Medicinals

- No collections/donors
- Large lots
- high throughput
- term sterile
- control of starting material
- complex processes
- Stable complex protocol
- unknown recipient



Cells and Tissue

- Donors and collections
- single product lots, high value batches
- low throughput
- Partial closed system, no term sterile
- Traditionally labour intensive
- limited control of starting material
- Evolving research based protocols,
- Known recipients

Challenges - Cells & Tissues during pre-clinical development

- A dose-related mechanism of action?
- A suitable animal model?
- Relevant animal toxicity data?
- Persistence, distribution?
- Unique risks with cells & tissues?
- Product characterisation, a suitable potency assay?
- Process changes during clinical development?
- Possible to fit the product into a medicinal approval framework?

Relative risks Auto vs Allo

- Infectious Disease risk
- Animal derived products
- Transformation
- Uncontrolled proliferation
- Mode of action
- Risks considered differently in different markets
- USA, EU, Asia
- Risk of a variable product vs risk of an allo product

What do regulators fear?

Unexpected toxicity?

Malignant transformation?

Inappropriate differentiation?

Times Online

March 15, 2006



Myfanwy Marshall outside Northwick Park hospital today. She said that her boyfriend was unrecognisable (Edmond Terakopian/PA)

Two fight for lives after drug trial poisoning

BY PHILIPPE NAUGHTON AND AGENCIES

The distraught girlfriend of one of two men fighting for their lives in a London hospital after being poisoned in a drug trial today said she had barely recognised him because his head was so swollen.

Myfanwy Marshall, 35, said that her boyfriend looked "like the Elephant Man" after being given a dose of the drug, TGN 1412.

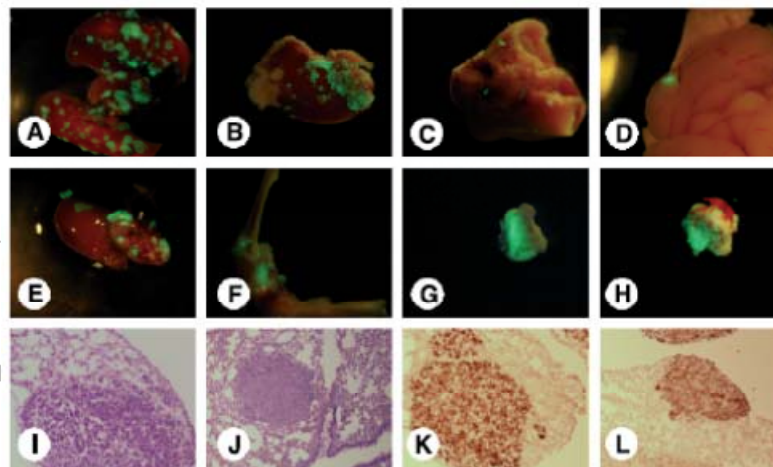
Her boyfriend is a 28-year-old landlord who had

[*Cancer Research* 65, 3035-3039, April 15, 2005]
© 2005 [American Association for Cancer Research](#)

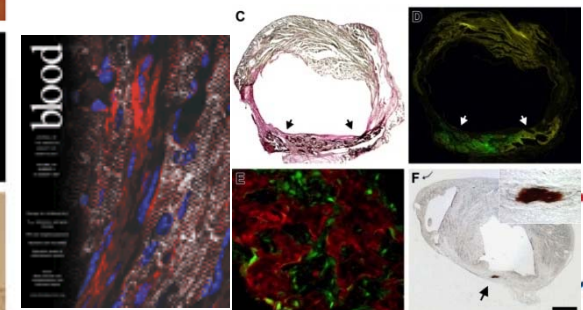
Priority Reports

Spontaneous Human Adult Stem Cell Transformation

Daniel Rubio¹, Javier Garcia-Castro^{1,2}, Maria C. Martin³, Ricardo de la Fuente¹, Juan C. Cigudosa³, Alison C. Lloyd⁴ and Antonio Bernad¹



Potential risks of bone marrow cell transplantation into infarcted hearts
Martin Breitbach et al
Blood 2007 110: 4 1362-9



Other risks...

Biomaterials?

Diabetes. 1997
Jul;46(7):1120-3. Improved
human islet isolation using
a new enzyme blend,
liberase.

Linetsky E, Bottino R,
Lehmann R, Alejandro R,
Inverardi L, Ricordi C.

STREET JOURNAL

2008

Newspaper My Online Journal Multimedia & Online Extra

Blocked Advertisement

Legislators Review Inspection Policy Amid Heparin Fallout

BY JON KAMP

Word Count: 663 | Companies Featured in This Article: Baxter International

In the wake of hundreds of reactions in patients who took Baxter International Inc.'s blood thinner heparin, two U.S. lawmakers said they are considering changes in law to guard against the marketing of drugs made at plants that haven't been inspected by regulators.

It isn't yet known what factors are behind 350 bad reactions and four fatalities among U.S. patients who took Baxter-made heparin, as tallied by the Food and Drug Administration last week, when Baxter temporarily halted heparin production. Questions have been raised, though, about how the FDA failed to inspect a Chinese plant that supplies much of the ...

Animal derived materials...
Enzymes? Serum?



... bare-handed workers at Yuan
Intestine & Casing Factory, untangle and
flush pig intestines that will be used to
make heparin...

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Other risks in healthcare- Auto products



Pathology errors

- F .33-.61% of tests, .05-.11% patients
- Almost always pre-analytical (up to 75%)
- Australian data
 - Data with surgical biopsies
 - Incorrect transcription of Patient ID
 - Median of 1% of all requests
- Local experience
 - 0.006% wrong blood/correct tube detected

- Tissue harvesting
- Tissue & cell implantation
- IDS and other tests
- Procurement regulated in EU and Australia, not US

Testing

- Purity and impurity- US vs others
- Identity
- Safety testing- issues in each market
 - Which monographs
 - Multiple methods during development
 - Retention specimens
- Mycoplasma & Endotoxin
- Potency- candidate methods

FDA world view

- GTP vs GMP to separate risk
- Inflexible law- not risk adapted
- Drug rather than CT framework
- GTP cut-off in FDA warning letters:
- “your firm isolates cells from the lipoaspirate, and selects and expands through cell culture, adipose derived mesenchymal stem cells (AdMSC). The autologous product is administered to patients by **(b)(4)** for a wide variety of indications”

Qualified GTP exemption

- your processing with **(b)(4)** alters the original relevant characteristics of the adipose tissue relating to the tissue's utility for reconstruction, repair, or replacement. Therefore, your processing does not meet the definition of minimal manipulation for structural tissue such as adipose tissue
- the clinical uses detailed in your protocols do not meet the definition of homologous use

Why is the FDA 'exemption' qualified

- FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP)
- Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile
- Failure to establish and follow written production and process control procedures
- There were numerous in-process sterility failures for AdMSC batches.
- Bacterial and fungal limits have been exceeded
- 29 major GMP breaches

FDA and GTP and Medical Boards

- Texas Medical Board April 2012
Injection of stem cells into patients requires FDA approval **or** IRB approval
- FDA ruling
Law requires that **or** must be replaced by **and**
- FDA ruling on the Texas Applied Biotech Research Cttee (TABS RCC IRB)
 - Failed to manage COI
 - Failed to manage safety for human subjects
 - Prevented from accruing further patients
- Current issue with 'fig-leaf' IRBs

GTP methods- a quick observation...

- High cell numbers (5 to 20 million cells/gram) reported by kit/device manufacturers such as MediVet-America (Lexington, KY), Intellicell Biosciences (New York, NY), and Adistem, Ltd. (Hong Kong) in adipose stem cell therapy compared to academic reports
- INCELL verified SVF cells counts from MediVet Kits
- Automated analysers reported 20x higher counts due to micelle artifacts

GTP methods subject to very limited (if any) oversight...

Transparency of GTP failures?

- GTP Cells & Tissues have been associated with numerous product failures
- IDS failures, product failures
- Small changes can have unexpected outcomes- a GTP example...



“To save time a lab director ordered a quicker freeze. The stem cells died. From August 1998 to June 1999, the program treated 40 adult patients . A quarter of patients died within 100 days”

STEM-CELL TRANSPLANTS GO AWRY | Lawsuits allege fraud and negligence

Some cancer patients died after time-saving change

The leaders of a Kansas City treatment program say they provide “excellent” care to their patients, but lawsuits allege that a period of failings led to suffering and death.

By ALAN BAVLEY and JULIUS A. KARASH

<http://www.kansascity.com/mld/kansascity/news/local/15705281.htm> (2 of 13)17/10/2006 9:33:44 AM

Kansas City Star | 10/08/2006 | Some cancer patients died after time-saving change

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Australian framework

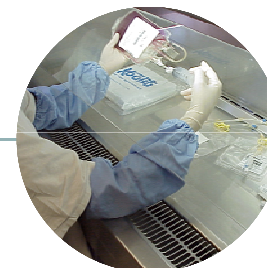


Biologic



Excluded

Unregulated
by TGA



Not
biologicals

Regulated

What is regulated?

- Not *fresh* organs, ART, *fresh* HPC, diagnostic tissues
- Not biological medicines (proteins, peptides, vaccines without living human cells), blood/components
- *Things that are excluded*
- *Things that are not biologicals*
 - Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011



Australian Regulatory Guidelines for Biologicals

Appendix 4 – Guidance on donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products

Version 1.1, August 2011

TGA Health Safety Regulation



www.tga.gov.au

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Risk based classes

1. how far removed they are from their naturally occurring state (extent of manipulation during the extraction and production process and how altered they are)
2. how closely their intended use matches their original biological function

Classes of biologicals

- Minimal is centrifugation, refrigeration, freezing, trimming, flashing, washing as well as processing steps used to minimise contamination or maintain and preserve function based upon use of additives
- Homologous unrelated to autologous use or not- defined as used of a biological that performs the same function in the recipient as in the donor.
- Previous iterations used to refer to storage or banking
- TGA reserves the right to declare any product as any class.
- A variety of exemptions available- trial, access, medical

Which scheme?

- Use of unapproved product for individual patients as part of clinical patient care → **Special Access Scheme**
- Use of unapproved product by a specified clinician for patients under their care → **Authorised prescriber Scheme**
- Use of unapproved product as part of a clinical trial to answer a specific scientific question → **CTN or CTX scheme**

Licensed Product Exceptional release

- Medical assessment of urgent need for a “serious” condition
- No alternative, for a single patient only
- Non conforming product best option for the patient
- Practitioner must state rationale, report patient consent, why non-conforming
- Sponsor approval & documentation, also explanation why consent not possible (if relevant)
- Sponsor must notify within 28 days with supporting docs
- Sponsor must provide 6 month report including any AE

Overview

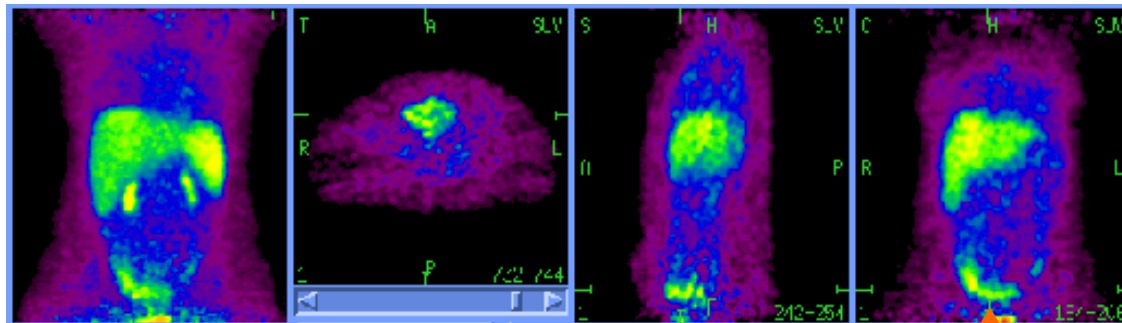
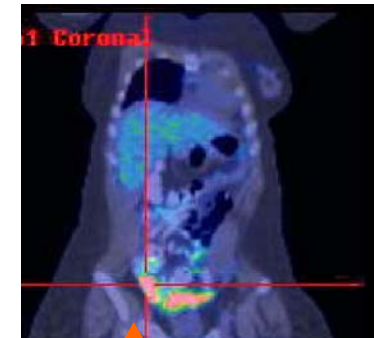
Human blood and blood components, human tissues and human cellular therapy products

Standards	Biologicals*				Blood and blood components*	HPC*
	Class 1	Class 2	Class 3	Class 4		
	Standards for minimising infectious disease transmission					
	Sector specific requirements	Product specific standards, e.g. cardiovascular, musculoskeletal, ocular, skin, blood, HPC				
	General standards, e.g. default pharmacopoeial standards, labelling standards					
Manufacturing requirements	Manufacturer quality system requirements, e.g. Code of GMP					
Submission requirements	Certification		Dossier		Technical master file (TMF)	
Guidance documents	Australian Regulatory Guidelines for Biologicals				TMF guideline	
		Adoption of relevant international guidance documents				

Some concessions...

- Adjusted trial requirements between class 3 and 4
- “Conventional tox studies may not be either feasible or appropriate”
- “Justification for use or omission of animal models”
- “Conventional ADME studies usually not relevant”

But requires “kinetics, migration, persistence studies”



Medical practice exemptions

excludes human tissue and cells that are:

- Collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory;

and

- Manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner.

TGA vs the world

- TGA has the only unqualified medical exemption for auto products in the PICs membership
- TGA has no orphan scheme for Cell & Tissues
- TGA's CTN scheme for trials
- TGA's CTX scheme for trials
- TGA has very limited licensing of trials beyond Phase 1

EU vs AU Biologics clinician exemptions

- EU still requires GMP & competent authority oversight
- 'non-routine'- but variably applied across EU
- TGA unrestricted compared to EU provisions
- AHPRA are responsible for clinician practice

EC 1394/2007

There are two narrowly drawn exemption schemes available in the UK that may allow the supply of unlicensed ATMPs (ie ATMPs that are not the subject of a marketing authorisation granted by the European Commission).

1) The hospital exemption

If an ATMP is prepared within the UK on a non-routine basis for use in the UK only in a hospital in accordance with a medical prescription for an individual patient it may fall under the hospital exemption inserted as Article 3 (7) of Directive 2001/83/EC by Article 28 (2) of the ATMP Regulation.

2) The 'specials' exemption

The existing exemption from the requirement to hold a marketing authorisation provided by Schedule 1 (the 'specials' exemption) of the Marketing Authorisation Regulations (SI 1994/3144) as amended, may also apply to an unlicensed ATMP if it is "supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility in order to fulfil the special needs of those patients..."

It should be noted that a qualified person (QP) is not required under either of these

EU and CA

- Ongoing difficulties with alleged corruption of CA mediated approvals for devices- CE mark
- UK Health secretary (October 2012):

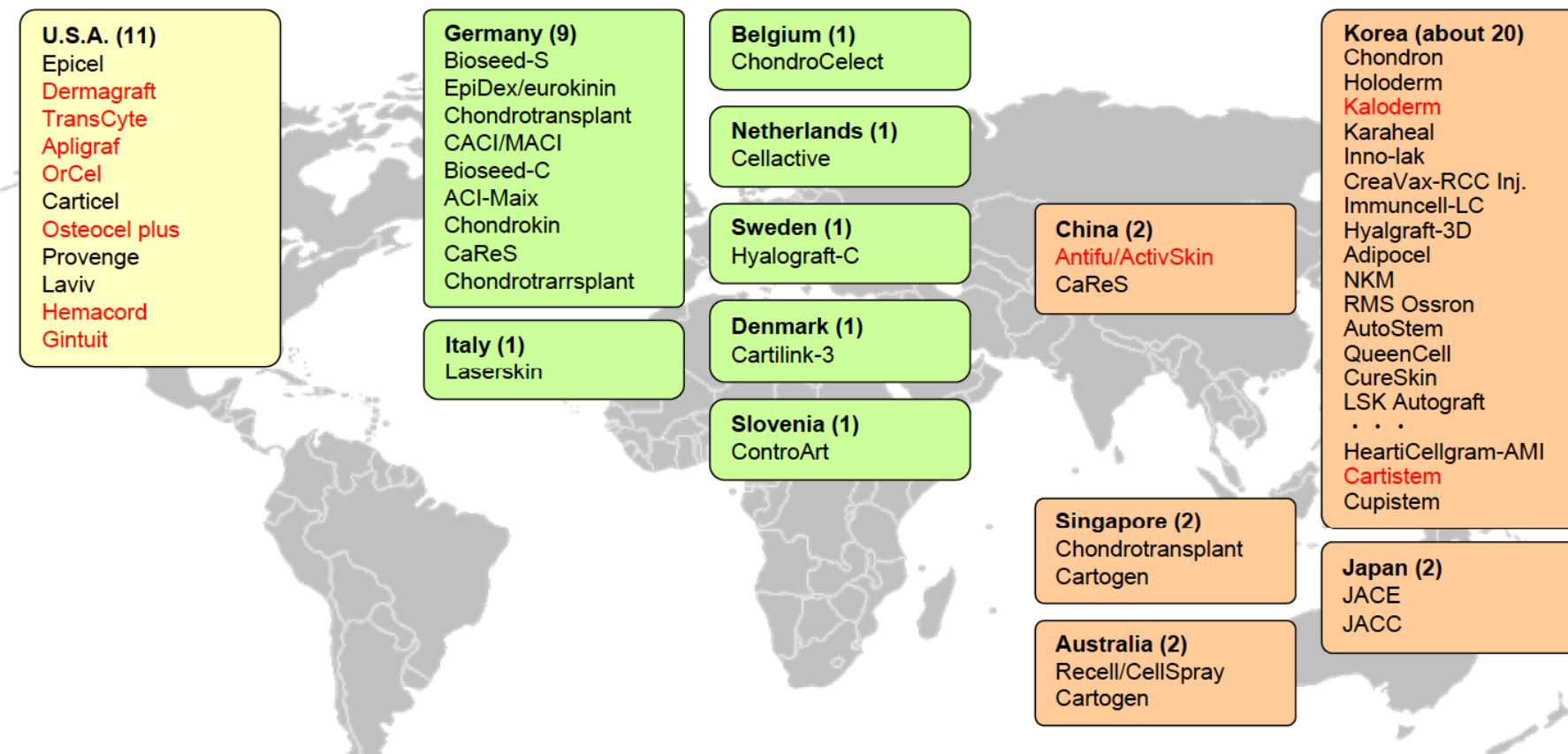
There are problems in the European regulatory system which needed to be addressed and that patient safety could be compromised. The system cannot guarantee that companies determined to put profits before patients will not get approval for improperly tested products.

Commercial impacts of exemption

- Cost of “real” market approval vs
- Insertion of manufacturing into clinical centre
- Why develop in Australia?
- Medical tourism “therapeutic haven” vs evidence-based product development
- Investment in product characterisation & automation
- Competitive neutrality
- Regulatory credibility is paramount
- 10% GDP, largest contributor to state GSP Vic & NSW

Approved TE&RM Product

in red: Allogeneic product



Source) Seed Planning, J-TEC, others

Reimbursement

- Much broader issue than marketing approval
- Competing product costs- ensure right comparisons

	MACI/ACI		Mosaicplasty		Microfracture		Source
	units	costs	units	costs	units	costs	
Equipment							
Autologous chondrocyte transplantation	1	\$11,400.00					Prostheses List
TISSEEL fibrin sealant syringe	1	\$380.00					Prostheses List
Surgical kit			1	\$1,000.00			Applicant
Operational							
Pre-anaesthesia consultation - MBS 17610	2	\$30.45	1	\$30.45	1	\$30.45	MBS Online
Co-payment	2	\$30.17	1	\$30.17	1	\$30.17	DOHA
Initiation anaesthesia - MBS 21382	2	\$56.10	1	\$56.10	1	\$56.10	MBS Online
Co-payment	2	\$208.33	1	\$208.33	1	\$208.33	DOHA
Biopsy - MBS 49557	1	\$193.50					MBS Online
Anaesthesia - MBS 23061	1	\$84.15					MBS Online
Assistance - MBS 51300	1	\$61.20					MBS Online
Co-payment	1	\$0.00					DOHA
Osteochondral graft - MBS 49563*	1	\$564.75	1	\$564.75			MBS Online
Anaesthesia - MBS 23063	1	\$84.15	1	\$84.15			MBS Online
Assistance - MBS 51303	1	\$112.95	1	\$112.95			MBS Online
Co-payment	1	\$97.89	1	\$97.98			DOHA
Arthroscopic surgery - MBS 49561					1	\$477.80	MBS Online
Anaesthesia - MBS 23043					1	\$56.10	MBS Online
Assistance - MBS 51300					1	\$61.20	MBS Online
Co-payment					1	\$30.81	DOHA
Hospital stay (2,2,1)	1	\$454.05	1	\$454.05	1	\$227.03	AR-DRG I18Z
Consumables		\$11,780.00		\$1,000.00		\$0.00	
MBS fees		\$1,273.80		\$1848.40		\$908.68	
Out-of-pocket		\$1,028.95		\$790.45		\$496.34	
TOTAL COSTS		\$14,082.75		\$2,638.85		\$1,405.01	

MACI
\$14,082

M'Plasty
\$2,638

M'Fracture
\$1,405

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Risks with exemption frameworks

- Rapid Availability of novel therapies, versus
- No marketing approval or manufacturing oversight
- Risk and harm to patients and markets
- Competitive neutrality and market damage
- Loss of 'real' investment in innovation
- Trials vs med exemption
- SAS, AP available
- Reimbursement?
- IRBs and medical boards...

Deadly meningitis outbreak puts spotlight on custom-mixed drugs from 'compounding pharmacies'

By: Marilyn Marchione, The Associated Press

Posted: 10/4/2012 10:39 AM | Comments: 0 | Last Modified: 10/4/2012 11:44 PM

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Meningitis outbreak

An outbreak of a rare form of fungal meningitis has killed five people and sickened 35 across six states.

Originated from
Massachusetts
drug maker



Two people blinded in Washington, D.C., in 2005. Three dead in Virginia in 2006 and three more in Oregon the following year. Twenty-one dead polo horses in Florida in 2009. Earlier this year, 33 people in seven states with fungal eye infections.

And now, at least five people dead and 35 sickened with fungal meningitis that has been linked to steroid shots for back pain.

All these disasters involved medicines that had been custom-mixed at what are called "compounding pharmacies" — laboratories that supply hospitals, clinics and doctors to a much wider degree in the U.S. than many people realize.

These pharmacies mix solutions, creams and other medicines used to treat everything from menopause symptoms and back pain to vision loss and cancer. Unlike manufactured drugs, these products are not subject to approval by the Food and

An aerial photograph of Central Park in New York City. The park is a large, green, tree-filled area in the lower half of the image, surrounded by a dense urban landscape of skyscrapers and buildings. The Hudson River is visible on the left side, flowing through the city. The image shows the contrast between the natural space of the park and the built environment of the city.



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