A Tale of Two Cities: Journey to ATMP Manufacture in Newcastle and Galway

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the age of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope it was the winter of despair, we had everything before us, we had nothing before us..."
(Charles Dickens, 'A Tale of Two Cities', 1859)

Making Gene & Cell Therapy A Reality, Dublin 10Jul2012.
Bertie Craig CCMI, REMEDI, NUI Galway

CCMI Centre for Cell Manufacturing Ireland

sfi Fondúireacht Eolaíochta Éireann Science Foundation Ireland

NUI Galway OÉ Gaillimh

REMEDI

Agenda

- Background
- Regulation & Competent Bodies
- Finance
- Facilities
- People
- Operational Practicalities

Background – Universities and Cities

- **Newcastle**

Major provincial University with well established Medical School with a strong background in teaching, research and clinical development of novel therapies.

Well developed links with funding bodies, the local community and the local NHS Hospitals Trust.

The city is the main centre for the North and North East of England, a maritime city with strong sea going traditions

- **Galway**

A major provincial University with a well established Medical School with strong background in teaching, research and clinical development.

Well developed links with the local community, the local hospital and with funding bodies.

The city is a principal centre in the West of Ireland, a maritime city with strong sea going and cultural traditions.

Background – The Basic Process

Clinicians
/Academics

FREE ZONE
~~Clinicians~~
~~/Academics~~
FREE ZONE

Clinicians
/Academics

Background – Facility Purpose

Newcastle Biomedicine Manufacturing Facility

MIA(IMP) & MS Authorisation to manufacture cell therapies & tissue engineered products from a number of sources e,g. Limbus, bone marrow, dendritic cells. These products to be used in clinical trials or cases of 'Special' unmet medical need

Centre for Cell Manufacture Ireland

MIA(IMP) for the manufacture of mesenchymal stem cells for use in clinical trials

Background – Good Manufacturing Practice

WHAT IS THE PURPOSE OF GMP?

Product Safety → Product Efficacy → Product Quality

Protect the Patient, do no more harm to their health than the condition we seek to cure

Background – Good Manufacturing Practice

WHAT IS GMP?

GMP is that part of Quality Assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing Authorisation or product specification. GMP is concerned with both production and quality control activities. www.mhra.gov.uk 2007

Regulation & Competent Bodies

Medicine Law, Regulation & Guidance Originates with the European Commission

A level playing field across the continent?

Principal European Directives

Procurement: European Tissues and Cells Directive, 2004/23/EC

GMP: Medicines Directive 2001/83/EC

GCP: Clinical Trials Directive 2001/20/EC

ATMP: Regulation EC/1394/2007

Regulation & Competent Bodies

Constant Revision? Directives & Regulation 2006 - 2011

Directive No	Area	Regulation	Area
2008/29/EC	Implementing the powers of the European Commission (e.g. creation of the EMA[1])	EC/507/2006	Permit conditional Marketing Authorisation for products with limited data available (e.g. orphan drugs)
2009/53/EC	Variation to Marketing Authorisations	EC/1901/2006 EC/1902/2006	Paediatric Medicines (paediatric investigation plan)
2009/120/EC	Amendment to Annex 1 to incorporate ATMPs	EC/1394/2007	Advanced Therapy Medicinal Products
2010/84/EU	Pharmacovigilance	EC/668/2009	Implements ATMP with respect to evaluation and the certification of quality, together with non-clinical data for ATMPs produced from micro, small or medium enterprises.
2011/62/EU	Falsified Medicines	EU/1235/2010	Establishes the EMA, as modified by EC726/2004 and EC/1394/2007
Commission Communications			
2006/C 133/ 05	Guideline on definition of serious risk to public health		
2008/C 243/01	Guidance on the development of paediatric investigation plans		

Regulation & Competent Bodies

Applying Directives and Regulations

Directives and regulations from the EU have varying degrees of legal standing, however applying these in the real world requires a degree of knowledge that is not readily available; to assist with this guidance on interpreting directives and regulations is provided in the form of a compendium by the European Commission…**Eudralex**

Key Elements of Eudralex for Cell & Gene Therapy

Eudralex Volume 4 **GMP for Human Medicines**

Eudralex Volume 10 **Clinical Trials**

Regulation & Competent Bodies

Constant Revision? Eudralex Vol 4 2006 - 2011

Area	Date	Main Impact
Part 1, Chapter 1	January 2006/July 2008	Consolidated product quality review
Part 1, Chapter 6	June 2006	On-going stability testing and reference sample update
Part 1, Chapter 8	February 2006	Covers reporting of counterfeit medicines to competent authority and raise awareness that a reported quality fault may be due to counterfeiting.
Part 2	July 2010	Application of quality risk management to arrangements for active substances used as starting materials
Part 3	June 2010	Site Master File
Part 3	June 2011	Internationally harmonised requirements for batch certification
Annex 19 (*New*)	June 2006	Reference for starting and packaging materials and finished products and retention samples for finished product
Annex 20	March 2008	Quality Risk Management
Annex 3	March 2009	Manufacture of Radiopharmaceuticals
Annex 7	Sept 2009	Guidance on the manufacture of herbal medicines
Annex 6	July 2010	Manufacture of medicinal gasses
Annex 13	July 2010	Investigational Medicinal Products, update includes batch certification, QC and production staff separation in small organisations
Annex 11	June 2011	Computerised systems update to reflect increased use and complexity of this type of system

Regulation & Competent Bodies

Competent Bodies

Galway

Irish Medicines Board
European Medicines Agency

Newcastle

Human Tissue Authority
Medicines & Healthcare Products Regulatory Agency
European Medicines Agency

Finance

Galway

Initial SFI, NUI Galway; HRB (€5-6 million)
Current: NUI Galway (current running costs)

Newcastle

Initial: ONE NorthEast, MRC & Newcastle University £3 – 4million
Current: Newcastle University (current running costs)

Both Facilities have received considerable seed/start up funds from public sources; however to achieve authorised status and continue operation until Clinical Trials Start further funds from the respective Universities have been required

Quick Pit Stop!

Similarities:

1. The Universities have similar backgrounds and focus and regional significance.
2. They both have deep connections with their hospitals and have formed a network with the hospital and their clinical research facilities for the development of cell therapies
3. Both received significant start up funds and are meeting current running costs from their own funds
4. Both operate in the EU and are governed by European rules governing medicines, in addition to any supplementary national regulations

Differences

1. Newcastle has a wider focus in terms of cell types it is able to work with.
2. Galway has fewer competent bodies to deal with, a one stop shop at national level

Facilities

Galway

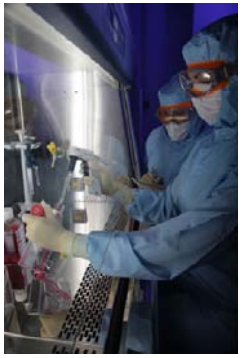
Greenfield site new build, specifically built for gene therapy, based on model seen in USA. No design stage discussions with regulators or ex regulators. Facility process, people and air flows significantly remodelled over last 2 years for cell therapy

Newcastle

Re-allocation of space in recent build. Specifically for cell therapies with consideration given to separation of embryonic stem cells from other source cells. Ex MHRA/MCA inspector part of project team. Limited time to finalise design/build to keep grant funds

Facilities

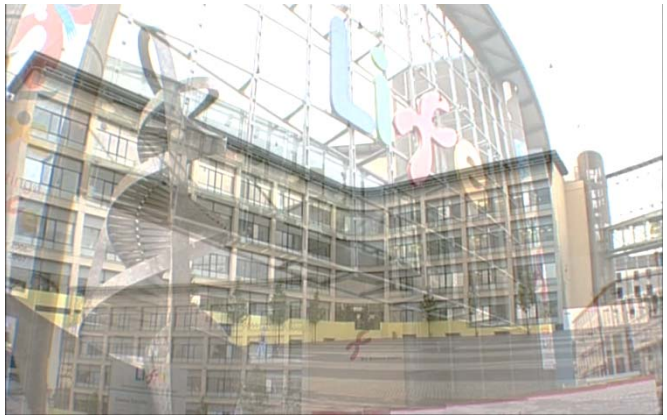
ORBSEN Building NUI Galway

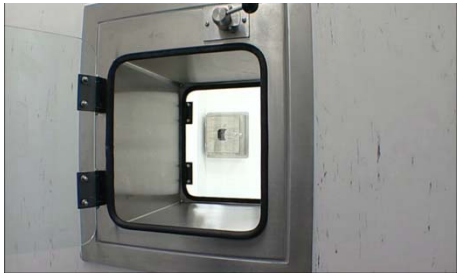


CCMI Occupies the top floor of the left hand portion of the building, with two processing suites.
Air is single pass, terminally HEPA filtered to the rooms with dedicated air handling units for each processing area and the ancillary zones (e.g. change areas, support corridors).
Currently only one process suite is (*nearly*)qualified for use.
Process areas EU Grade B with Grade A for product handling .
The facility has a dedicated QC Microbiology lab on the ground floor

Facilities

Bioscience Centre International Centre for Life Newcastle





Refurbished third floor East wing of building, facility split in to 2 operating suites. Single AHU, single pass air terminal HEPAs in each processing room (9 total). QC Microbiology within overall footprint of facility (not 'clean zone'). Process areas EU Grade B with product handling at Grade A

Facilities - Equipment

Galway

Class II MBSC (provides EU Grade A); with continuous non-viable particle monitoring
Bench top centrifuge
CO_2 Incubator
Controlled rate freezer
LN_2 Plant
-150ºC Incubator
Inverted Microscope

Newcastle

Class II MBSC (provides EU Grade A), with continuous non-viable particle monitoring
Bench top centrifuge
CO_2 Incubator
Controlled rate freezer
LN_2 Vapour Phase storage
-80ºC Incubator
Inverted Microscope

Facilities - People & Process Flows

Newcastle

Omni-directional, opportunity for potential crossing of staff from different projects, product and waste materials. Controlled by temporal measures

Galway

Unidirectional, limited opportunity for crossing of staff from different projects, or product and waste materials, no further control measures required (since 2011 – 2012)

People

A Problem – very limited availability of suitably qualified staff.

Particularly in: GMP Manufacture
Product Testing
Environmental Monitoring
Qualified Person(s)

Solutions, raid biotech – similar aseptic driven products (different scale and final product but many similarities); train in house.
QPs still an issue

People

Newcastle

Stable dedicated team 4-5 years
QA & Facility Manager
QC Microbiologist
Production Technician
Additional Process staff in-house trained from research groups.
Some recent changes to staff profile as long serving staff moved on.
Contract QP

Galway

Fluctuated: Initially team of 7, followed by fallow period
Core group (4).
Now 7 dedicated staff, Operations Manager, Quality Manager + 2 staff
Production Manager + 2 staff.
(Includes core group)
Contract QP

Operational Practicalities

Common Issues:

1. Suppliers – they group according to sector can be difficult to access materials used by e.g. Biotech as not in scope of assigned rep.
2. Common buying practices – established supply contracts for types of material suitable for research but not GMP manufacture, difficult to get buy in from purchasing groups. Tendering policies and practices.
3. Establishing aspects of QMS such as vendor management in particular auditing
4. Appropriately packaged and treated materials for use in clean rooms
5. Waste management – everything is clinical waste
6. Cleaning – who does it, how frequently
7. Locating suitable and appropriate suppliers, particularly in areas such as facility and equipment qualification
8. Priority of supply/testing from contractors

Operational Practicalities

Common Issues (Contd):

9. Poor understanding of the cost of testing (in terms of product, money and time) by academic/clinicians involved in process
10. Lack of time – implementing GMP procedures takes time, this is not always accepted or understood
11. Archiving and data storage, University ISS departments not always sympathetic with the electronic back up requirements of GMP facilities.
12. Paper archives, rarely available to provide suitably long storage capability
13. Mind set – getting new (former research) staff to think GMP and not research
14. Environmental monitoring buy in to the need to do it, the amount that has to be done and the value of an in-house facility are often poorly understood (especially when academics are in control!)

Operational Practicalities

Differences:

1. Larger pool of support services (e.g. for equipment and facility qualification) available to Newcastle
2. Number of focussed sector support groups e.g. Regener8, SSCN and LRMN available in UK
3. Specialist sector group in BIA
4. *Approach* of regulators difference in culture and national regulations and guidance between Ireland and UK
5. Size of sector

Final Pit Stop

Similarities:

1. The facilities have similar levels of equipment and qualification
2. The facilities deliver similar quality of air to the production areas.
3. Finding, training and ultimately retaining staff is an issue
4. Both facilities use the services of contract QPs
5. University systems (as public bodies) can cause supply issues
6. The same general practical operational issues affect both Newcastle & Galway

Differences

1. Unidirectional (Galway) process and people flow minimises product risk compared to Newcastle
2. Historical staffing stability in Newcastle
3. Reconfiguration of Galway facility for cell therapy from gene therapy, compared to Newcastle's dedicated build.
4. Greater support network in UK compared to Ireland

Facility Authorisation

Newcastle

Applied for MIA(IMP) and MIA(MS) early 2011 as site on NUTH Pharmacy authorisation.
Site inspection June 2011.

Authorisation Awarded subject to satisfactory response to observations & comments

Galway

Applied to IMP for MIA(IMP) June 2011
Site inspection July 2011
Authorisation NOT awarded.

Changes made to facility, staffing and procedures following inspection.
New application to be made Q42012 – Q12013

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"It is a far, far better thing that I do , than I have ever done; it is a far, far better rest that I go to than I have ever known…"
(Charles Dickens, 'A Tale of Two Cities', 1859)