Cell and Gene Therapy GMP Manufacturing in the UK:

Capability and Capacity Analysis October 2017

CATAPULT
Cell and Gene Therapy

Contents

1 Executive summary

The Cell and Gene Therapy Catapult continues to review the status of MHRA MIA(IMP) licensed GMP manufacturing facilities in the UK and publish on an annual basis. The report is designed to provide an overall picture of the capability and capacity of UK MHRA-licensed cell and gene therapy manufacturing facilities that are open for collaboration. The review was initiated in 2013 and has been continued following a request in the government response to the recommendation of an annual stocktake by the House of Lords 2013-14 inquiry into Regenerative Medicine. Previous Years' reports can be viewed at https://ct.catapult.org.uk/our-approach and we remain grateful of the support of all participating centres. The recommendations published in the industry-led Advanced Therapy Manufacturing Action Plan in 2016 highlight the important opportunity cell and gene manufacturing affords to UK economic growth.

In 2017, the number of facilities has increased by 1 giving a total of 23 - through the addition of the NHSBT facility at Filton. The UK's MHRA licensed GMP manufacturing facilities employ around 400 people full-time, who are spread across 13 dedicated cell therapy sites, 6 dedicated gene therapy sites and 4 multifunctional sites. The addition of the above site and expansion of pre-existing facilities of King's College, Oxford Biomedica and Roslin Cells has driven growth in the total building footprints and cleanroom footprints by around 6% and 19% respectively.

Over 50% of the total cleanroom operational space is dedicated to gene therapy (~2,951m^2) whilst the dedicated cell therapy footprint is ~1,300 m^2. Multi-functional facilities manufacturing both cell and gene therapies have a footprint of ~895 m^2. Over 90% of the gene therapy capacity is commercially owned space. The remainder of the gene therapy cleanroom space is distributed between UK academia and the NHS with 3 cleanrooms per site being the median. National booked capacity is running at 71% for cell therapy and 77% for gene therapy (including multifunctional facilities), compared to 76% and 84% for 2016. This reduction in booked capacity is likely indicative of projects at these sites coming to completion, freeing up capacity for new project cycles.

The network of facilities, operated by 20 organisations, is supported by a strong workforce with a diverse track record for a broad range of skills over all major cell and gene technologies. During 2017, it is expected that there will be an additional ~800m^2 of total footprint from MHRA-licensed facilities, representing a national year on year increase of around 6 %. In addition, substantial new cell and gene manufacturing space will be added by delivery of the Cell and Gene Therapy Catapult manufacturing centre. The phase 1 build consists of 7,000m^2 of shell and core construction with 3,405m^2 of fitted-out clean module, warehouse, QC, business and support spaces. This includes 6 highly flexible and fully supported 150 m^2 clean-modules. The centre will be available for industry to develop their products in a supported GMP environment.

2 Introduction and methodology

Through conducting a UK-wide GMP manufacturing survey, national resource and manufacturing capability can be identified, and used as a basis for decisions about future infrastructure investment provided. With this in mind, the Cell and Gene Therapy Catapult performed an initial review of the capacity and capability of the cell and gene therapy manufacturing base within the UK in April 2013. A report based on these data was published in April 2014 and has been subject to annual review every successive year since.

Cell and gene therapy products offer unprecedented promise for long term healthcare impacts and the Advanced Therapy Manufacturing Taskforce was set up to identify actions that the UK should consider taking in order to capture manufacturing in the UK. The recommendations are listed in the Action Plan published in 2016 and highlights the important part manufacturing and development plays in creating health and economic impact for the UK.

The aim of the report is to collect and summarise information on each of the MHRA-licensed manufacturing sites in the UK with GMP capacity accessible to the market. An overview of the technical and quality capabilities at each of the facilities, alongside predictions of their available operational capacity has been compiled. All facilities listed in the preceding report were contacted for updates with regards to their capability and capacity. In this year's report, the response rate was ~ 87%; that is, 3 of the 23 facilities were unable to respond to the survey and we remain grateful for the support of all the facilities. In cases where no updated data could be provided, data were based on figures gathered for the 2016 review. The facilities analysed are found below:

MHRA-licensed cell therapy manufacturers

- Cellular Therapeutics Ltd
- Guy's & St Thomas' Hospital, GMP Facility
- Imperial College London, John Goldman Centre for Cellular Therapy*
- Moorfields Eye Hospital, Institute of Ophthalmology, Cells for Sight ATMP Manufacturing Unit
- NHSBT – Birmingham
- NHSBT – Filton
- NHSBT – Speke
- Royal Free Hospital, CCGTT (Includes operations of Advent Bioservices)
- Scottish Centre for Regenerative Medicine (SNBTS and Roslin Cells)
- University College London, Great Ormond Street Hospital Cellular Therapy Laboratories*
- University of Birmingham, Cell Therapy Suite
- University of Manchester GMP facility
- University of Newcastle Biomanufacturing Facility

MHRA-licensed multifunctional cell and gene therapy manufacturers

- Cancer Research UK, Biotherapeutics Development Unit
- King's College London Cell Therapy Unit, Clinical Research Facility
- Kings College London, Rayne Cell Therapy Suite
- University of Oxford, Clinical Biomanufacturing Facility

MHRA-licensed gene therapy manufacturers

- Bioreliance Ltd
- Cobra Biologics, Keele
- NHSBT – CBC Langford
- Oxford Biomedica, Harrow House, Oxford
- Oxford Biomedica, Yarnton, Oxford
- Wolfson Gene Therapy Unit*

**Based on 2016 data*

3 Glossary of terms

- AAV – Adeno-associated virus
- CMO – Contract Manufacturing Organisation
- CoG – Cost of Goods
- DoP – Dependent on Process
- FTE – Full Time Employees
- HTA – Human Tissue Authority
- IMP – Investigational Medicinal Product
- GMO – Genetically Modified Organism
- GMP – Good Manufacturing Practice
- MBSC – Microbiological Safety Cabinet
- MHRA – Medicines and Healthcare Products Regulatory Agency
- MIA(IMP) – MHRA manufacturing authorisation licence for Investigation Medicinal Products
- QA – Quality Assurance
- QC – Quality Control
- Auto – Autologous, patient is treated with their own cells (i.e. each patient requires their own product)
- Allo – Allogeneic, all patients are treated with cells derived from one donor (i.e. one product for all patients)
- PE – Previous experience; meaning that key staff have experience in a particular technique or cell therapy manufacturing process but not at their current organisation.

4 National picture of cell and gene therapy manufacture

4.1 Geographic locations of cell therapy and gene therapy facilities

The map below (Figure 1) highlights the diverse geographical spread of sites across the UK, with a clear cluster around the Greater London area (8 facilities). Licensed facilities specialising in cell therapy manufacture are shown by red markers; gene therapy manufacture by blue markers and both cell and gene therapy manufacture by purple markers.

Figure 1 Location of MHRA-licensed cell and gene therapy manufacturing sites within the UK

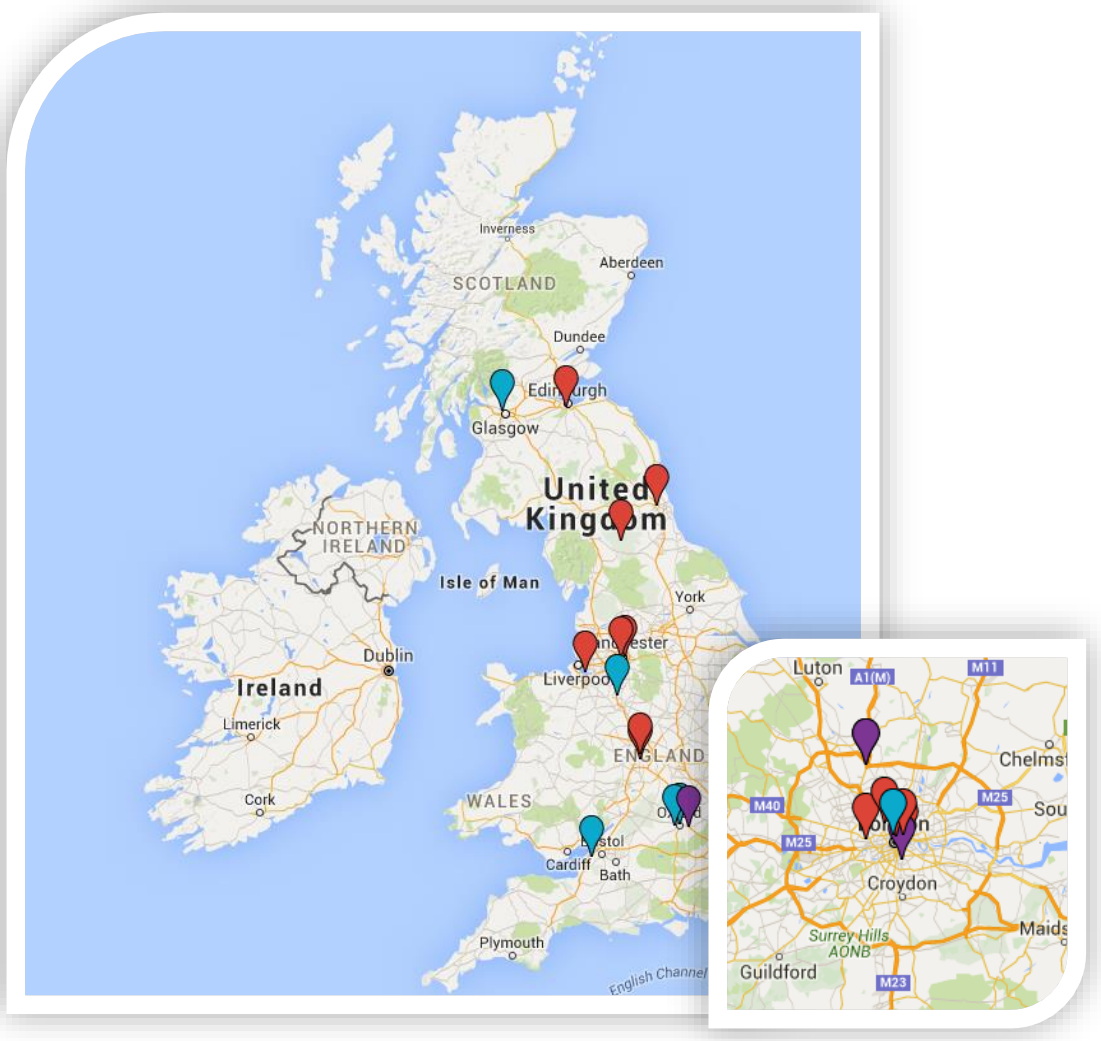


Figure 2 on the following page shows a snapshot of overall capabilities for cell and gene therapy manufacture within the UK. Table 1 provides details of the total cleanroom footprint and, furthermore, the distribution of the number of cleanrooms nationwide; London, South England (non-London), Midlands and Northern England and Scotland. Total booked capacity for these sites is running at 77% and the median number of cleanrooms per site is 3. It can be observed that London has an equal number of cleanrooms compared to the remainder of

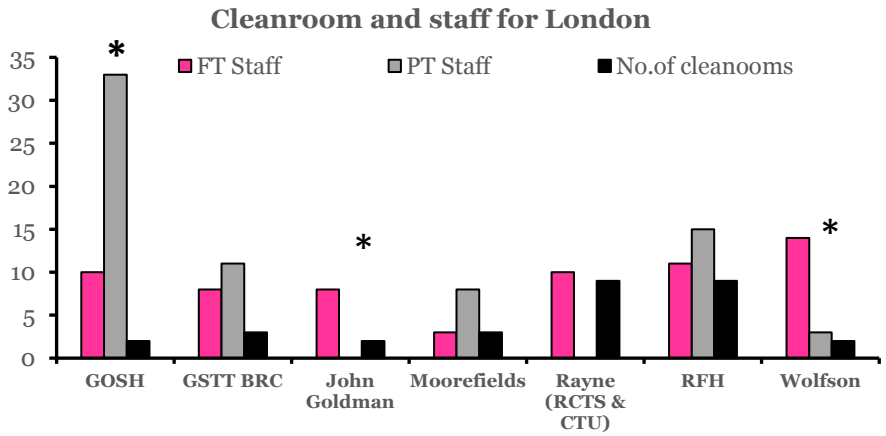
South England. However, the total footprint in the South of England is significantly higher – more than twice the size. This feature demonstrates the dominance of early translational facilities in London compared to commercial facilities located outside of the Capital. The cleanroom footprint for the Midland and Northern regions are comparable to London with Scotland having the least cleanroom footprint. Figure 3 on the following page provides a more detailed breakdown of the total cleanroom footprint within the UK with respect to both cell and gene therapy manufacture. It should be noted that for this analysis cleanroom footprint is defined to include essential personal airlock (PAL) and material airlock (MAL) areas.

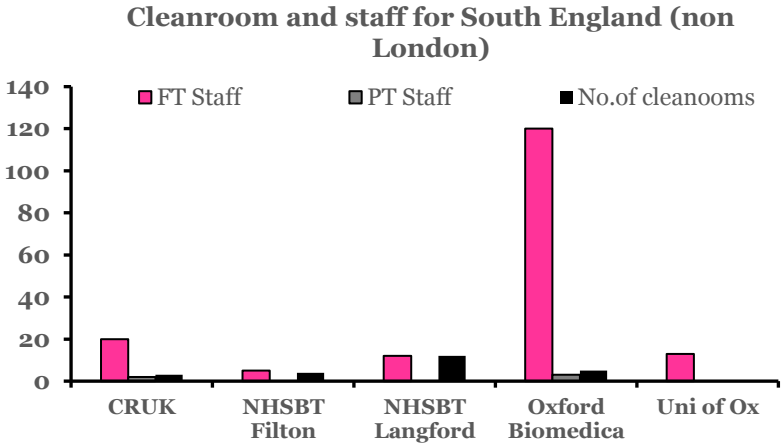
Figure 2 Snapshot of cell and gene therapy facilities in the UK

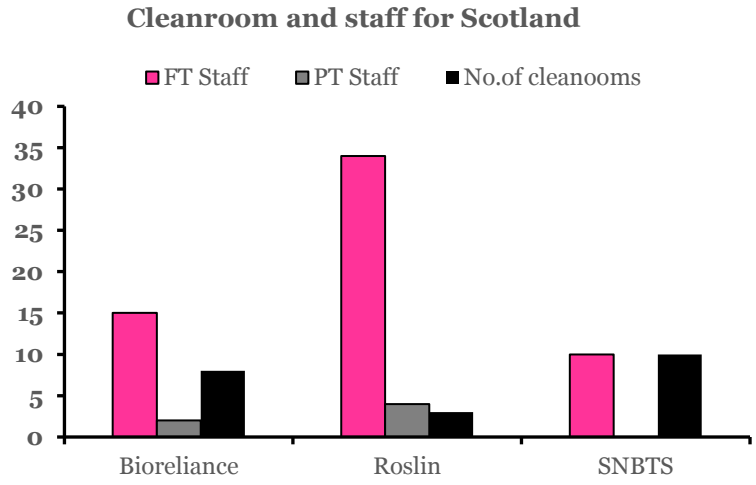
Table 1 Cleanroom footprint in the UK for cell and gene therapies

UK Location	Cleanroom Footprint (m²)	FT Staff	PT Staff	No. of cleanrooms
London	836.5	64	70	30
South England (non- London)	1975.3	170	5	30
Midlands and North	869.5	95	19	18
Scotland	1,443	61	6	21
UK Total	5,124.3	390	100	99

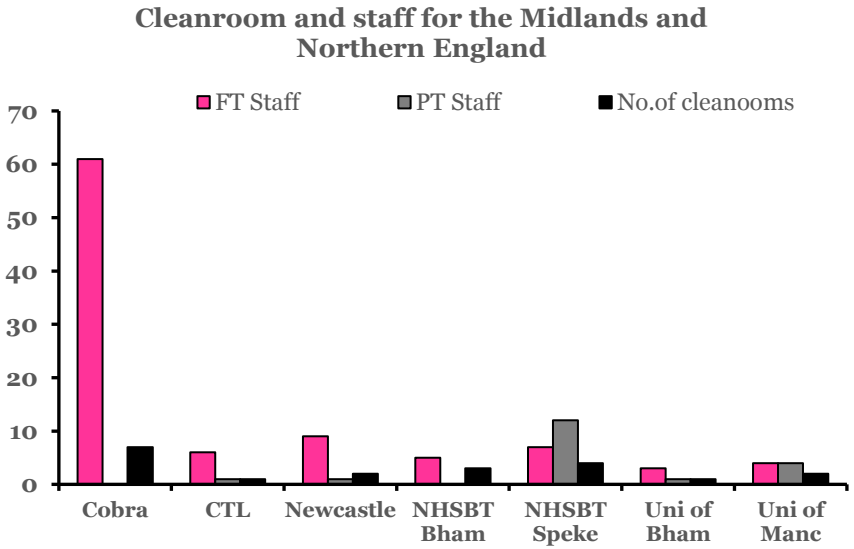
Figure 3 Distribution of cleanroom number and staff across the facilities in London, South England (non-London), Midlands and North England and Scotland (these charts incorporate cell therapy sites, gene therapy sites and multifunctional sites).







*based on 2016 data



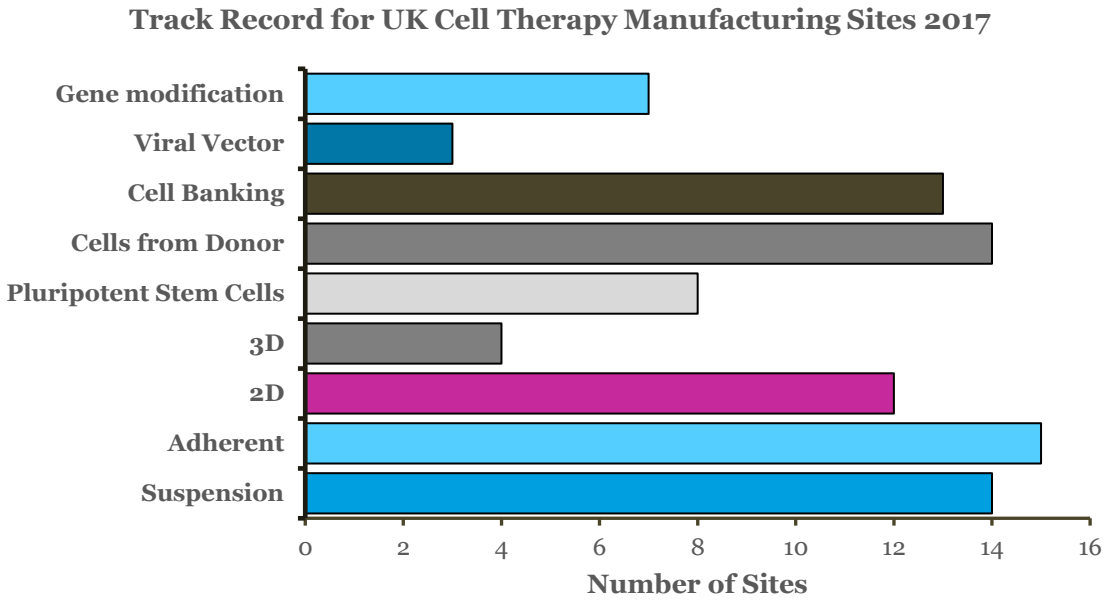
4.2 UK GMP cell therapy manufacture

A snapshot of the nation's GMP cell therapy manufacturing resource for 2017 is captured in Figure 4. A network of 17 GMP manufacturing facilities are in place, 4 of which have multifunctional cell and gene therapy production capabilities. The facilities supply nearly 2,200m² of licensed total cleanroom space between them for the manufacture of cell therapies (ca. 1,950m² in the hands of UK academia, charities and the NHS, and ca. 250m² commercially owned). The sector has an extremely positive outlook with numerous planned expansion projects on the horizon. The extensions, scheduled to come online before the end of 2018 (detailed in section 5.1), aim to increase current licensed cleanroom space by approximately 1,500m². The figures in this report do not include these as they are yet to be licensed facilities. The figures below combine the dedicated cell therapy manufacturing sites with multifunctional facilities.

Figure 4 Snapshot of cell therapy facilities in the UK

The current UK capability covers the whole technology sphere of expected manufacturing requirements. The figure below shows a breakdown of the types of processes and cell types that the various organisations have dealt with in the past or are currently working with. In this section of the analysis the multifunctional sites are included; 3 of which (King's College's CTU site, CRUK and the University of Oxford's CBMF site) are capable of viral vector manufacture.

Figure 5 Summary of cell therapy process capability in the UK



Key: Gene modification – *ex vivo* modification of cells to be used as a medicinal product; Viral vector – manufacture of viral vectors for gene modification purposes; Cell banking – laying down of master cell banks and working cell banks including any necessary testing; Cell from donor – handling primary tissues and cells; pluripotent stem cells – culture of induced pluripotent stem cells from donor tissue or culture of human embryonic stem cells from donor tissue; 3D – culture of cells in a 3D environment; 2D – culture of cells in a 2D environment; Adherent – culture of anchorage dependent cells; Suspension – culture of anchorage independent cells. N.B. regarding pluripotent stem cells, 8 sites have capability to culture hESCs and 4 sites have capability to culture iPSCs.

Figure 6 highlights the projected booked capacity for cell therapy manufacture from 2017 to 2019 in different regions in the UK; London, South England, Midlands and North England and Scotland. Capacity is available in 2017 and 2018. However, the size of facility and cleanroom needs to be considered, in addition to the technical expertise available; a more detailed breakdown is shown in Table 2, highlighting the strong and diverse manufacturing base in the UK for clinical development. Spare capacity is predicted in 2018 and this is indicative of project cycles ending, creating new opportunities for further collaboration. The opening of the Cell and Gene Therapy Catapult large-scale manufacturing centre in 2017 will provide significant growth, capacity and supply for the industry, and will support prospective cell therapies currently in early development to commercial supply.

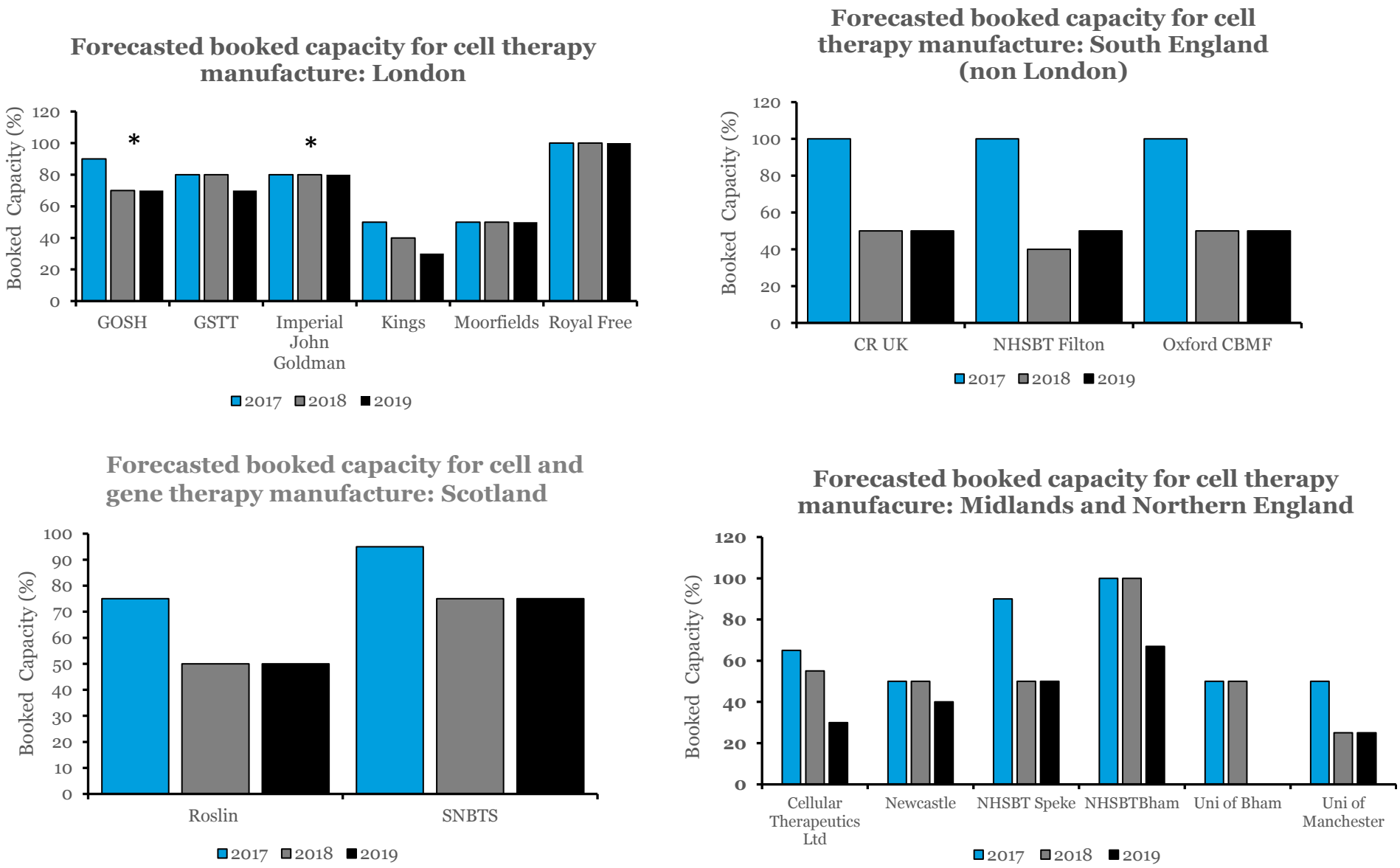


Figure 6 Forecasted booked capacity for cell therapy manufacture in London, South England, Midlands and Northern England and Scotland

**Based on 2016 data*

Table 2 GMP Cell Therapy capability and availability summary at UK organisations for 2017

Organisation	Parallel products (open/closed)	Capability										Availability 2017
		Auto suspension	Allo suspension	Auto adherent	Allo adherent	2D	3D	Human ES	iPS	Cells from donor	Other	
Cancer Research UK, BDU	2		✓		✓			✓		PE	CB, VV	0%
Cellular Therapeutics Ltd	6 (4/2)	✓	✓	✓	✓					✓	GM	35%
Guy's & St Thomas' Hospital, GMP Facility	4 (1/1)*	✓	✓	PE	PE	PE	PE	PE	PE	PE	GM (PE of CB)	20%
Imperial College London, John Goldman Centre for Cellular Therapy	4 (4/0)	✓	✓	✓	✓	✓				✓	CB	20%
Kings College London, RCTS and CRF	4	✓	✓		✓				✓	✓	CB, VV, GM	50%
NHSBT - Speke	2 (1/1)	✓	✓	✓	✓	✓	✓			✓	CB, GM	10%
Roslin Cell Therapies	4	✓	✓	✓	✓	✓		✓	✓	✓	CB	25%
SNBTS	DoP	✓	✓	✓	✓	✓				✓	CB	5%
University College London, GOSH Cellular Therapy Laboratories	5	✓	✓	✓		✓				✓	GM	10%
Moorfields Eye Hospital, ATMP Manufacturing Unit	2			✓	✓	✓	✓	✓		✓	CB	50%
University of Newcastle Biomanufacturing Facility	9	✓	✓		✓	✓		✓		✓	CB	50%
Oxford Clinical BioManufacturing Facility	DoP		✓		✓					PE	CB, VV	0%
Royal Free, CCGTT	7 (7/0)	✓	✓	✓	✓	✓	✓	✓	✓	✓	CB, GM	0%
University of Bham, CTS	2 DoP	✓	✓	✓	✓	✓				✓	CB	50%
University of Manchester	2-3	✓	✓	✓	✓	✓		✓	✓	✓	CB, GM	50%
NHSBT Birmingham	3	✓	✓	✓	✓	✓				✓	CB	0%

Key: PE – Key staff have previous experience but not at this organisation; DoP – Dependent on Process; CB – Cell Banking; VV – Viral Vector Manufacture; GM – Gene Modification; * remaining parallel products can be open or closed.

4.3 UK GMP gene therapy manufacture

Licensed facilities specialising in the manufacture of viral vectors and/or essential plasmid DNA for *in vivo* or *ex vivo* cell modification was again tracked this year. Figure 7 gives a snapshot of the gene therapy manufacturing facilities in the UK. The number of facilities remains at 6. However, over 20% expansion in cleanroom footprint has taken place over the last year predominantly via expansion of Oxford Biomedica's Harrow House facility. The company has increased this site's cleanroom footprint to a total of 1,200m².

Figure 7 Snapshot of gene therapy facilities in the UK

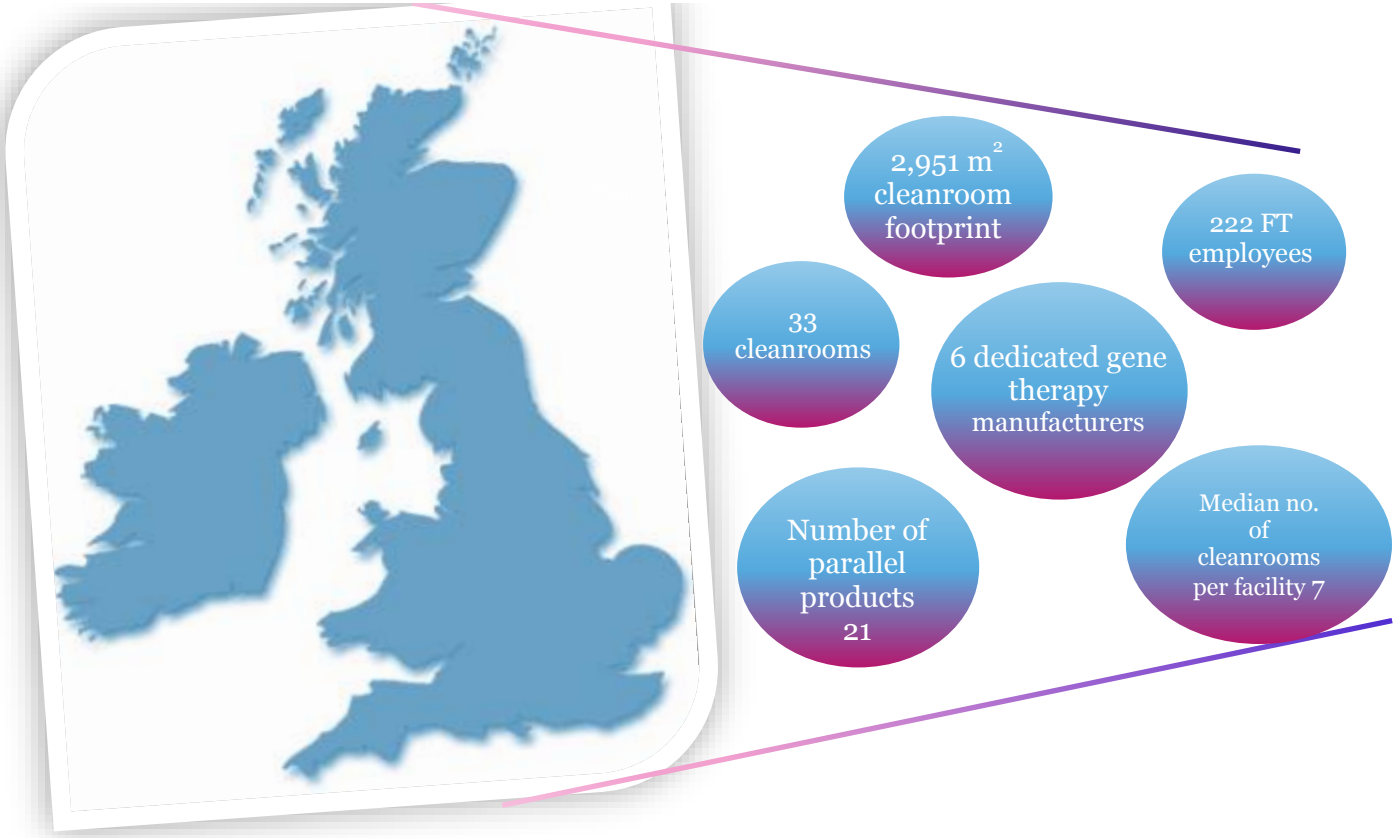


Figure 8 shows a breakdown of the types of plasmid, vector and cell producer systems in which facilities with gene therapy capabilities are experienced. This includes dedicated manufacturers (NHSBT CBC Langford, CobraBio, Oxford Biomedica, Bioreliance and Wolfson) and multifunctional gene therapy facilities (CRUK, Kings College and The University of Oxford). There is broad coverage of capabilities, from supporting plasmid DNA through to GMP-grade manufacture of lentivirus and gamma-retrovirus, two of the main viral vectors used in *ex vivo* gene modification processes. On the other hand, the supply of AAV used predominantly for *in vivo* gene modification is severely restricted. This lack of viral vector manufacturing has been identified by the Advanced Therapy Manufacturing Task Force and was a key recommendation to Government in its 2016 published action plan as an important opportunity for the UK. With the announced £18M investment by CobraBio for its UK manufacturing operations, the situation should start to improve. In addition, 6 x 150m² flexible modules will become available through the Cell and Gene Therapy Catapult's new manufacturing centre in 2017.

Figure 8 Summary of gene therapy activities across UK facilities

Key: Plasmid DNA – material used directly as IMPs and/or starting material used for transient infection to enable manufacture of viral vectors; Adenovirus/Gamma Retrovirus/Lentivirus/Adeno-associated virus (AAV) – key types of viral vectors used directly as IMPs and/or starting material used for transduction of cells *ex vivo*; Adherent – culture of anchorage dependent cells; Suspension – culture of anchorage independent cells.

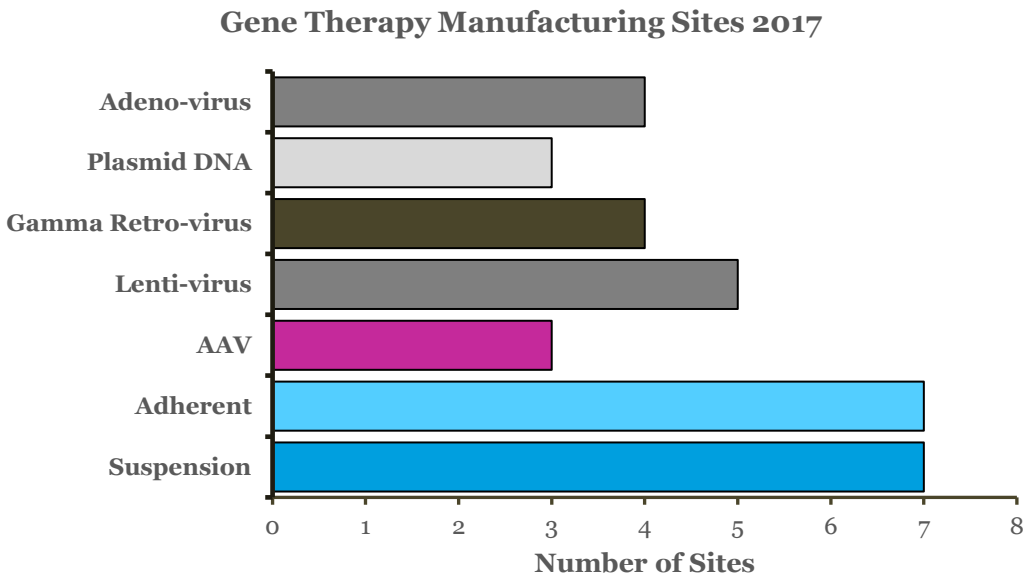
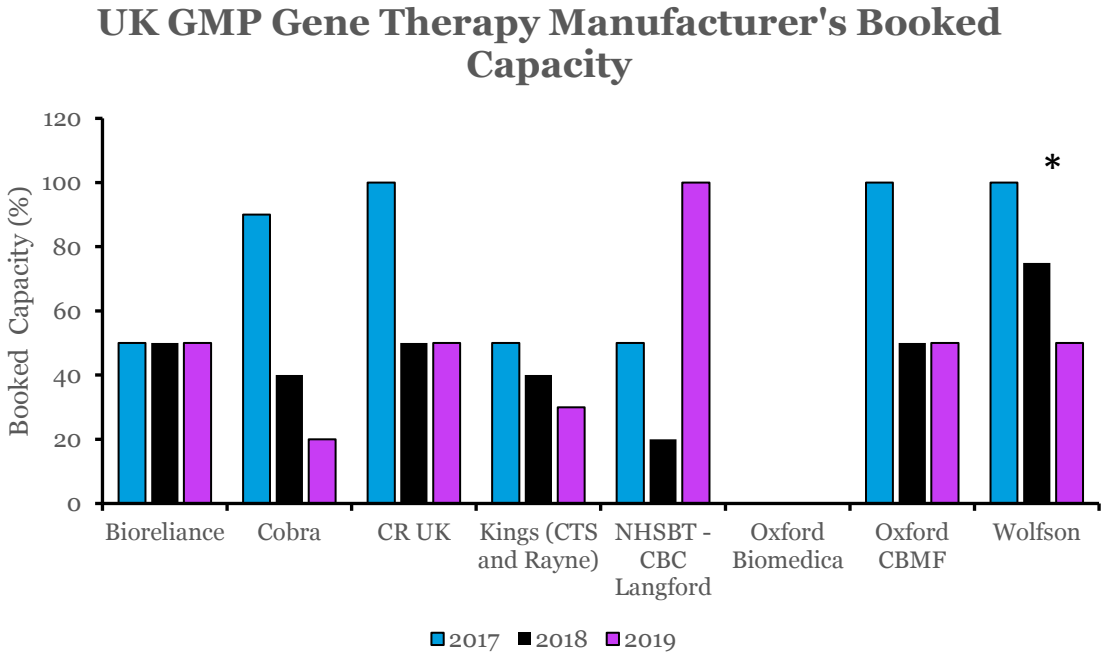


Figure 9 Predicted booked capacity for gene therapy manufacturing facilities in the UK



**Based on 2016 data. N.B booked capacity data from Oxford Biomedica were not available for the purpose of this analysis.*

Figure 10 shows a summary of the capability and availability at all the gene therapy production centres. Spare capacity at the manufacturing centres is essential for prospective growth within the UK gene therapy sector. A number of the facilities have spare capacity for 2017 and beyond. The opening of the Cell and Gene Therapy Catapult manufacturing centre in 2017 will further enhance the existing viral vector manufacturing network and facilitate the largescale manufacture and initial commercial supply of gene therapies.

Figure 10 Gene therapy capability and capacity for 2017

Organisation	Capability									Availability 2017
	Parallel products	Suspension	Adherent	AAV	Lenti-virus	Gamma retro-virus	Plasmid DNA	Adeno-virus	HTA Licence	
Cancer Research UK	1	✓	✓	✓	✓		✓	✓		0%
Kings College London, RCTS and CRF	4	✓	✓		✓	✓			✓	50%
NHSBT – CBC Langford	2	✓					✓			50%
Oxford Clinical BMF	DoP	✓	✓		PE	PE		✓		0%
Cobra Biologics	4 or 5	✓	✓	✓	✓		✓	✓		0%
Oxford Biomedica, Harrow House and Yarnton	DoP	✓	✓		✓	✓				Unavailable
Bioreliance Ltd	8	✓	✓			✓		✓		50%
Wolfson Unit	1		✓	✓						0%

Key: DoP – dependent on process; PE – previous experience

N.B For the purpose of this figure, Oxford Biomedica's two sites have been incorporated together, as have the sites for King's College.

4.4 UK GMP multifunctional gene and cell therapy production facilities

Four facilities remain multifunctional with cell and gene therapy production capabilities. Summary data from the 4 facilities; Cancer Research UK, King's College London RCTS, King's College CTU and University of Oxford CBF are shown in figure 11. These facilities, identified in this report as cell therapy production sites, offer additional resources which can be deployed to gene therapy production and further strengthen the UK gene therapy industry. See section 6 of this report for more detailed information on these multifunctional facilities respectively. N.B. King's College RCTS and King's College CTU are combined for analysis throughout this review.

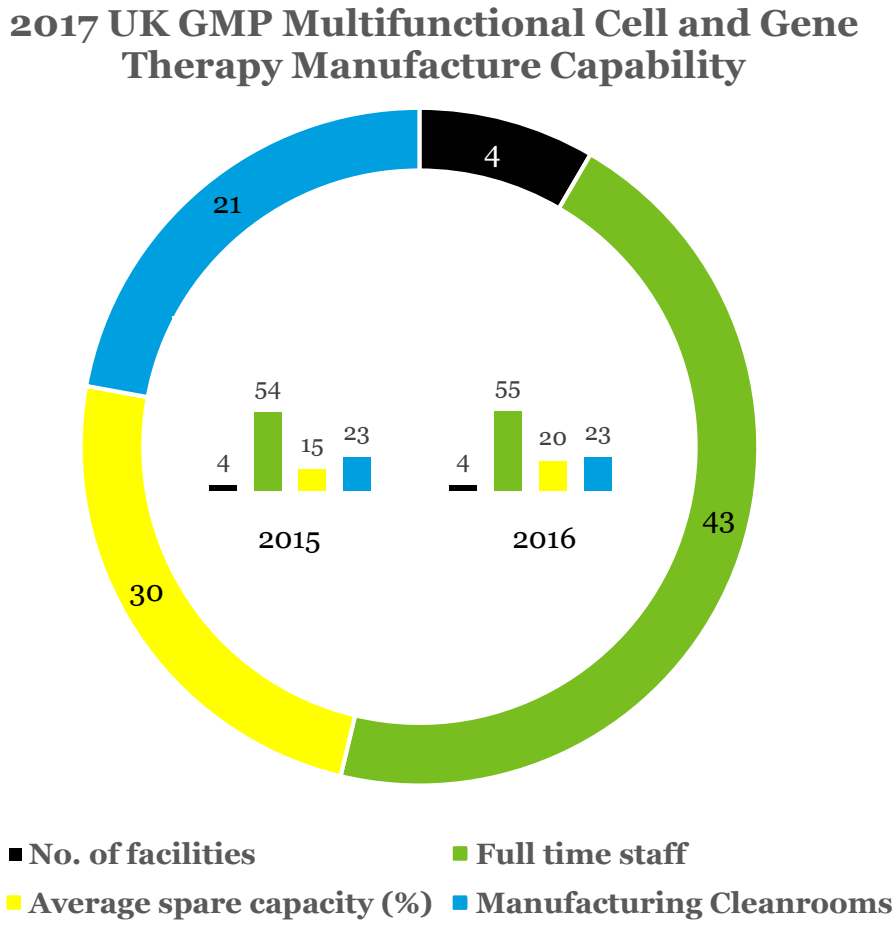


Figure 11 Summary Data for Multifunctional Cell and Gene Therapy Facilities 2017 (2015 & 2016 data inset)

5 Future Capacity and Expansion

Annual reviews of the UK manufacturing landscape are important to identify facility expansions, increase in personnel numbers and track records and the opening of new facilities. As a forward-looking statement, a description of upcoming expansions of existing facilities or newly licensed sites has been outlined below:

- A new NHSBT site in Filton (Bristol) has this year obtained licences for IMP cell therapy manufacture, bringing future additional capacity to the UK's cell therapy manufacture capabilities. The site currently operates 3 clean rooms. However, a 4th is scheduled for refurbishment in Q4 of this year.

- A purpose-built National Centre is being created for the Scottish National Blood Transfusion Service at Heriot-Watt Research Park in Edinburgh. The centre will contain a suite of cleanrooms (1 x Grade B cleanroom, 1 x Grade C cleanroom and ~300m^2 Grade D manufacturing space) for cellular therapies, generating extensive additional manufacturing capacity for the SNBTS. The National Centre is anticipated to be operational from late 2017.

- Expansion plans remain at Cellular Therapies, Great Ormond Street to significantly extend manufacturing cleanroom space. Seven new cleanrooms will occupy the top floor of the Zayed Centre for Research and allow multi-product processing. Construction started in Q1/Q2 2016 and completion will be towards the end of 2018, creating an additional 697 m^2 of space for the organisation.

- The Rayne Cell Therapy Facility at King's College London is in the process of building a new suite of cleanrooms, which will boost vector production capacity between 2 and 3-fold. The additional ~60m^2 of cleanroom space is scheduled to be available later this year.

- Expansion plans are also on the horizon for the University of Oxford CBF, and the facility has applied for planning permission with Oxford city council. Further details regarding the expansion project will be provided when available in the 2018 review.

- Phase 1 of Advent Bioservices' own new facility in Cambridgeshire, is due to be licensed and operational from Q1 2018 and includes two completed suites (185m^2 each), comprising B, C and PD/QC labs, offices and storage space. This facility is due to bring to market 199 m^2 of cleanroom footprint (including MAL & PAL areas) in its first phase. However, the site has capacity for a further ~7,500 m^2 of additional development.

- To our knowledge no other new MHRA-licensed cell or gene therapy manufacturing sites are due to come online in 2017/2018, which offer collaborative potential. However, please contact gmp@ct.catapult.org.uk if you have any information regarding new facilities of which we are not aware.

6 The Cell and Gene Therapy Catapult Manufacturing Centre

6.1 Large-scale commercial supply capacity

The Cell and Gene Manufacturing Centre will open in 2017. It will offer collaborators flexible manufacturing solutions without the capital investment of an own build. It will provide acceleration of commercial scale production and offer certainty of manufacturing future. The centre location will provide a highly-skilled workforce, cluster development and excellent logistics infrastructure. Collaborators can access segregated modules to manufacture their own products.

6.1.1 Facilities at the Cell and Gene Therapy Catapult manufacturing centre

Modules

- Collaboration model to accelerate manufacturing innovation
- 6 x 150 m^2 highly flexible grade B to C clean modules (in phase 1)
- Another 6 larger modules under design for delivery in phase 2 with existing building
- Architectural segregation
- Individual access control
- Segregated material and personnel flow

Quality control labs

- Central and independent quality control units
- Environmental monitoring in-house
- Raw material testing and bioanalytical facilities.

Warehousing

- Segregated multi temperature storage facilities
- Packing and dispatch area
- Raw material sampling facilities
- Short-term cryostorage
- Controlled rate freezer

Office space

- Dedicated and secure office space
- Segregated and fully flexible IT system

Facilities management and soft services

- Services including cleaning and reception

Cell and Gene Site Cluster

- Fisher Bioservices Cryohub on site
- Stevenage Bio-incubator Catalyst development and support facilities

6.1.2 Licence

This facility will be licensed by the UK MHRA (MIA & MIA (IMP))

Figure 12 provides images taken of the interior of the facility as of July 2017. The bottom left panel provides a schematic representation of the inside of the facility. The top left panel is an example of one of the available clean modules within the centre. Phase 1 will deliver 6 clean modules within 2017. Planning is already underway to deliver a further 6, bringing total in the facility to 12 architecturally and operationally segregated modules. This will allow companies to bring their own dedicated staff to manufacture products and to take on more modules with growth. The facility has been designed to facilitate production of cell and gene therapy products respectively and multiple ATMP processes. In addition, the facility has been designed for large manufacturing processes and can accommodate large volume bioreactors.

Figure 12 images of the interior of the Cell and Gene Therapy Catapult Manufacturing Centre.

6.1.3 Personnel

Cell and Gene Therapy Catapult staff will provide central quality control with EQMS and LIMS systems, warehousing, clean area, cleaning, waste management, reception, soft services, quality assurance.

The centre is supported by a team of specialists across the cell and gene therapy lifecycle, who will collaborate with you as you need them. The team includes:
• Health economics
• Regulatory support
• Clinical trial support
• Industrialisation

6.1.4 Contact

Sharon Brownlow PhD
sharon.brownlow@ct.catapult.org.uk

7 Manufacturing Organisations

7.1 Biomedical Research Centres (BRC) GMP Unit at Guy's and St Thomas'

7.1.1 Details

Address

Advanced Therapy Manufacturing (GMP) Unit

NIHR Guy's and St Thomas' Biomedical Research Centre Clinical Research Facility

15th Floor, Tower Wing

Guy's Hospital

Great Maze Pond

London SE1 9RT

Contact: Drew Hope Andrew.hope@gstt.nhs.uk

Tel: 0207 188 7188 (ext 52362 or 52703)

Web:
http://www.guysandstthomasbrc.nihr.ac.uk/Professionals/Corefacilities/GoodManufacturingPractice(GMP)Facility.aspx

7.1.2 Facility

Guy's and St Thomas' BRC Advanced Therapy Manufacturing (GMP) Unit is a 125m² facility located on the 15th floor of Guy's Hospital Tower Wing. The main manufacturing area houses three grade D clean rooms which are in total 95m². Closed processing occurs within the clean rooms and each is equipped with an isolator for open processing.

Processing equipment

- 3 x Rigid four-glove Grade A isolators
- Incubators
- Controlled-rate freezer
- Centrifuges
- CliniMACS Plus, CliniMACS Prodigy cell isolators
- Sepax and SynGenX1000 cell isolators
- MACS Quant Tyto FACS cell isolator
- Xuri Bioreactor
- GentleMACS tissue processor

Analytical equipment

- Scepter cell counter
- Inverted microscopes
- MACS Quant Flow Cytometer
- FORTESSA Flow Cytometers
- 7900 HT quantitative PCR

Figure 13 Example of clean rooms at Guy's and St Thomas'

7.1.3 Licence

MHRA licences for IMPs and Specials; HTA licence for procurement, donor testing and processing.

7.1.4 Track record and experience

Experience with autologous T cells and autologous T-Reg cells at the facility. A summary of the experience can be found in Table 3.

Table 3 Summary of experience for Guy's and St Thomas'

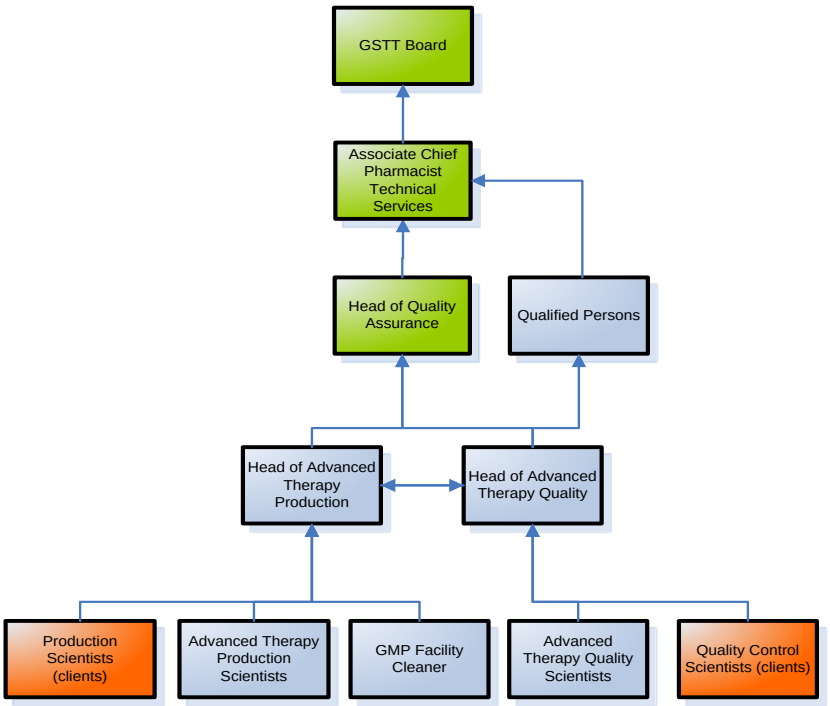
	Suspension	Adherent	2D	3D
Auto	✓			Previous Experience
Allo	✓	Previous Experience	Previous Experience	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
Previous Experience	Previous Experience	Previous Experience

Personnel

Two members of staff are permanently employed in the Unit to oversee the quality management system; a Head of Advanced Therapy Production and a Head of Advanced Therapy Quality. Two contract QPs are used for batch release. Four advanced therapy production scientists and two advanced therapy quality scientist are employed to assist with projects being undertaken within the unit. Client-teams of up to four operators may work in a hotel-like system, trained by the Unit to work in production and analytical roles.

Figure 14 Organogram of Guy's and St Thomas' CRF



7.1.5 Capacity

Guy's and St Thomas' CRF has indicated that it would be possible for them run up to five open and 10 closed projects per year. Forecasts of future booked capacity can be found below.

2017 – 80%
2018 – 80%
2019 – 70%
2020 – 70%
2021 – 60%

7.2 Bioreliance Ltd

7.2.1 Details

Site address:
BioReliance Ltd
Todd Campus
West of Scotland Science Park
Glasgow
G20 0XA

Reception: 0141 946 9999
www.bioreliance.com

Contact: Susan Livingston
Tel: 0141 576 2462
susan.livingston@bioreliance.com

Additional contacts:
Contact: Angela Waugh, Laboratory Manager
Tel: 0141 946 9999

7.2.2 Facilities at BioReliance Ltd

BioReliance has a long established facility for:

- Mammalian/ Insect Cell and Viral Banking
- Bulk Viral production
- Investigational Medicinal Products manufacture

BioReliance has 8 cleanrooms. These are EU grade B with grade B and D change areas. Each cleanroom has a separate air handling system supplying HEPA filtered air and a local EU Grade A Laminar flow hood where open manipulations are carried out. On-site in Glasgow there are local Facilities Management and Equipment Support staff. The site also has a full service biosafety testing operation where cell banks, viral seeds, clinical lots and commercial lots can be rapidly tested and released to clients.

Figure 15 Glasgow facility at BioReliance Ltd

7.2.3 Licence

MHRA MIA(IMP) licence no.: 22774 (Site 4473)

FDA Facility establishment Identifier: 3005343934

7.2.4 Track record and experience

Experienced manufacturing team for handling a wide variety of cell types and culture platforms.

Cell culture technology and expertise;

- culture condition optimisation
- cell line adaptation to serum free
- optimising MOI and infection strategy
- stability studies
- long-term storage

Collective experience in Mammalian and insect cell banking in GMP cleanrooms on a campaign basis. Also Viral Manufacturing experience producing viral vectors and vaccines (viral seed stock material and viral clinical trial batches). Culture systems include T flasks, shaker & spinner flasks, cell factories, cell cubes and Wave bioreactors. Downstream purification methods used include ultracentrifugation (including density gradient), TFF/UFF, chromatography methods and filtration.

7.2.5 Personnel

We have a Director of Operations for our Manufacturing facility with a Laboratory Manager (Angela Waugh) reporting to them. Angela has been a member of the BioManufacturing team since 2001, and has been leading cell and virus manufacture, supporting client campaigns from initial cell banking right through to commercial approval. Running a facility with routine FDA and MHRA inspections, she has significant expertise in the requirements to ensure processes and facilities maintain compliance both inside and outside the cleanroom.

Our Laboratory Manager has a team of highly experienced scientists running our client projects. More senior scientific staff will liaise with clients to define the scope of the project and then a processing team from our scientist group will perform the work. Average tenure amongst our senior scientific staff is over 12 years.

In addition to the Manufacturing team, Bioreliance Ltd has a dedicated Programme Manager to ensure smooth running of the projects. The site also has dedicated QA resource ensuring approval of manufacturing documentation prior to processing and subsequent batch record review. Finally, BioReliance has on hire 2 part-time consultant QPs for release of material to our clients.

7.2.6 Capacity

Forecasted booked capacity:

2017 – 50%
2018 – 50%
2019 – 50%

7.3 Cancer Research UK Biotherapeutics Development Unit

7.3.1 Details

Address
Clare Hall Laboratories,
Blanche Lane,
South Mimms,
Potters Bar,
Hertfordshire EN6 3LD

Contact: Heike Lentfer heike.lentfer@cancer.org.uk
Tel: 01707 625700
Web: http://www.cancerresearchuk.org/science/research/drug-development/scientists/manufacturing-other-capabilities/biotherapeutics-development-unit/

7.3.2 Facility

Manufacturing suites

- Two segregated manufacturing suites each with grade C clean rooms for closed processing and a separate 6-glove isolator for aseptic filling.
- Grade B clean room operation has been successfully qualified
- HVAC is fully segregated between suites allowing multi-product manufacture. Areas are all designed for cat II containment.

Cell culture processing and analytical equipment

- Various Microbiological Safety Class II and Laminar Air Flow Cabinets
- Static and Shaking Incubator with CO_2 control, some with humidity control
- AppliFlex Bioreactor 20L and 50L (disposable)
- Single-use Bioreactor (SUB Hyclone) 50L, 100L, 250L
- NucleoCounter, Vi-Cell for automated cell counting
- CubiAnalyzer for metabolite analysis
- CellMetric Clone Imager

Other processing equipment

- Millipore Mobius Disposable Mixer System
- Disposable TFF System
- AKTA Explorer, AKTA Pilot and AKTA Ready (Disposable) Chromatography Controller

Sterile filling equipment

- Flexicon FP50 Filling Machine
- Two 6-Glove Isolators

Analytical equipment

- UV/VIS Spectrophotometers
- Plate Readers (visible light only - can be upgraded to bioluminescence or fluorescence)
- HPLC
- FTIR
- TOC Analyzer
- Q-PCR
- FACS
- Zetasizer Nano SP
- Stability Cabinets
- Sterility Test Isolator

Photos showing the finish of the clean rooms can be seen in Figure .

Figure 16 Example photos of CR UK BDU facility

7.3.3 Licence

MHRA licence for IMPs has been granted, and includes cell therapy products.
The site does not have a HTA licence.

7.3.4 Track record and experience

The main experience to date has been with biologics production (recombinant proteins, monoclonal antibodies, DNA and viruses etc.). Adherent and suspension cell cultures have therefore been used for this purpose (CHO, A549, various Hybridoma cell lines). Technology transfer of a manufacturing process for expansion of human embryonic stem cells and their differentiation into dendritic cells has been completed successfully. The GMP manufacture has commenced and is likely to continue until Q4 2017. A summary of staff experience can be found in.

The organisation has experience with manufacture of cell and virus banks and has established cell line development technology for generating high yielding, recombinant cell lines for antibody and protein production using a commercial proprietary expression system.

The organisation has experience of large (250L) scale stirred tank and rocking bioreactors. This applies to both single use and CIP/SIP vessels.

Table 4 Summary of experience for CR UK BDU

	Suspension	Adherent	2D	3D
Auto				
Allo	✓	✓		

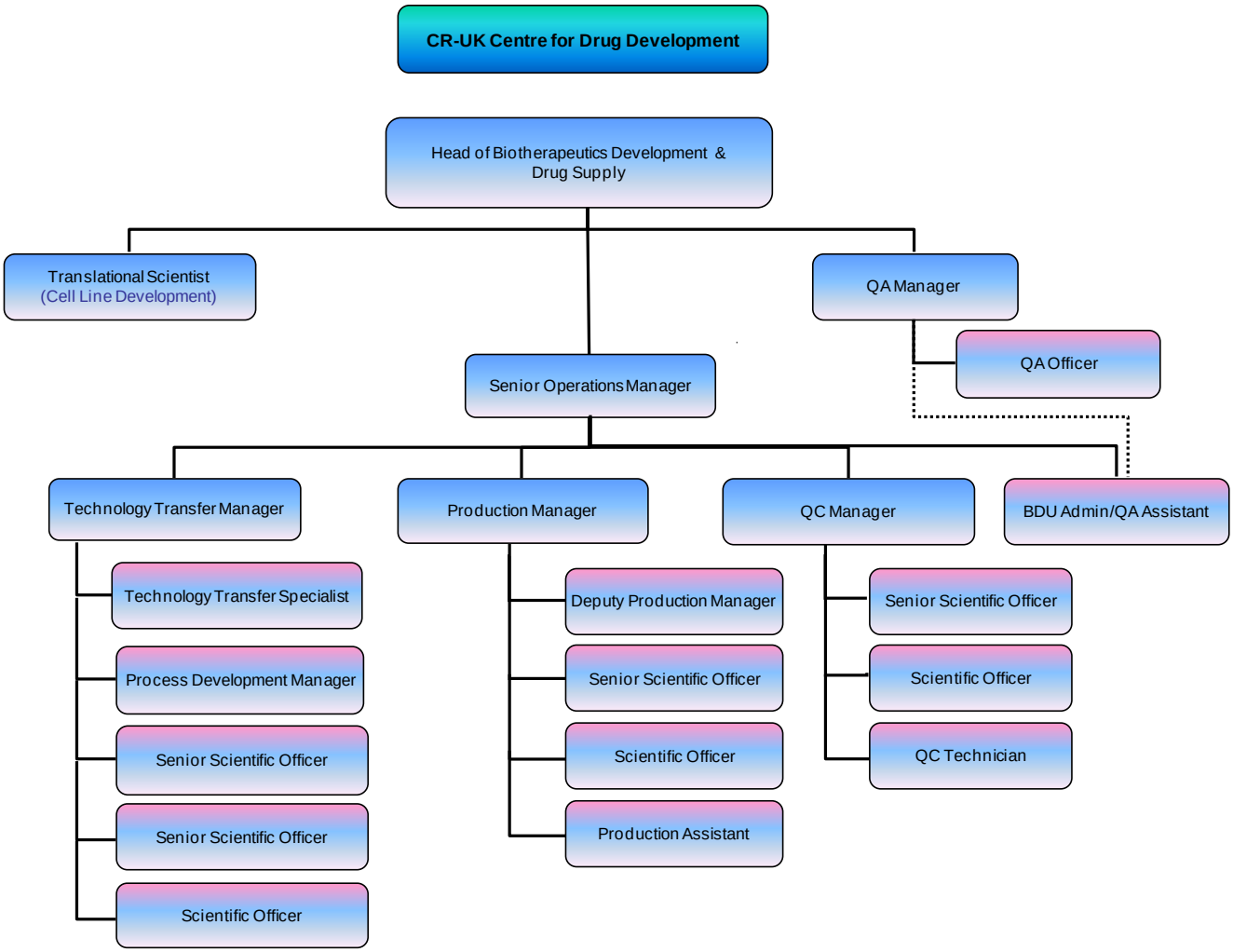
Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓		Previous experience

7.3.5 Personnel

In total there are 20 members of staff working within the facility. Staff are deployed where necessary but strict controls are in place to prevent staff working on multiple different product streams. Main areas of experience have been focused on production of biologics from various cellular expression systems.

An organogram showing the organisation structure of the team can be found in Figure .

Figure 17 CR UK BDU Organogram



7.3.6 Capacity

CR UK BDU indicated that they could run up to three projects per year on the assumption that each would require lengthy tech transfer activities prior to GMP manufacture. The multiple GMP suites with separate air handling, personnel, material and waste segregation would enable up to two simultaneous production campaigns.

Forecasted booked capacity:

2017 – 100%
2018 – 50%
2019 – 50%

7.4 Cellular Therapies, Great Ormond Street Hospital

7.4.1 Details

Address
Cellular Therapies
Great Ormond Street
London WC1N 3JH

Contact: Sue Swift s.swift@ucl.ac.uk
Tel: 0207 905 2830
Web: n/a

7.4.2 Facility

There are two suites within Cellular Therapies. The first consists of a grade C clean room with a grade A positive isolator for aseptic processing. The second suite has a grade C preparation room and aseptic processing with two grade A negative isolators. The facility is licensed for gene and cell therapy products by the MHRA (MIA (IMP) and MS 17328). There is an adjacent stem cell facility for routine cell manipulation licensed by the HTA.

Processing equipment

- Centrifuges (various)
- Incubators (various)
- Plasmatherms
- Tube welders and sealer and bag sealers
- Dynal ClinExVivo (magnetic particle concentrators for removal of beads)
- CliniMACS cell separator
- Wave Bioreactors
- CliniMacs Prodigy

Analytical equipment

- Nikon stereoscopic and inverted microscopes

Figure 18 Example of clean room at GOSH Cellular Therapies

7.4.3 Licence

MHRA licence for IMP and specials. The facility is also licensed by the HTA.

7.4.4 Track record and experience

The facility has the experience of manufacturing gene and cell therapy products for Phase I / II trials. In total around 10 products have been manufactured for clinical trials and another 10 are in progress.

Table 5 Summary of experience for GOSH Cellular Therapies

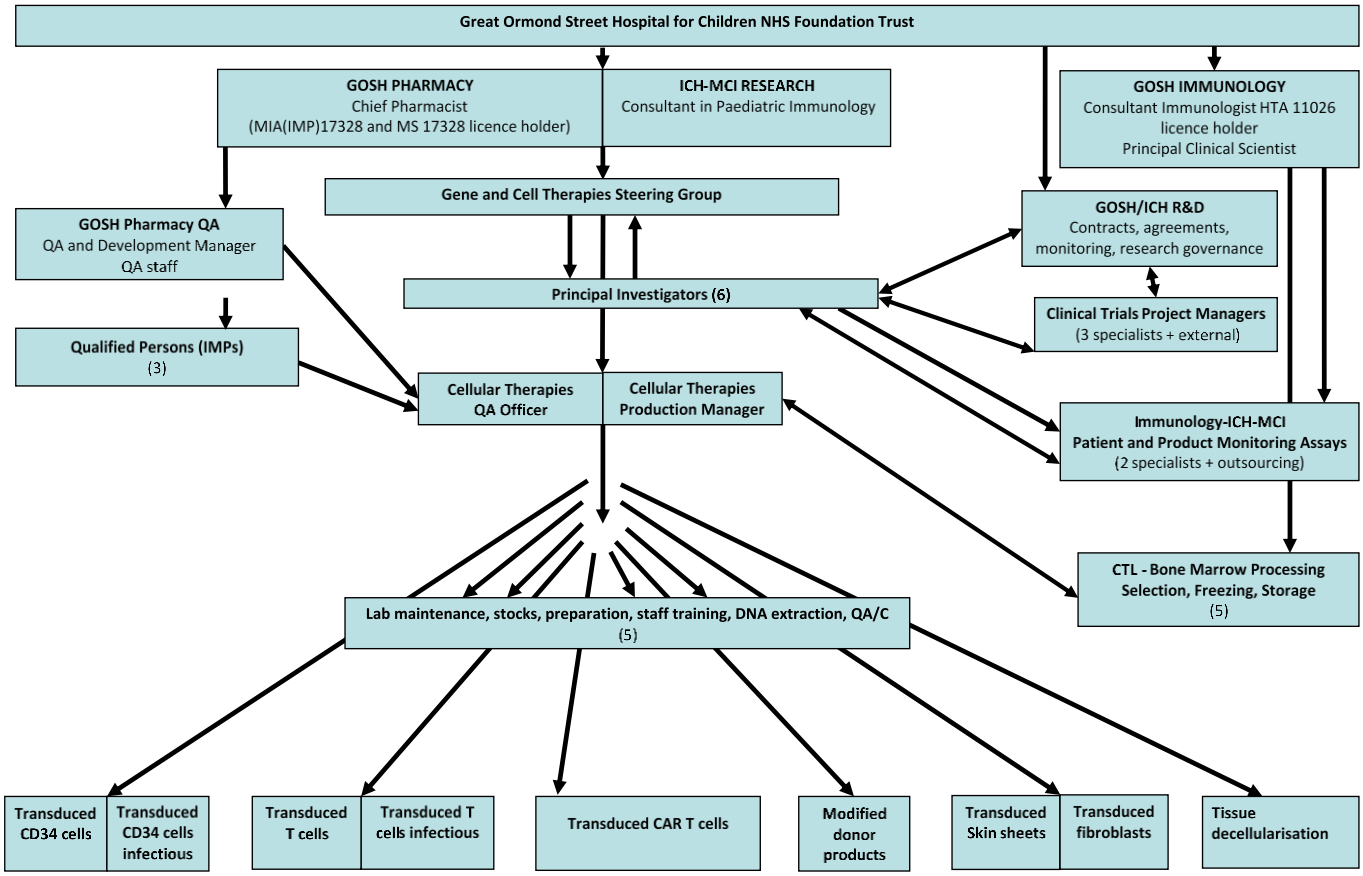
	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓		✓	

Human ES Cell	IPS Cell	Cell isolation from donor tissue
		✓

7.4.5 Personnel

The unit is organised under a chief pharmacist with an aseptic services manager, a quality assurance manager and a contract QP.

Figure 19 Organogram of Cellular Therapies at GOSH



7.4.6 Capacity

The facility has indicated that it is capable of manufacturing up to 30 open or closed products per year in the facility.

Forecasted booked capacity:

2017 – 90%
2018 – 70%
2019 – 70%

7.5Cellular Therapeutics Ltd (CTL)

7.5.1 Details

Address
Cellular Therapeutics Ltd
48 Grafton Street
Manchester M13 9XX

Contact: info@cellulartherapeutics.co.uk
Tel: 0161 606 7278
Web: www.cellulartherapeutics.co.uk

7.5.2 Facility

This facility comprises of one large multiproduct manufacturing suite (grade D) with three isolators (grade A) and associated transfer hatches (grade B). Each open product is incubated within a product specific secondary containment system to avoid cross contamination.

Processing equipment

- Process development laboratory
- Environment Monitoring System to log parameters (particle count, pressures, temperature etc) from the isolators, incubators and storage locations.
- CliniMACS – bench top platform enabling the separation of different cell types within a closed system using magnetic bead conjugates.
- Automated closed system to aseptically concentrate and wash cells.
- Standard incubators for static cell culture
- Bag/closed vessel centrifuge and 'bag squeezer' (to remove supernatant).
- Perfusion bioreactors for actively managed cultures (10L scale)
- Cryopreservation

Analytical equipment

- Flow cytometer
- Microbiology QC
- GMP and process development assays

Figure 20 Example of clean room at the Cellular Therapeutics Unit

7.5.3 Licence

CTL holds MHRA Authorisation for Investigations Medicinal Products (IMPs) and Manufacturing Specials (MS) (#44168).
HTA licence (#22657).

7.5.4 Track record and experience

CTL has experience of manufacturing both closed and open cell therapy products, manufacturing gene modified T cell (viral vectors) and Tumour Infiltrating Lymphocyte products: having completed two cell therapy trials; four trials ongoing; and further trails in the pipeline. A summary of their experience with cell therapies can be found in Table 6.

Table 6 Summary of experience for Cell Therapeutics Unit

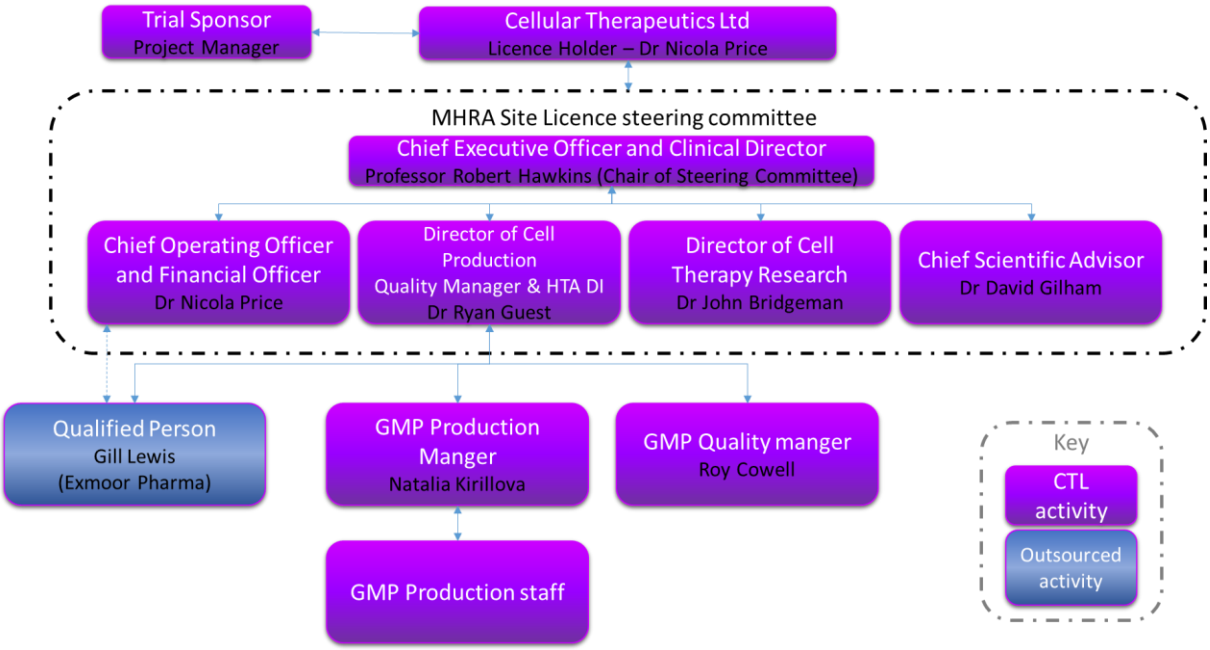
	Suspension	Adherent	2D	3D
Auto	✓	✓		
Allo	✓	✓		

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		✓

7.5.5 Personnel

An organogram for CTL can be found in Figure . The unit operates under the CTL Board which is responsible for determining the direction and oversight of products in the pipeline and in process. There are individual board members responsible for finance and contracts; production and quality and process translation, scientific review; and GMP research and development. Within the facility we have access to consultant qualified personnel and dedicated product management and production staff.

Figure 21 Organogram for Cellular Therapeutics



7.5.6 Capacity

Cellular Therapeutics have the capability to manufacture six different products simultaneously with a current maximum of four open processes at any one time. This assumes a manufacturing cycle of two to three weeks per product. This allows to manufacture between 60 and 100 complex ATMP products per year.

Forecasted booked capacity:

2017 – 65%
2018 – 55%
2019 – 30%

7.6 Cobra Biologics

7.6.1 Details

Site address

Cobra Biologics
Stephenson Building
Keele Science Park
Keele
ST5 5SP

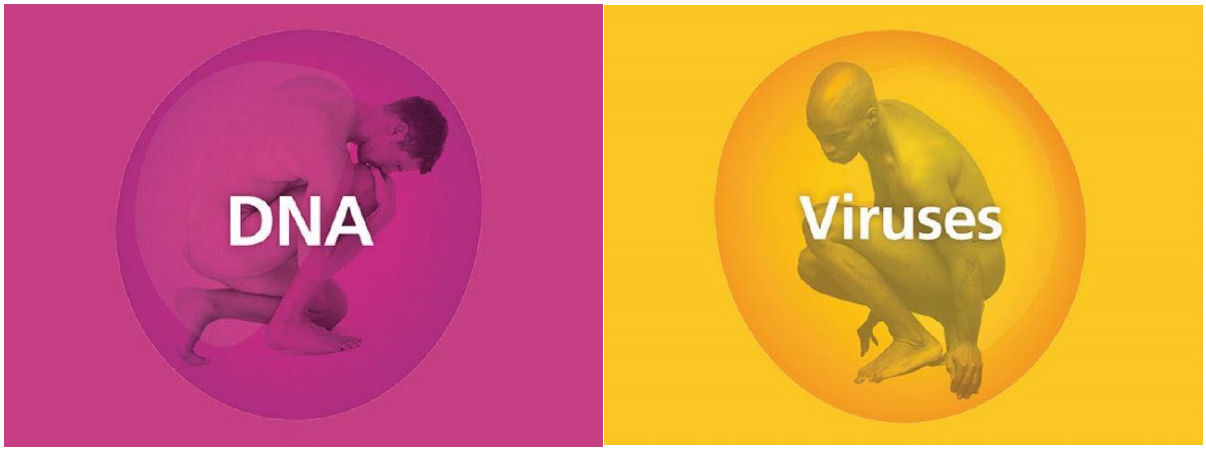
www.cobrabio.com

Contact: Philip Ridley-Smith, Sales & Marketing Director
Tel: +44 208 246 5895

Additional contacts:
Contact: Steve Garland, Director of Operations
Tel: +44 1782 714 181

7.6.2 Facilities at Cobra Keele & Matfors

Cobra is a development and manufacturing organisation producing materials for pre-clinical, Phase I/II/III clinical trials and in-market products with over 252 employees (96 based in UK). Cobra has a commercially licensed fill / finish and secondary manufacturing facility and supplies commercial products to Europe, North America and the rest of the world. The company routinely produces a wide range of bio-therapeutics ranging from plasmid DNA, HQ plasmid DNA, viral vectors, microbial/ mammalian proteins and microbiota for over 16 years. Within Cobra there are three operating facilities, based at Keele, UK, Södertälje, Sweden and Matfors, Sweden, which have been inspected and found compliant on a regular basis by the relevant regulatory authorities in the UK and Sweden.



7.6.3 Licence

All of Cobra's facilities are cGMP licensed under the EU clinical trials directive and inspected on a regular basis; MHRA and MPA licence for IMPs for the respective country locations. Cobra has a QP employed at each of its three manufacturing sites.

7.6.4 Track record and experience

Cobra has 16 years of experience as a contract manufacturer providing services for gene therapy with viral vector and DNA production. In the UK the main gene therapy site is designed for BLS-2 handling. The company has worked with over 50 customers and produced 85+ GMP batches for customers in Europe, North America and Asia in Phase I to Phase III clinical trials.

Over the last 16 years Cobra has developed a number of platform services key in helping their gene therapy customers:

- Platform process for GMP adenovirus production
- Platform process for GMP DNA production for Phase I-III
- Platform process for the supply of HQ DNA requiring traceability for AAV and lentivirus production

An AAV production process is currently being developed to meet the demands of the gene therapy market.

7.6.5 Personnel

Key personnel working in the gene therapy facility in Cobra Biologics, Keele, UK are shown in the organograms below

Figure 22 Key production personnel at Cobra Biologics, Keele facility

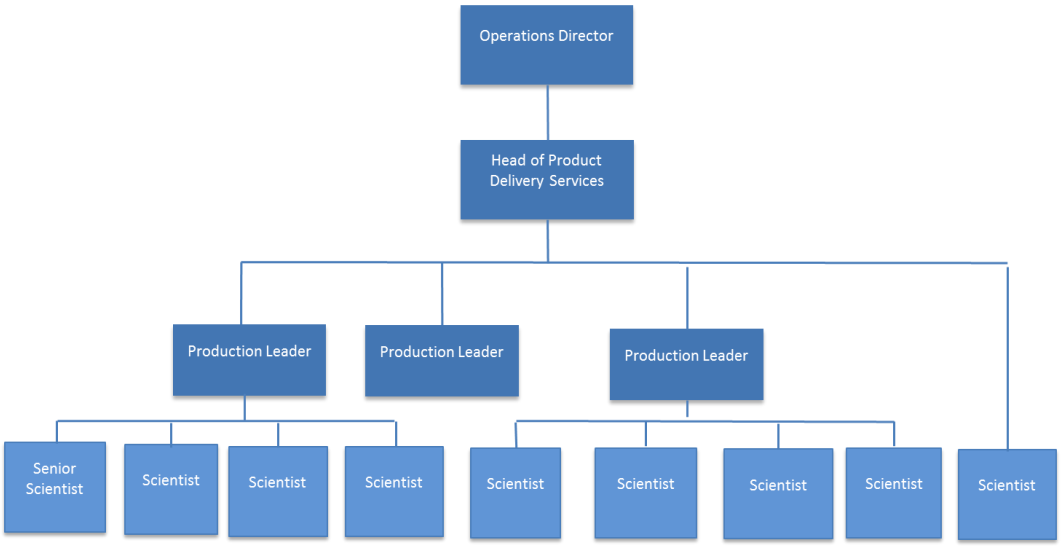
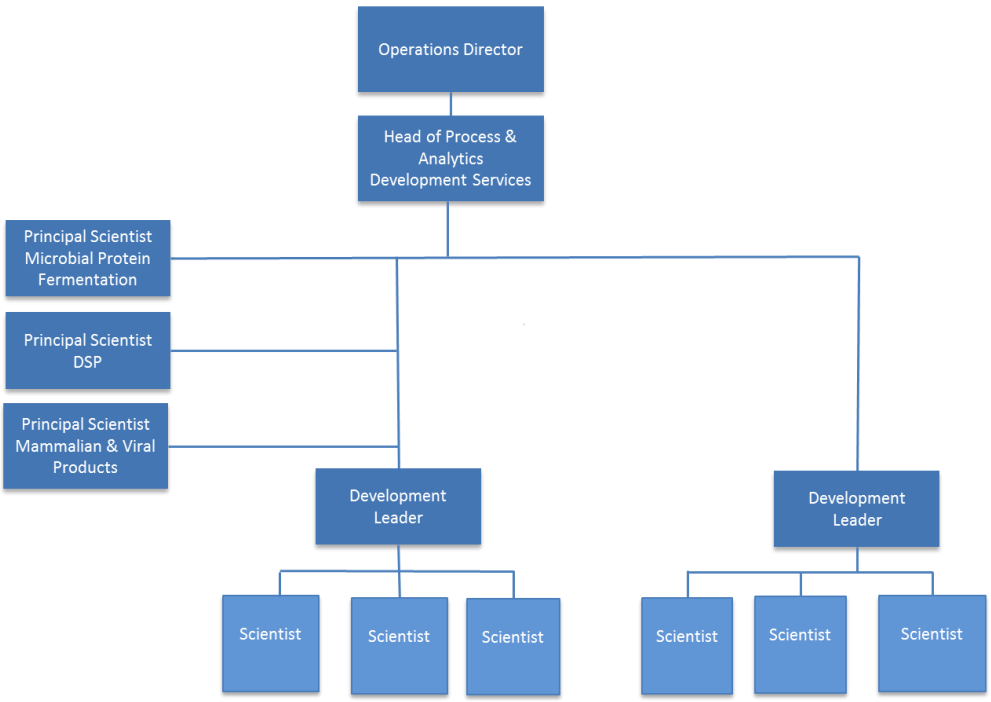


Figure 22 Key analytical personnel at Cobra Biologics, Keele UK



7.6.6 Capacity

The forecasted booked capacity at the Keele facility for the next 3 years is listed below:

2017 – 90%
2018 – 40%
2019 – 20%

7.7Imperial College London, John Goldman Centre for Cellular Therapy

7.7.1 Details

Address
Catherine Lewis Building,
Hammersmith Hospital,
Ducane Road,
LONDON W12 0HS

Contact: Anne Bradshaw anne.bradshaw@imperial.nhs.uk
Tel: 0203 313 2056
Web: n/a

7.7.2 Facility

The centre is equipped with two independent clean room suites. Each suite has two grade B rooms for processing and a grade C room for preparation. Class II MBSCs provide grade A environments for open processing. One of the suites is designed to work with GMO level 2 material (for example for gene replacement work). Work with genetic modification would require an update to the IMP Licence however.

Processing equipment

- Class II ducted cabinets
- Laminar airflow stations (LAF)
- Cell separators e.g. Cobe 2991
- Immunoselection devices e.g. Miltenyi CliniMacs, Miltenyi Prodigy
- Tubing heat sealers
- Automated Cell washer – Sepax
- Sterile Docker – Terumo SCDC
- Tissue Culture incubators
- Vacuum wrapping device
- Pharmacy grade fridge/freezer
- Controlled rate freezer

Analytical equipment

- Flow Cytometer
- Bench top centrifuges
- Pharmacy grade fridge

Figure 23 Example of clean room at John Goldman Centre for Cellular Therapy

No photographs provided.

7.7.3 Licence
MHRA Licences to manufacture IMPs and Specials. HTA licences have also been awarded for various operations.

7.7.4 Track record and experience
The centre has a long history of experience immune-selection and separation (CD34+) using devices such as the CliniMACS. The centre has experience with Haematopoietic Progenitor Cells and T lymphocytes for both autologous and allogeneic use. A summary of the centre's experience can be found in Table 7.

Table 7 Summary of experience for John Goldman Centre for Cellular Therapy

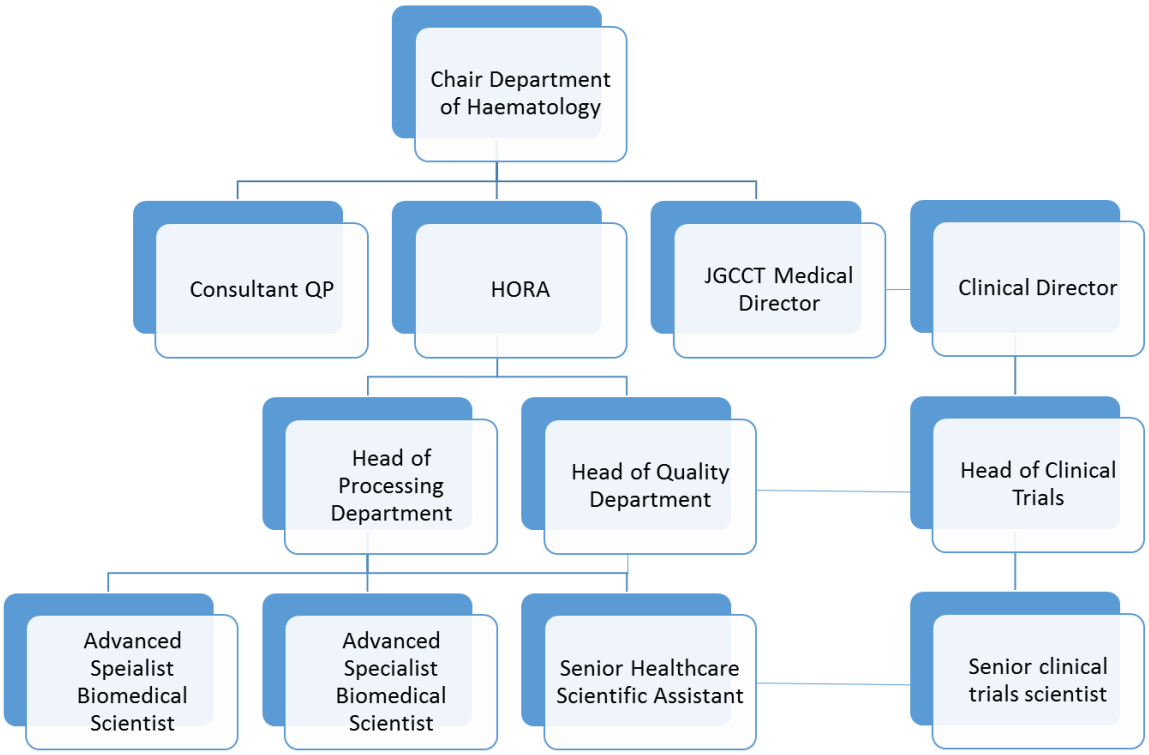
	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓	✓	✓	

Human ES Cell	iPS Cell	Cell isolation from donor tissue
		✓

7.7.5 Personnel
Key personnel at the centre include a head of operations and regulatory affairs, a medical director, consultant QP, head of processing and a head of quality. A description of the organisation of the centre can be found in

Figure 24.

Figure 24 Organogram of John Goldman Centre for Cellular Therapy



7.7.6 Capacity

The centre has two independent suites each with two grade B rooms enabling up to four simultaneous projects. The forecasted booked capacity over the next few years is indicated below:

2017 – 80%
2018 – 80%
2019 - 80%

7.8 Moorfields Eye Hospital, Cells for Sight Cell Research Unit

7.8.1 Details

Address

UCL Institute of Ophthalmology

11-43 Bath Street

London, EC1V 9EL, UK

Contact: Julie Daniels j.daniels@ucl.ac.uk

Tel: 0207 608 6893

Web: http://www.ucl.ac.uk/cells-for-sight/cell-therapy

7.8.2 Facility

The manufacturing facility is a cleanroom suite that includes two Grade B processing laboratories (2 Person Lab and 3 Person Lab), a Grade B Lab Airlock, a Grade C Prep Area, a Grade D Change Room and an unclassified Vestibule. A schematic representation of the manufacturing facility is shown in Figure 1. The different areas of the manufacturing facility are used for the following purposes:

The Vestibule is the initial point of entry into the facility, where cells, reagents and consumables are transferred into, and out of, the graded areas via a transfer hatch (PTH1). The Vestibule also serves as the control centre for the unit because it houses Magnahelic gauges that monitor differential pressures between the rooms, a computer that displays the status of parameters monitored by the continuous monitoring system installed within the facility, and a CCTV camera display that relays images from the Grade B laboratories.

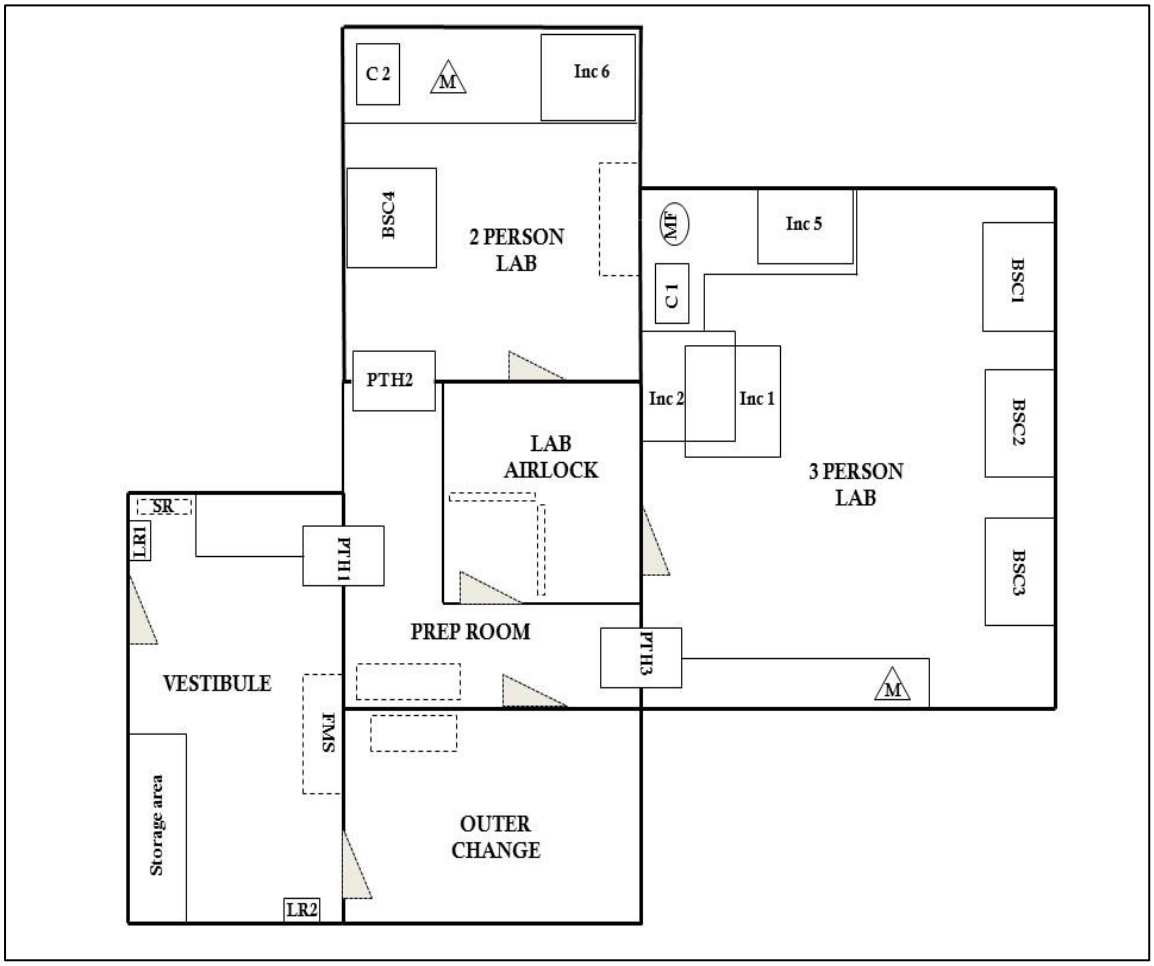
Entry into the graded areas is initially via the Change Room (Grade D/C), where outdoor clothes are removed and cleanroom undergarments are donned.

The Prep Area (Grade C) is where items are collected from the transfer hatches to be passed into or out of the facility. This area could also serve as an initial processing preparation area if required.

Within the Lab Airlock (Grade B), cleanroom garments are donned over the undergarments before entering the labs.

Finally, all tissue-processing operations are performed within the class II Biological Safety Cabinets (Grade A) in either the 2 Person Lab or 3 Person Lab (both Grade B).

Figure 1: Schematic diagram of the Cells for Sight facility



BSC: Biological Safety Cabinet SR: Shoe Rack MI: Mini-incubator

I: Incubator LR: Labcoat Rack S: Shelves

C: Centrifuge MF: Microfuge M: Microscope

PTH: Pass Through Hatch FMS: Facility Monitoring System

Processing equipment

- Validated continuous monitoring system to log all parameters associated to the facility and equipment within it (particle counts, pressure differentials, fridge and freezer temperatures, incubator CO2, RH, O2 and temperatures etc.)
- 4 x Class II BSCs
- 3 x CO_2 incubators
- 1 x multigas incubator
- 1 x mini incubator

- 4 x Fridges
- 4x Freezers
- 1 x -80°C freezer
- 2 x Bench-top Centrifuges (600 ml max capacity)
- 1 x Microfuge
- Potential for GMP cell cryopreservation, if required

Analytical equipment

- 2 x Nikon inverted light Microscopes
- 3 x Microbiological incubators
- Access to licensed QC labs for outsourced testing activities
- Also available on-site for early stage development work (not to GMP grade):
    - FACS
    - Q-PCR
    - HPLC
    - Plate readers
    - Spectrophotometer
    - Confocal microscopes
    - Transmission Electron Microscope
    - Cell sorting and separating facilities
    - Multiplex Reader- cytokine and chemokine assays

Figure 25 Example of clean room at Cells for Sight

7.8.3 Licence

The facility has an MHRA licence for MIA (IMP) manufacture, a Specials licence (MS) and a HTA licence.

7.8.4 Track record and experience

Cells for Sight have extensive experience as a cell therapy manufacturer working alongside both academic and commercial partners. The Cells for Sight Stem Cell Therapy Research Unit was established in 2005 and was the UK's first Medicines and Healthcare products Regulatory Agency (MHRA) accredited cultured stem cell facility. The team consists of a highly experienced, multi-skilled personnel and has a proven track record as:

a) Contract manufacturer, including the compilation and independent quality review of GMP documentation

b) Tech transfer activities, including the translation of research based protocols to GMP and subsequent validation of protocols at GMP

c) Early stage product development helping define the GMP process for future potential cell therapy products.

Cells for Sight has a wealth of expertise in the culture of both allogeneic and autologous limbal epithelial stem cells on tissue engineered scaffolds, for transplantation to patients (Specials). Within the stem cell field, we have experience of culturing limbal epithelial stem cells, buccal mucosal stem cells, corneal stromal stem cells, keratocytes and mixed population cells.

The team has also been responsible for, and been involved in the development of, two tissue engineered scaffolds, fibrin gels and collagen gels (RAFT). We have recently cultured epithelial cells on the fibrin scaffold for patients affected with Limbal Stem cell deficiency ('Specials').

They also recently manufactured a pioneering human embryonic stem cell based IMP for Pfizer Neusentis and The London Project. Our team was involved with process development for the product from its infancy all the way to clinical manufacture and product release. This involved development meetings, protocol writing, material risk assessments, equipment/process validations, training, and the successful continuous cell manufacture lasting many months.

The team is due to begin training for processing and labelling of blood products and for manufacture of cell banks, for other projects

Table 8 Summary of experience for Cells for Sight

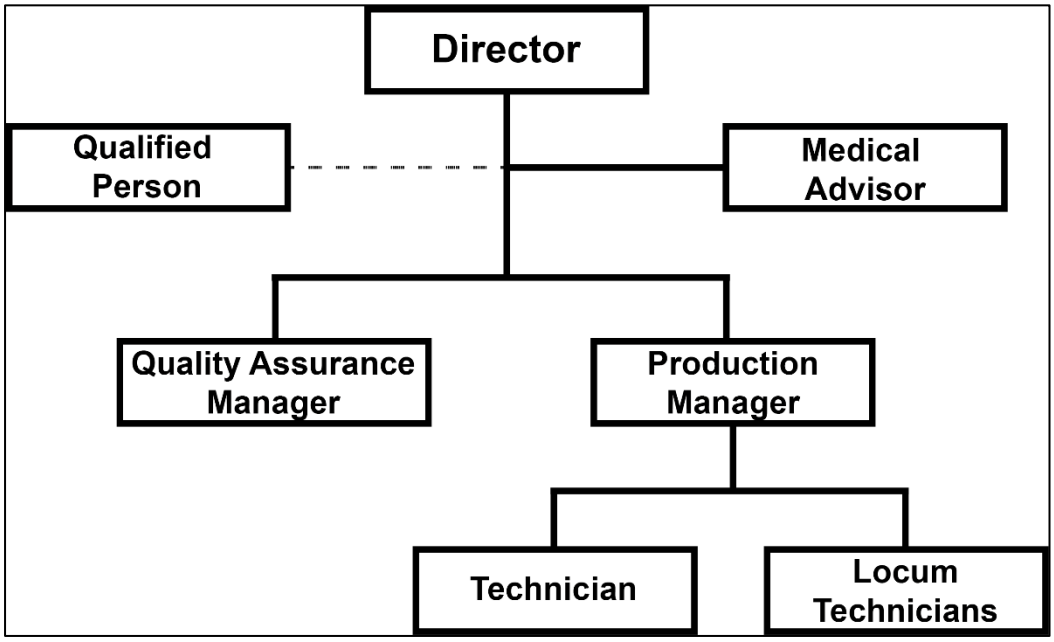
	Suspension	Adherent	2D	3D
Auto		✓	✓	✓
Allo		✓	✓	

Human ES Cell	IPS Cell	Cell isolation from donor tissue
✓		✓

7.8.5 Personnel

Key personnel include the Director (DI/licence holder), Production Manager, Quality Assurance Manager and one Research Assistant.
A contract QP is available for consultations, regular audits and batch release.
The Medical Advisor is available for consultations, clinical feedback and care of patients.
Additional staff may be supplied by the client, if required.

Figure 26 Organogram of Cells for Sight



7.8.6 Capacity

Depending upon the nature of the campaign, two different projects can be delivered concurrently at any one time in each grade B room. Different projects are run on a campaign basis with validated decontamination procedures in between each product type

Forecasted booked capacity:

2017 – 50%
2018 – 50%
2019 – 50%

7.9 NHS Blood and Transplant (NHSBT)

7.9.1 Details

NHS Blood and Transplant (NHSBT) has four sites with MHRA Manufacturer's Authorisation for IMPs covering cellular and molecular therapies. In addition, there are a further four laboratory sites with HTA licences.

Site address one
NHS Blood and Transplant
Advanced Therapies Unit
14 Estuary Banks
Estuary Commerce Park
Speke
Liverpool L24 8RB

Contact: Dr Eric Austin, Head of Laboratory, eric.austin@nhsbt.nhs.uk
Tel: 0151 268 7200

Site address two
NHS Blood and Transplant
Clinical Biotechnology Centre
Langford House
Lower Langford, near Bristol BS40 5DU

Contact: Dr Paul Lloyd-Evans, Head of Laboratory, paul.lloyd-evans@nhsbt.nhs.uk
Tel: 0117 928 9388

Site address three
NHS Blood and Transplant
Advanced Therapies Unit
Vincent Drive
Edgbaston
Birmingham
B15 2SG

Contact: Dr Phil Jenkin, Head of Laboratory, phil.jenkin@nhsbt.nhs.uk
Tel: 0121 278 4147

Site address four
NHS Blood and Transplant
Advanced Therapies Unit
500 North Bristol Park
Northway
Filton
Bristol BS34 7QH

Contact: Chris Bailey, chris.bailey@nhsbt.nhs.uk
Tel: 0117 912 5700

Additional contacts:

Contact: Teresina Pinnington, Business Development Manager,
teresina.pinnington@nhsbt.nhs.uk
Tel: 07889 304615

Contact: Dr Jon Smythe, Head of Cellular and Molecular Therapies, jon.smythe@nhsbt.nhs.uk
Tel: 01865 38 7967
Web: http://www.nhsbt.nhs.uk

7.9.2 Facilities at Speke

The NHSBT Speke facility has two grade B rooms currently dedicated to the manufacture of cell therapies. There are also additional grade B and grade C rooms shared with the NHSBT Tissue Services department. The department also has a dedicated QC laboratory.

Processing equipment

- Class II cabinets
- Isolator
- Bioreactors
- CO_2 incubators
- Sterile connecting devices
- Controlled rate freezers
- Liquid nitrogen storage vessels
- Centrifuges
- Orbital shaker
- 4°C storage pharmacy fridges
- Peristaltic pump
- Filter integrity tester
- Endosafe PTS
- Cytospin
- Line sealers
- Sepax 2
- Microscopes

Analytical equipment

- Haematology analyser
- Flow cytometer

Figure 17 Example of clean room at NHSBT (Speke site)

7.9.3 Licence

The Speke site has a MHRA licence for IMPs and a HTA licence.

7.9.4 Track record and experience

The ATU has experience of the genetic manipulation of T cells, cell selection and depletion protocols and broad cell culture knowledge. The unit also has experience of the isolation and culture of mesenchymal stem cells from bone marrow and umbilical cord plus peripheral blood stem cells for clinical trials. The laboratory has prepared master and working cell banks under GMP.

Table 9 Summary of experience for NHSBT

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	✓
Allo	✓	✓		

Human ES Cell	IPS Cell	Cell isolation from donor tissue
		✓

7.9.5 Personnel

The NHSBT site in Speke has six dedicated staff for IMP manufacture.

7.9.6 Capacity

Forecasted booked capacity:

2017 –90%
2018 –50%
2019 – 50%

7.9.7 Facilities at the Clinical Biotechnology Centre, Langford

The NHSBT Clinical Biotechnology Centre has four grade D rooms and three grade C rooms. One grade C room is dedicated to the aseptic filling of products in a pharmaceutical grade positive pressure isolator with a state of the art closed-vial sterile filling station. Class II MBSC or laminar flow cabinets are present in the other rooms dedicated to the manufacture of gene therapy and biotechnology products.

Processing equipment

- HVAC System
- Class II cabinets / laminar flow hoods
- Pharmaceutical grade positive pressure isolator with BioQuell Clarus L-3 VHP generator capabilities
- Fermentation systems
- AKTA chromatography equipment
- Highly purified water plant
- Incubators and shaker incubators
- Freezers, fridges and storage areas including liquid nitrogen storage vessel
- Centrifuges
- Peristaltic pumps
- GMP grade Autoclave
- Laboratory grade dishwasher
- Emulsiflex high pressure homogeniser
- Aseptic Technologies Crystal M1 closed-vial sterile filling station for dispensing of products

Analytical equipment

- UV / Visible spectrophotometer
- Filter integrity tester
- Endosafe PTS
- Microplate plate reader with fluorescence capability
- Osmometer
- pH & Conductivity meter
- Turbidity meter
- PCR equipment
- HPLC
- Electrophoresis equipment
- Gel analysis and documentation system
- Access to DNA capillary sequencer
- Environmental testing equipment

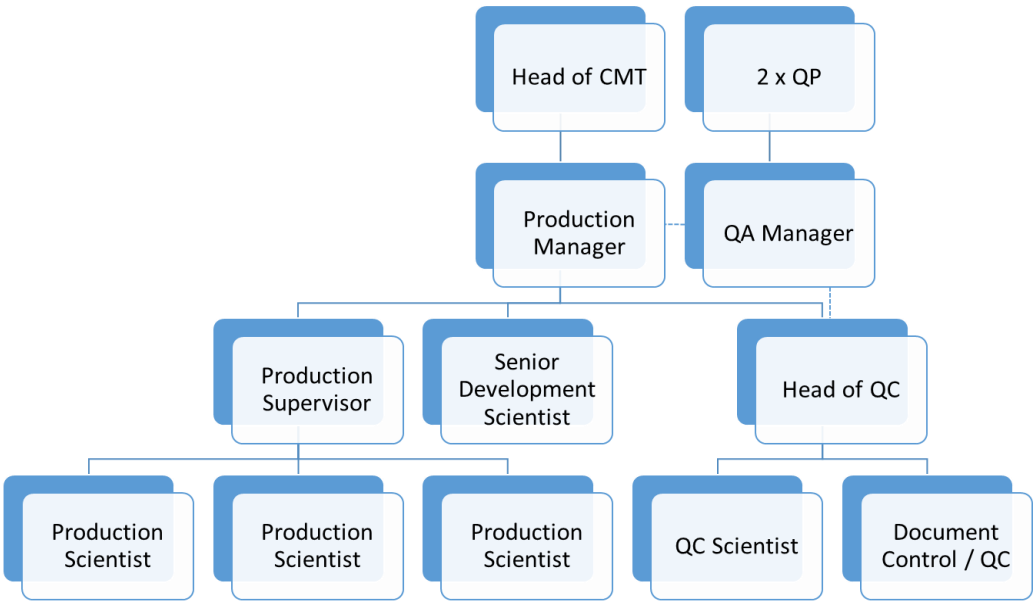
Figure 28 Examples of clean rooms and equipment at NHSBT (CBC site)

7.9.8 Licence
The CBC site has a MHRA licence for the manufacture and importation of molecular IMPs.

7.9.9 Track record and experience
The facility has experience in the manufacture of plasmid DNA vectors as direct vaccines or for use in viral vector manufacture, production of recombinant proteins, production of monoclonal antibodies and the conjugation of antibodies for therapy. To date the facility has manufactured over 50 plasmid DNA vectors, five recombinant proteins and been involved in over 14 clinical trials since 2001 (with over 400 patients treated). The CBC has developed an expertise in the manufacturing and testing of patient-specific DNA vaccines to current regulatory requirements.

7.9.10 Personnel
The NHSBT site in Langford has ten dedicated staff for IMP manufacture.

Figure 29 Organogram of CBC site



7.9.11 Capacity
CBC can process two products in parallel with a capacity of up to 15 to 20 products per year, depending upon scale. The current forecast for booked capacity is shown below:

2017 – 50%
2018 – 20%
2019 – 100%

7.9.12 Facilities at Birmingham

The NHSBT Birmingham facility has three grade B rooms with Class II MBSC dedicated to the manufacture of cell therapies. The department also has dedicated closed system processing, QC, advanced QC and development laboratories.

Figure 30 Images of the interior of the NHBTS Birmingham Facility

Processing equipment

- Class II cabinets
- CO_2 incubators
- Hypoxic incubator
- Terumo Sterile connecting devices
- Planar Controlled rate freezers
- Planar Dry Shippers & Ships Logger devices
- Liquid nitrogen bulk supply tank 17,000 Litres, supplying
- Liquid nitrogen storage vessels
- Vacuum Sealers
- Centrifuges
- Gambro 2991 cell washer / processor
- 4°C storage blood / pharmacy fridges
- -30°C storage freezers
- -80°C storage freezer
- Miltenyi CliniMACS immunomagnetic cell selector / depletor
- Endosafe PTS
- 22°C microbiological plate incubator
- 35°C microbiological plate incubator
- Ice machine
- Hand held non-viable particles counters
- Static non-viable particles counter
- Hand held viable particle counter
- Line sealers
- Sepax 2 cell processor
- Video / Light Microscopes

Analytical equipment

- Haematology analyser
- Flow cytometers

7.9.13 Licence
The Birmingham site has a MHRA licence for IMPs and an HTA licence.

7.9.14 Track record and experience
The Birmingham ATU has experience of cell selection and depletion protocols and broad cell culture knowledge. The unit also has experience of the isolation and culture of mesenchymal stromal cells from umbilical cord tissue for clinical trials.

7.9.15 Personnel
The NHSBT site in Birmingham has five dedicated staff for IMP manufacture plus another 10 staff for the broader workload.

7.9.16 Capacity
2019 – 33%

7.10 Newcastle Biomedicine Cellular Therapy Facility Newcastle Cellular Therapy Facility

7.10.1 Details

Address
Newcastle Cellular Therapies Facility
Newcastle University
3rd Floor, West Wing
Bioscience Centre
Times Sq
Newcastle University NE1 4EP

Contact: Anne Dickinson anne.dickinson@ncl.ac.uk
Tel: 0191 2086794
Web: www.ncl.ac.uk/ctf

7.10.2 Facility

The facility contains two suites one with four grade B clean rooms and a second with five grade B rooms. These processing labs are supported by two grade C preparation rooms that also provide access to the rooms.

Processing equipment

- MBSC (Class II)
- CO_2 incubators
- Refrigerated centrifuges
- Caridion Cobe 2991 cell processing equipment
- Water baths
- Blood warmer
- CliniMACS Plus
- Miltenyi Prodigy

Analytical equipment

- Microscope
- FACS
- PCR Thermocycler

Figure 31 Example of clean room at Newcastle Cellular Therapy Facility

7.10.3 Licence
MHRA licence for manufacture of IMPs and "Specials". The Facility also has a HTA licence.

7.10.4 Track record and experience
The Facility has experience with stem cell cryopreservation using controlled rate freezing, cell manipulation using COBE 2991 (separation of blood and bone marrow) and isolation of sub-populations using a CliniMACS. Development and culture of dendritic cells and mesenchymal stem cells, limbal stem cells and tolerogenic dendritic cells for ATMP clinical trials. Processing engineering experience and contract manufacture.

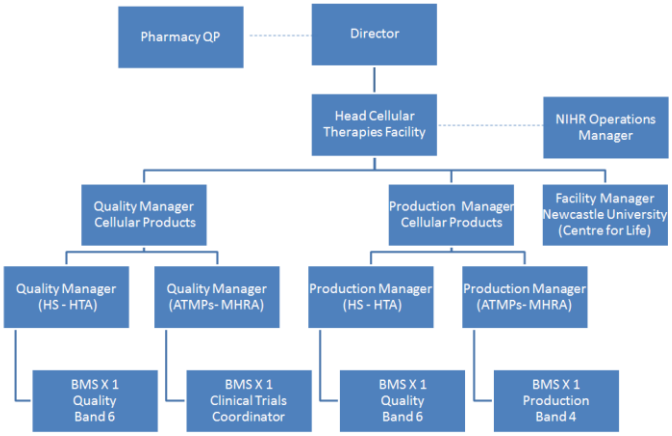
Table 10 Summary of experience for Newcastle Cellular Therapy Facility

	Suspension	Adherent	2D	3D
Auto	✓		✓	
Allo	✓	✓		

Human ES Cell	IPS Cell	Cell isolation from donor tissue
✓		✓

7.10.5 Personnel
The Facility employs 10 staff, including one QA/QC manager, production managers and one QP. An organogram for the company can be found in figure 31.
Figure

Figure 32 Organogram of Newcastle Cellular Therapy Facility



7.10.6 Capacity

The Facility has nine separate clean rooms and depending on the demand per project, it currently runs up to 5-6 separate projects during any one year. The predicted booked capacity at the facility for the next four years is listed below:

2017 – 50%
2018 – 50%
2019 – 40%

7.11 Oxford BioMedica

7.11.1 Details

Site addresses

Harrow House manufacturing facility
Oxford BioMedica (UK) Limited
Harrow House
Transport Way
Oxford
OX4 6LX

Yarnton manufacturing facility
Oxford Biomedica (UK) Ltd
Unit 5 Oxford Industrial Park
Yarnton
Oxford
OX5 1QU

Contact: Peter Nolan enquiries@oxfordbiomedica.co.uk
Tel: +44 (0) 1865 785300
Web: www.oxfordbiomedica.co.uk,

7.11.2 Facilities at Oxford BioMedica

Oxford BioMedica is a leading gene and cell focused biopharmaceutical company specialising in lentiviral based vectors for gene and cell therapy. Oxford BioMedica has a platform of technologies, intellectual property including know-how for underpinning the design, development and manufacture of unique gene-based medicines.

Oxford BioMedica has capabilities encompassing the full range of GMP manufacturing and analytical activities to support pre-clinical, research and bioprocessing development through to GMP manufacture and supply of clinical trial materials.

The company has three independent cleanroom facilities totalling 1200 m^2/12917 ft^2 of cleanroom area spread over two sites in and around Oxford. Each cleanroom suite/facility is configured with dedicated Upstream, Downstream, and media processing rooms, and utilise single use consumables for the entirety of the processes. Oxford BioMedica's third facility (GMP2), became operational in April 2016 delivering an additional 250m^2/2691 ft^2 of extra clean room space. Designed around a suspension lentiviral vector process, the facility incorporates a 50L/200L Single Use Bioreactor skid enabling routine GMP manufacture up to 200L. Both the GMP2 and Yarnton (GMP4) facilities can be configured to run adherent or suspension processes.

Each manufacturing site is operated independently, thereby providing a robust dual supply strategy for both Oxford BioMedica's own products and those of their partners. Adjacent to

the production cleanroom areas are an additional ~1100 m^2/11840 ft^2 of space providing warehouse, QC microbiology, offices and utilities.

Processing equipment:

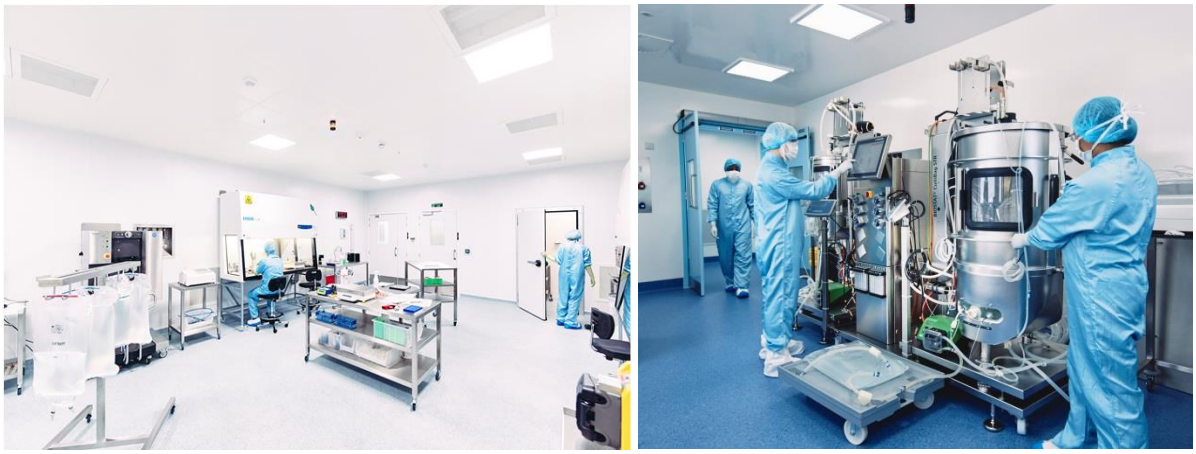
- CO_2 incubators (static and shaker)
- Microbiological Safety Cabinets
- Pallet tank mixers
- 50L/200L dual Single Use Bioreactor skid
- Peristaltic pumps
- Clarification rigs
- Filter integrity testers
- ÄKTA Ready liquid chromatography systems
- Centrifuges
- -150°C, -80°C and -20°C freezers

Analytical equipment

- HPLC System
- Flow cytometer
- Micro Plate Reader
- Automated nucleic acid extraction systems
- qPCR instruments
- UVP Biospectrum 500 gel documentation system
- Class II Biological Safety cabinets
- UV/Vis Spectrophotometer
- Cell culture equipped containment level 3 laboratories
- Cell counters
- Microscopes
- Centrifuges (floor and bench-top)
- Temperature mapped CO_2 incubators
- 4°C storage pharmacy fridge
- Temperature mapped -80°C and -150°C freezers
- pH meter
- Electrophoresis equipment
- LAL endotoxin reader
- TOC analyser

An example cleanroom at Oxford BioMedica is shown in figure 32

Figure 33 Example cleanrooms at Oxford BioMedica



GMP manufacturing is supported by a comprehensive array of validated analytical methods all housed within the companies new Windrush Court laboratory complex. The total laboratory space covers 2136 m^2/22992 ft^2, of which 470 m^2/5059 ft^2 comprises of GMP analytical lab space; the facility has 3 dedicated CAT3 suites for performing critical RCL testing.

7.11.3 Licence

Oxford BioMedica is MHRA licensed for IMP manufacture

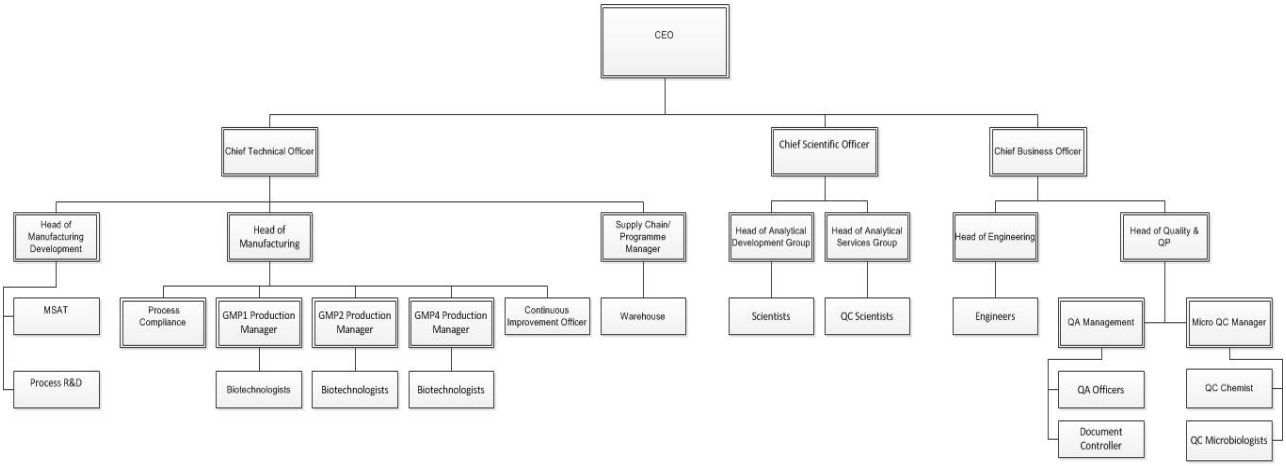
7.11.4 Track record and experience

Oxford BioMedica does not operate as a traditional contract manufacturing organisation (CMO). Instead Oxford BioMedica is a platform and product development company with a unique combination of technical expertise, vector-related intellectual property, a proprietary LentiVector® platform coupled with process development and in-house GMP manufacturing/analytical testing services and clinical & regulatory expertise. Multiple facilities that can be independently operated allows for the production of lentiviral based vector products for Phase I/II, Phase III clinical trials, and to support market supply.

7.11.5 Personnel

The manufacturing department currently consists of >50 biotechnologists who are supported by a process compliance team, warehouse, engineering, QC micro and MSAT functions. QC release testing is performed by the Analytical Service Group (ASG) overseen by the Chief Scientific Officer (CSO). Batch release is performed by the Qualified Person (QP) who also manages the QC micro function and QA officers.

Figure 34 The Staff Organogram for Oxford BioMedica



7.11.6 Capacity

Capacity is 1200m² of cleanroom processing space.

7.12 Rayne Cell Therapy Suite (RCTS) and The Wellcome Trust / BRC Clinical Research Facility and Cell Therapy Unit (CTU) at King's College London

7.12.1Details

Address
Cell and Gene Therapy at King's (CGT-K)
King's College London,
The Rayne Institute,
123 Coldharbour Lane,
London SE5 9NU, UK

Contact: Farzin FARZANEH Farzin.farzaneh@kcl.ac.uk
Tel:+44(0) 7848 5902/2900

Web:
http://www.kcl.ac.uk/lsm/research/divisions/cancer/research/sections/haematooncology/services/celltherapysuite.aspx

7.12.2Facility

The Rayne Cell Therapy Suite (RCTS) premises contain 40 m^2 of grade D clean rooms with two grade A isolators. This facility has operated as a GMP facility for the production of cell and gene therapy-based investigational medicinal products since 2001.

The Cell Therapy Unit (CTU) facility has a floor area of 420 m^2 and is separated into 7 clean rooms. The Cell and Gene Therapy at King's (CGT-K) suite contains two independent grade D areas complete with isolators. Each area is designed to handle separate products. Production runs in the CGT-K are conducted on a campaign basis with a "deep clean/decontamination" between the manufacture of different products. The Cell Isolation Suite has two grade C areas with Class II MBSC (Microbiological Safety Cabinet) for initial isolation of the starting material from donor tissue. The final steps of processing are carried out in an isolator in the same grade C background. Although the grade C areas in this suite are declared as such they are designed to function as Grade B rooms.

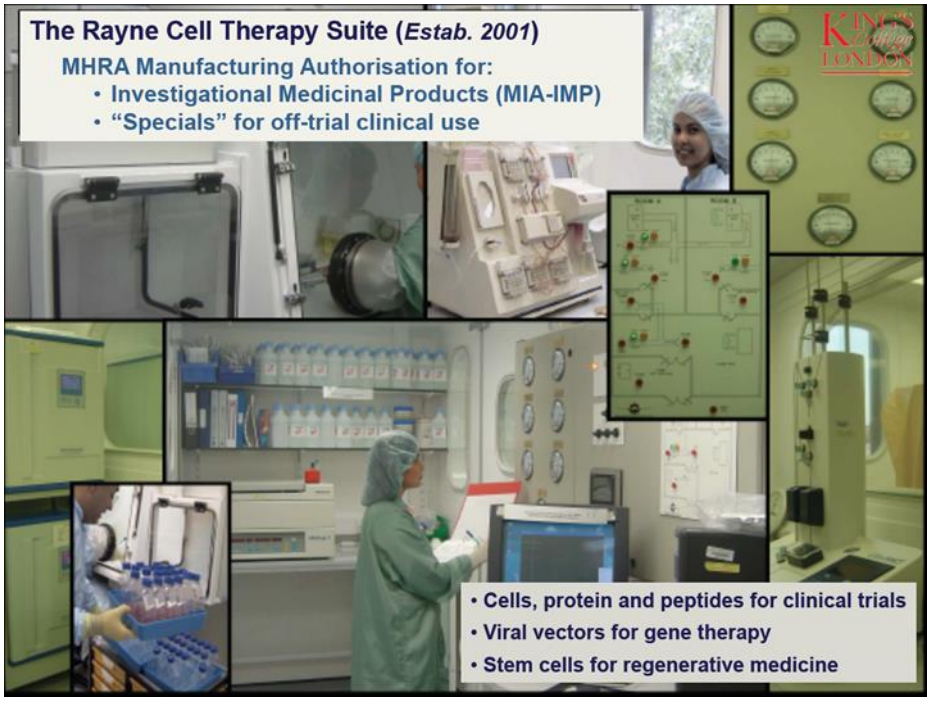
Processing equipment

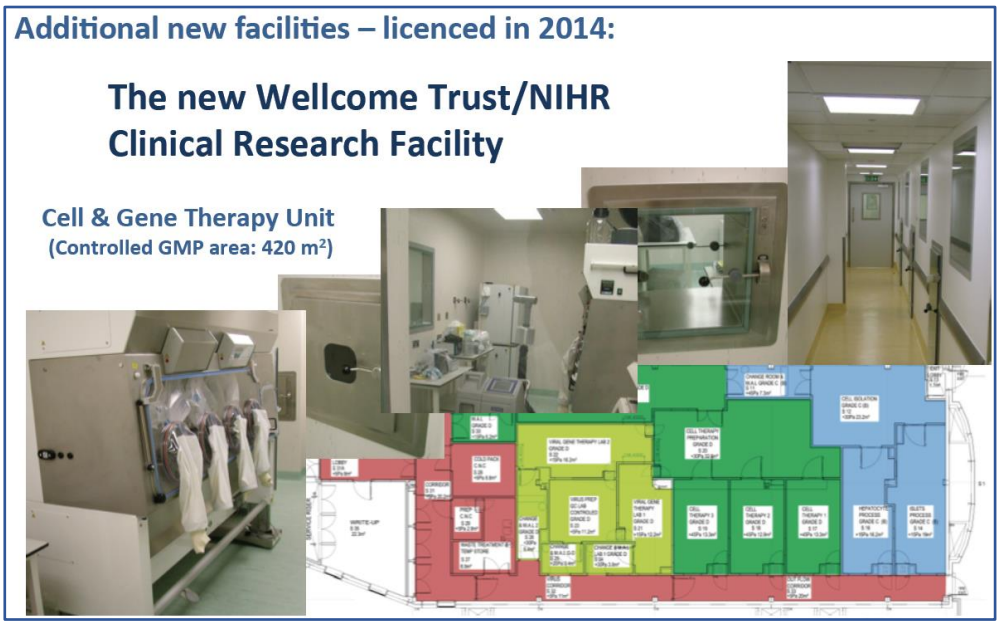
- Cell Culture Incubators.
- CO^2 Incubators.
- Centrifuges.
- Cryovial Filler/Capper.
- Controlled-Rate Freezer.
- 2 x Plasmatherm.
- Micro-Encapsulator.
- 2 x CliniMACS Cell Processing Systems.
- Plasma Expressor.
- Sepax Cell Separation System.

Analytical equipment

- 4 x Microscope – inverted.
- 2 x Microscope – fluorescent.
- 5 x Microscope – upright.
- Multi laser/colour FACSCanto and LSR Fortesa Analysers.
- FACSAria cell sorting.

Figure 35 Example of clean room at The Rayne Cell Therapy Suite



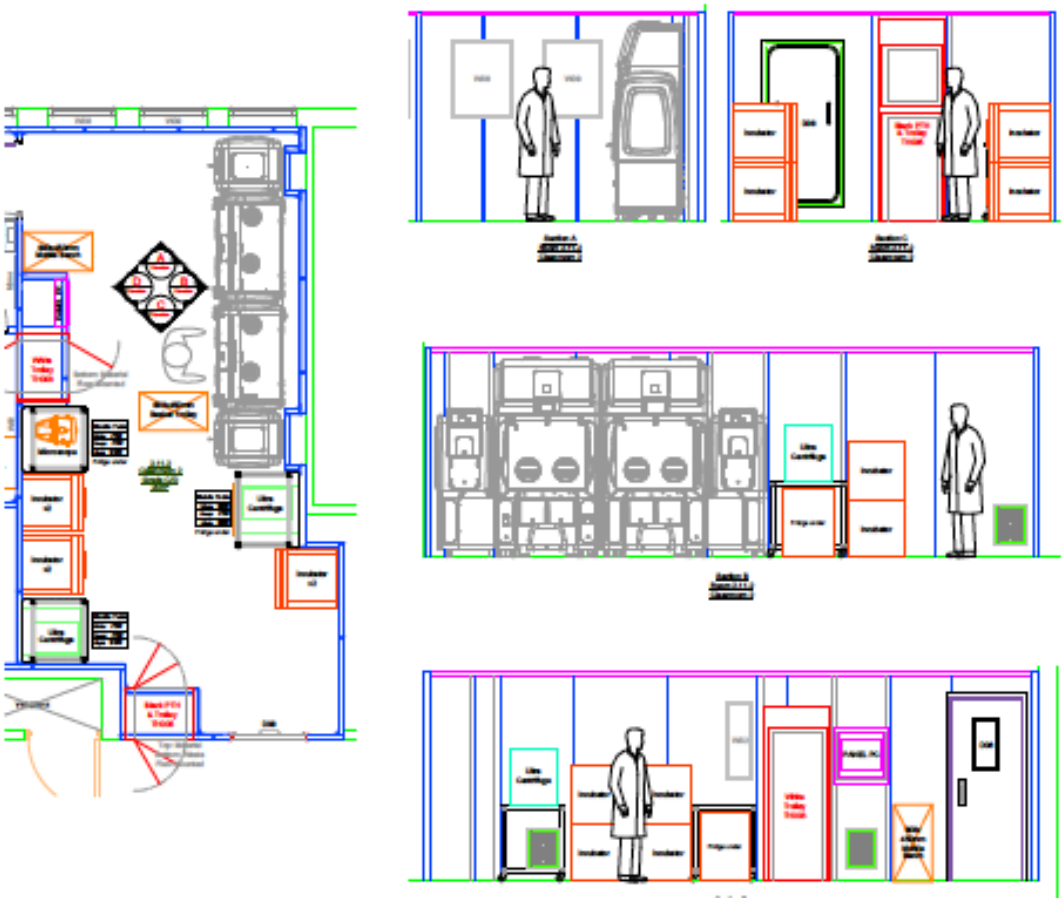


7.12.3Construction of New GMP Facility

Summer 2017 will see the expansion of our production capacity following the refurbishment of the RCTS, and completion of the construction of a new, state-of-the art GMP Manufacturing Suite in the Rayne Institute.

With a floor area of 59 m², the new facility will comprise, 2 grade D clean rooms housing isolators, incubators, centrifuges etc. for open and closed processing, a grade D Preparation Room used to service the isolator rooms, an outer lobby separating the clean rooms from the general corridor, and separate personnel airlocks between the Preparation Room and the isolator rooms.

Figure 36 Plan of new CGT-K manufacturing suite



7.12.4Licence

The RCTS facility holds MHRA Manufacturing Authorisation for Investigational Medicinal Products (MIA(IMP)) and a "Specials Manufacturer's" (MS) licence for the production of cell and gene therapy products for their off-trial clinical use. In addition it also has a HTA licence for the procurement, testing, processing, storage, distribution and/or import and export of tissues and/or cells intended for human applications. These licences cover the activities in both the RCTS and CGT-K facilities.

7.12.5 Track record and experience

The organisation has experience with dendritic cells for a variety of different indications, donor Natural Killer (NK) cells, mesenchymal stem cells and haematopoietic stem cells. They also have extensive experience with the manufacture of gene therapy products such as retrovirus and lentivirus vectors. This experience includes the manufacture of the largest number of retro- and lenti-virus based vectors for regulatory approved clinical trials in Europe and the manufacture of IMPs for a range of academic and industry sponsored Phase-I through to Phase-III clinical trials.

Table 11 Summary of experience for the Rayne Cell Therapy Suite and the Cell Therapy Unit

	Suspension	Adherent	2D	3D
Auto	✓			
Allo	✓	✓		

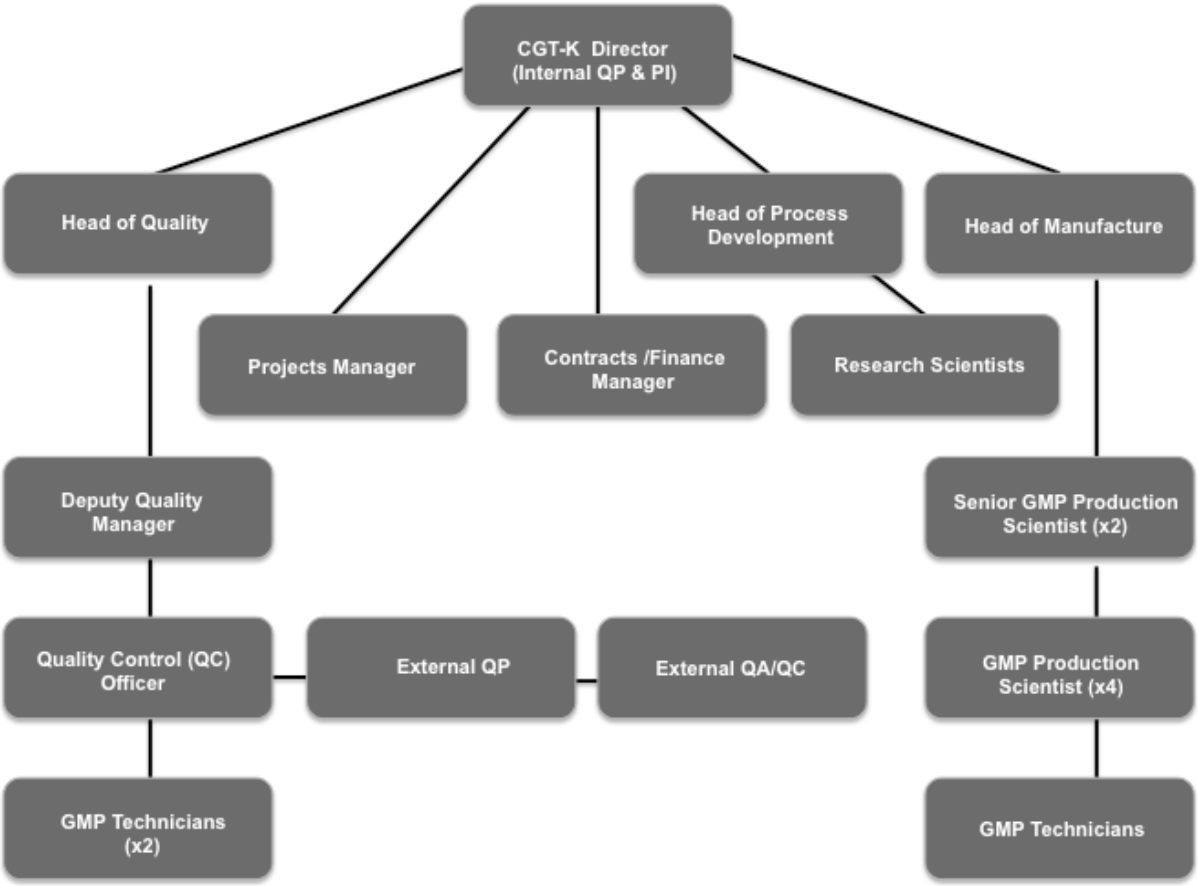
Human ES Cell	IPS Cell	Cell isolation from donor tissue
	✓	✓

7.12.6 Personnel

There are ten permanent members of staff at the RCTS and the CGT-K component of the Cell Therapy Unit. The current list of staff include:

To Be Appointed (TBA)	Head, Manufacture
Rebecca PRU	Head, Quality
David DARLING	Head, Process Development
Cristina TRENTO	Deputy Quality Manager
Yuqian MA	Senior GMP Production Scientist
Sabine DOMNING	Senior GMP Production Scientist
Alexandra ANDERSSON	GMP Production Scientist
Cameron BROWN	GMP Production Scientist
Philippa MARKS	GMP Production Scientist
Katarzyna WOLANSKA-HAJDUK	Quality Control Scientist
Mei-Mei FUNG	GMP Production Scientist
Emiljano RAKAJ	GMP Technician
x2 TBA	GMP Technician
Wendy COLLICOTT	External QA/QC (Pharma-Resolution)
David FARRER	External QP (Pharma-Resolution)
Felix MUNKONGE	Manager, Projects
Faith GREEN	Finance/Contracts
Farzin FARZANEH	Internal QP/PI/ Director

Figure 37 Organogram of the Cell and Gene Therapy at King's (CGT-K).



7.12.7 Capacity

The RCTS and the CGT-K components of the CTU can handle four separate projects at any time. In the current manufacturing campaigns the production of each batch of cell therapy product takes one to two weeks and the manufacture of each batch of gamma retrovirus or lentiviral vectors between 2 to 8 weeks.

Forecasted booked capacity

2017 – 50%
2018 – 40%
2019 – 30%

The new GMP manufacturing suite will provide a 50% increase in production capacity.

Roslin Cell Therapies Cellular Therapy Facility (Scottish Centre for Regenerative Medicine) and Nine Edinburgh bioQuarter

7.12.8 Details

Roslin Cell Therapies' manufacturing facility and Quality Control laboratories are situated within the Scottish Centre for Regenerative Medicine (SCRM). The company also has an established Cell and Gene therapy process development facility in Nine Edinburgh bioQuarter.

The facility was specifically designed for the development and manufacture of cellular therapies/ATMPS and contains 3 separate suites served by a dedicated Air Handling Unit.

Address

Cellular Therapy Facility
Scottish Centre for Regenerative Medicine
5 Little France Drive
Edinburgh BioQuarter
Edinburgh
EH16 4UU

and

Nine Edinburgh Bioquarter
9 Little France Road
Edinburgh
EH16 4UX

Contacts

Sue Bruce, Head of Commercial
Email: sue.bruce@roslincells.com
Tel 0131 658 5359

Janet Downie, Chief Executive Officer
Email: janet.downie@roslincells.com
Tel 0131 658 5182

Web: www.roslincells.com

7.12.9 Facilities at Roslin Cell Therapies

Manufacturing:

The Roslin Cell Therapies processing area is divided into 3 suites and consists of:

Suite 1:
1 Grade B processing room + 2 Grade A MSCs
1 Shared Grade C support room.

Suite 2:
1 Grade B processing room + 2 Grade A MSCs
1 Shared Grade C support room.

Suite 3:
1 Grade C processing room with CliniMACs and is awaiting fit out with a custom-built Cell Therapy Isolator.

Example cleanrooms at SCRM are shown in figure 37. Roslin Cell Therapies also has technology transfer cell culture facilities within the SCRM. The Cell Therapy Development team and the Process Development tissue culture facilities are based next door within Nine Edinburgh BioQuarter.

Processing Equipment:

- Cell culture incubators
- Centrifuges
- Controlled rate freezer (Planers and Asymptote)
- Ohaus Analytical Balance / Precision Balance
- Closed system cell processing – TSCD, Tube sealers, Transfer Bag centrifuges etc.
- CliniMACS plus cell selection system
- Portable ice-free cooling systems
- Dry block heaters
- Closed filtration system for large-scale media production
- Amaxa 4D Nucleofector

Quality Control:

Roslin Cell Therapies has an established GMP Quality Control department providing in house testing. In addition, Roslin Cell Therapies is located close to a number of GMP contract testing facilities with a full range of testing capabilities.

Analytical Equipment:

- AB 7900 HT Real Time PCR system
- 2720 Thermal Cycler
- Flow Cytometer (Guava EasyCyte)
- Biotek ELX808 Plate Reader
- Nanodrop ND1000 Spectrophotometer
- Pall Flowstar Filter Integrity Tester

Cell/Product Storage:

- Statebourne Vapour Phase LN_2 Storage Vessels
- Mechanical -150 °C Freezers

Cell Therapy Process Development

- qPCR / molecular suite and associated equipment
- gel tanks
- UV doc
- CliniMACS separation instrument
- Tissue culture and assoc equipment
- Quarantine Lab (primary cultures)
- Microscopy suite
- Flow Cytometer
- Controlled rate freezers (Asymptote)
- Mediboxes / dry shippers (for control temp shipment)
- Cryopreservation suite
- electroporators

Figure 38 Example of clean rooms at Roslin Cell Therapies

7.12.10 Licence

Roslin Cell Therapies holds an HTA licence, MHRA MIA (IMP) and Manufacturer's Specials licences for the facility.

7.12.11 Track record and Experience

Roslin Cell Therapies – Contract Manufacturing

The team at Roslin Cell Therapies has extensive cell therapy expertise and a wealth of experience to ensure projects progress to the highest quality from the very beginning, in a timely and cost effective manner.

The GMP team has many years' experience in the production and testing of cell therapies/ATMPs and GMP pluripotent stem cell banks. These include:

- Manufacturing drug substance cell banks for neuronal cell products.
- Manufacturing final product batches of pluripotent cell based products.
- Producing clinical grade cell banks for pluripotent stem cells.
- A range of adherent cell based products

They are also experienced in the practicalities of technology transfer of cell therapy/ATMP processes. The team has also performed the manufacture of some of the leading cell therapy clinical trials within the UK, including manufacturing for ReNeuron and Pfizer Neusentis.

Roslin Cell Therapies – Cell Therapy Process Development

The Cell Therapy Development team have many years of experience of translating academic cell therapy protocols to GMP, process development and the associated documentation required for GMP manufacturing. Specific services provided by the Cell Therapy Development Department includes;

- Vector design and production
- Transfection/transduction capability
- iPSC generation
- PSC culture
- Process scale up and automation
- Generation of cellular material for toxicology and engraftment study
- Cell characterisation
- Cell growth parameter optimisation
- Cell banking
- Gene editing
- GMP translation
- Assay design and qualification
- Process design, gap analysis, streamlining and qualification
- Differentiation strategy optimisation
- Final formulation optimisation
- Cryopreservation strategy optimisation
- Cold chain logistics and dispatch optimisation
- Reinfusion optimisation and logistics (clinical site)

Summary of experience at Roslin Cell Therapies

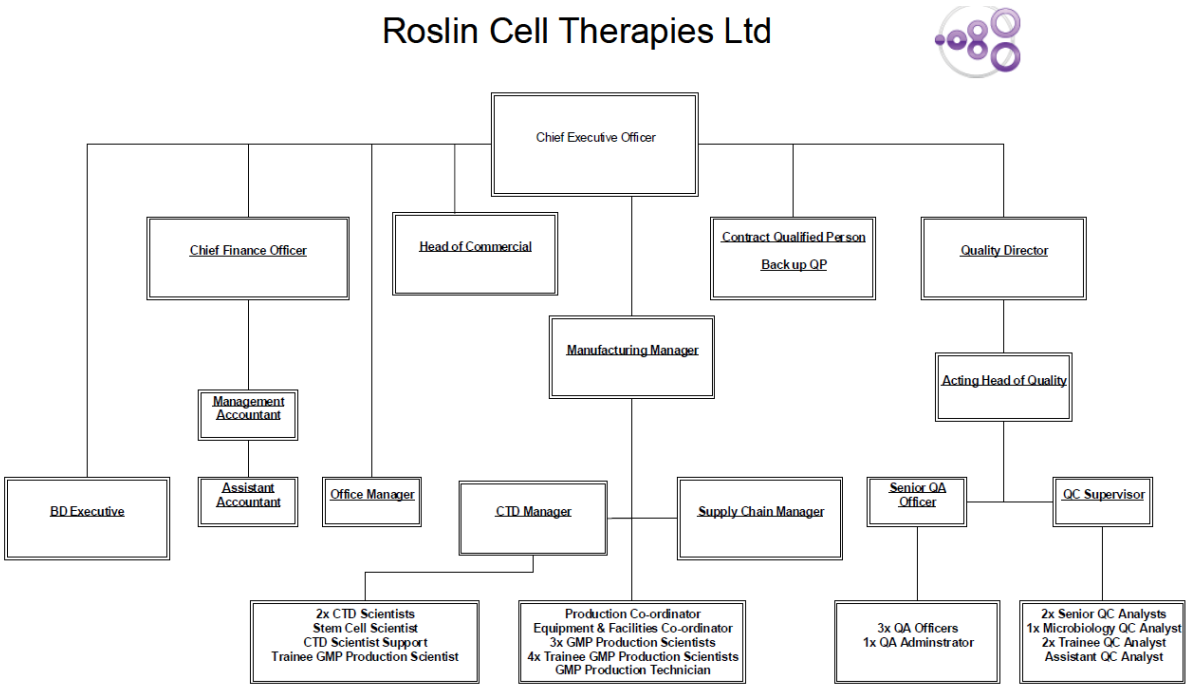
	Suspension	Adherent	2D	3D
Allo	✓	✓	✓	

Human ES Cell	IPS Cell	Cell isolation from donor tissue
✓	✓	✓

7.12.12 Personnel

Roslin Cell Therapies currently has 36 employees focused on our Cell Therapy Manufacturing and Development Services based in Edinburgh. The core team are organised into 4 departments; Production, Quality Control, Quality Assurance and Cell Therapy Development. The Organogram for Roslin Cell Therapies is shown in Figure 39

Figure 39 Organogram of Roslin Cell Therapies



7.12.13 Capacity

The amount of forecasted booked manufacturing capacity currently forecast at the facility can be seen below.

2017 – 75%
2018 – 50%
2019 – 50%

7.13 Royal Free Hospital London, Centre for Cell and Gene Tissue Therapeutics

7.13.1 Details

Site address
Royal Free Hospital
Pond Street
London NW3 2QG

Contact: Dr Mark Lowdell, Director of Cell Therapy & Qualified Person
Tel: 020 7830 2183

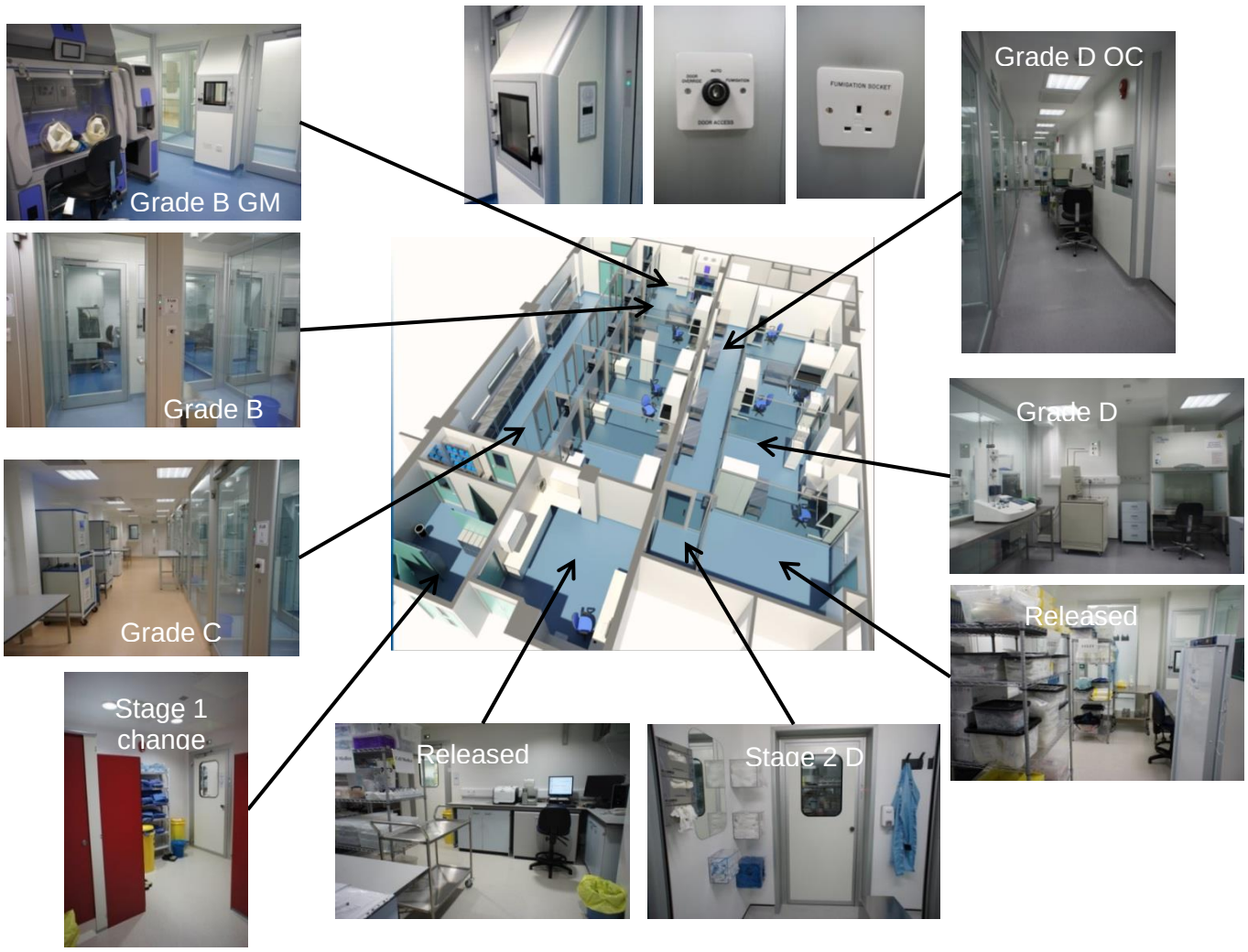
Additional contacts:
Contact: Dr Owen Bain, Head of QC
Tel: 020 7794 0500 x33140

7.13.2 Facility

The CCGTT is an ATMP manufacturing unit owned and operated by the Royal Free London NHS FT providing a core facility for the manufacture and storage of all three types of ATMP to full GMP compliance under licences from the MHRA (MIA IMP / MS) and the HTA. It consists of a suite of 10 GMP laboratories with 5 associated support rooms (two Quarantine Goods stores, two Released Goods stores and male/female changing rooms) on the lower ground floor at RFH plus two Quality Control labs, one GMP Process Development lab and three staff offices on the first floor, the RFH/UCL biobank cryogenic cell repository on the first floor and two offices on the second floor.

The suite consists of 4 grade D laboratories (including a lab for in-process QC accessible from D and B labs), 1 large grade C laboratory for long-term "closed" cell expansion and 5 individually isolated grade B labs with individual grade B gowning compartments to prevent cross-contamination. One of the grade B labs is dedicated to handling GM products under negative pressure within a positive pressure background.
Each B lab is maintained at +50Pa to atmospheric air pressure and there is a 10-15Pa air cascade through each grade of laboratory and there is no air recirculation; fresh air enters each laboratory through a terminal Hepa filter and is removed via a low level extract. Air change rates vary from 70 AC/H in the B labs to 28 AC/H in the D labs. Continuous particle monitoring is provided in each of the class II microbiological safety cabinets and the QUBE isolator which provide the grade A environments.
Each laboratory can be completely isolated from the others for fumigation with vapourised hydrogen peroxide. The GMP manufacturing facility is shown in figure 40.

Figure 40 GMP Manufacturing facility at CCGTT



7.13.3 Licence

MHRA MA(IMP) MS 11149 / HTA licence 11016

7.13.4 Track record and experience

The CCGTT has the skills and resources to undertake GMP conversion of almost any process for any type of ATMP and has taken multiple somatic cell therapies and now three tissue-engineered 3-D structures to clinical use. They have QA and QC skills and a QP in-house to release ATIMPs. They can draft IMPDs, IBs, PSFs, SOPs and BMRs and manage them within their in-house document control system. The CCGTT can train staff to work in a GMP compliant manner and have routinely done so. These resources are largely provided by the core NHS staff and the facility currently has no excess capacity.

The CCGTT has successfully supported 5 commercial clinical trials and has a number under negotiation at present.

- Pre 2001-83-EC
  - Autologous IL-2 primed NK cells in AML
  - Autologous TIL in RCC
  - Autologous LAK in Ca Ova
  - Allogeneic NK in AML
  - DC primed sib allo CMV-specific T cells
- Post 2001-83-EC
  - Sib allo CMV T cells by IfnG catch
  - DC-Vax in glioma
  - HuESC retinal epithelia – PhI commercial
  - Allogeneic NK cell therapy for AML – PhI/IIa PhII commercial
  - Two, matched allogeneic anti-viral T cell products - PhI/IIa commercial
  - Autologous stem cell seeded cadaveric tracheal tissue engineered products
  - Autologous stem cell-derived cell seeded biocompatible tissue structure tissue engineered products
  - Autologous stem cell seeded cadaveric laryngeal tissue engineered products
  - Large scale MCB and WCB of allogeneic MSC carrying a single gene insertion (lentiviral)
  - Autologous iPS cells
  - Autologous MSC for tendonopathy

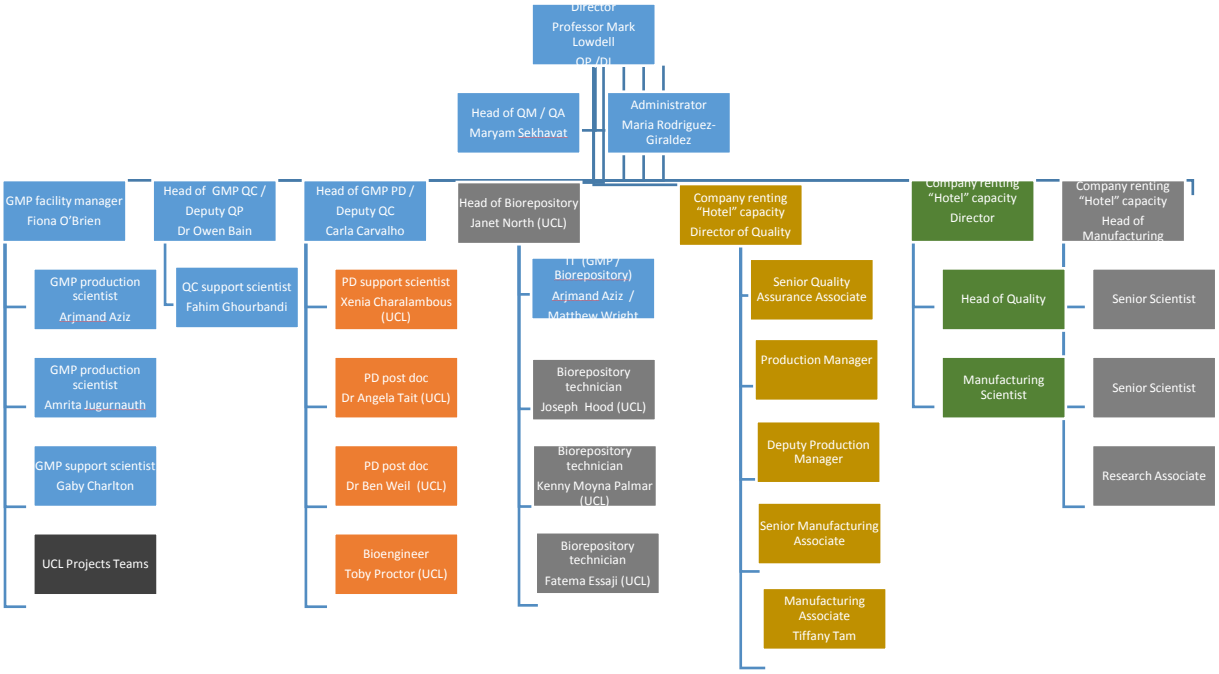
Table 12 Summary of experience at CCGTT

	Suspension	Adherent	2D	3D
Allo/ Auto	✓	✓	✓	✓

Human ES Cell	iPS Cell	Cell isolation from donor tissue
✓	✓	✓

7.13.5 Personnel

Figure 41 Organogram showing organisation structure at CCGTT



7.13.6 Capacity

The amount of booked capacity currently forecast can be seen below.

2017 – 100%
2018 – 100%
2019 – 100%

7.14 Advent Bioservices Ltd

7.14.1 Details

Site address

CCGTT
Room 1/458
1st Floor
Royal Free Hospital
Pond Street
London
NW3 2QG

(Under development)
Vision Centre
A1301 Sawston Bypass
Cambridgeshire
CB22 3JG

Contact:
Tina Crombie
Head of Business Operations
tcrombie@adventbio.uk

Tel: 0203 457 1080/ 07905 658843

Additional contacts:

Contact:

Angie Jamison
Director of Quality
ajamison@adventbio.uk

Tel: 0203 457 1080 / 07715 011188

7.14.2Facility

Advent Bioservices Ltd is a cell therapy Contract Manufacturing Organisation currently operating from the Royal Free's CCGTT manufacturing unit, under the CCGTT licences. The facility consists of GMP laboratories, two quarantine goods stores, two released goods stores, and male/female changing rooms, two Quality Control labs, one GMP Process Development lab and staff offices as well as RFH/UCL biobank cryogenic cell repository.

Advent Bio plans to build its own licensed facility in Cambridgeshire, the details of which are located in the forward looking statement in the previous section of this report. Images captured of the facility and further details are provided below.

Figure 43 Images of Advent Bioservices new Cambridgeshire facility

Sawston Vision Centre external

Sawston Vision Centre QC lab showing pass through from B lab

7.14.3 Licence

CCGTT MHRA MA(IMP) MS 11149 / HTA licence 11016

7.14.4 Track record and experience

Allo/Auto	Suspension	Adherent	2D	cells from tissue	cell banking
✓	✓	✓	✓	✓	✓

7.14.5 Personnel

2017:

GMP Team of 4
Quality Team 2
QP through CCGTT

7.14.6 Capacity

Forecasted booked capacity

2017 – 75%
2018 – 50%
2019 – 50%

7.15 Scottish National Blood Transfusion Service (SNBTS) Advanced Therapeutics (Scottish Centre for Regenerative Medicine and Jack Copland Centre)

7.15.1 Details

SNBTS has manufacturing facilities in Edinburgh based at the Scottish Centre for Regenerative Medicine (SCRM) and will open new facilities at the Jack Copland Centre (JCC) in 2017.

These facilities were specifically designed for the development and manufacture of cellular therapies/ATMPs and contain a total of 10 classified cleanroom areas of various grades, served by dedicated air handling units.

Address

SNBTS Cellular Therapy Facility
Scottish Centre for Regenerative Medicine
5 Little France Drive
Edinburgh BioQuarter
Edinburgh
EH16 4UU

SNBTS Jack Copland Centre
Research Avenue North
Heriot Watt University Research Park
Riccarton
Currie
Edinburgh
EH14 4AP

Contacts

Prof. John Campbell: Associate Director, Advanced Therapeutics
Email: johncampbell3@nhs.net
Tel: 0131 314 5677

Dr Neil McGowan: Cellular Therapy Project Manager
Email: neil.mcgowan@nhs.net
Tel: 0131 651 9572

Web: http://www.scotblood.co.uk

7.15.2 Facilities at SNBTS

Manufacture:

4 Grade B cleanrooms with a minimum of 2 Grade A MSCs in each.

4 Grade C cleanrooms with Grade A MSCs and/or isolators – tissues and closed processes.

Grade D manufacturing areas (3 enclosed rooms and extensive manufacturing 'pods').

Extensive Grade C support space.

Characterisation & QC:

GMP cell analysis, including Flow Cytometry and Cell enumeration.

Extensive in-house testing facilities (virology, bacteriology and endotoxin).

Equipment:

- 2x GE Excellerex 10L bioreactor
- 2x CliniMACS plus
- 3x CliniMACS prodigy
- >10 Cell culture CO_2 incubators
- >10 Centrifuges
- 4x Controlled rate freezer (Planers)
- Closed system cell processing – TSCD, Tube sealers

Analytical Equipment:

- FACS Canto II
  - Sysmex haematology analyser
  - Evos imaging microscopes (x4)
  - MACsQuant Tyto GMP Cell Sorter

Cell/Product Storage:

- Extensive -80^{o}C and Vapour Phase LN_2 Storage

7.15.3 Licence

SNBTS holds an HTA licence and MHRA MIA (IMP), MS, BEA and WDL.

7.15.4 Track record and Experience

SNBTS has experience in the manufacture of a range of cellular therapy products, under appropriate HTA, MHRA specials or MIA(IMP) licences. These include CD133+ autologous stem cells, EBV-specific cytotoxic T cells, corneal epithelial stem cells, autologous macrophage therapy for cirrhosis (MATCH trial) and an endothelial cell product for vascular repair.

This is in addition to the provision of blood products, tissues (bone, tendons, heart valves, skin) and well-established cell therapy products (haematopoietic progenitor cells and pancreatic islet cells for the treatment of a range of haematopoietic malignancies and diabetes respectively).

SNBTS also has extensive cell therapy translational research laboratories at SCRM and JCC which are involved in novel process development through to the final translation of several

other novel cell therapy products, in particular this includes establishing GMP banks of MSCs and iPSC cells.

7.15.5 Personnel

SNBTS employs 12 full time team members in the GMP manufacture of cellular therapies and receives extensive R&D and QA support from wider SNBTS.

7.15.6 Capacity

The amount of booked capacity currently forecast at SNBTS is as follows:

2017 – 75%
2018 – 50%
2019 – 50%

7.16 University of Birmingham, Cell Therapy Suite

UNIVERSITY OF BIRMINGHAM

7.16.1 Details

Site address:
Cell Therapy Suite
Advanced Therapies Facility
College of Medical and Dental Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

Contact: Dr Jane Steele
Email: j.c.steele@bham.ac.uk
Tel: 0121 414 7668

Contact: Professor Phil Newsome
Email: p.n.newsome@bham.ac.uk

7.16.2 Facility

The cleanroom suite includes 2 biological safety cabinets (BSC, Grade A), a processing laboratory (Grade B), change room (Grade B/C), preparation room (Grade C), change room (Grade C/D) and an unclassified store room, office, lobby and locker room. There is a separate QC laboratory, freezer room and cryostore containing liquid nitrogen storage and a controlled rate freezer.

The Cell Therapy Suite is joined onto the adjacent NIHR/Wellcome Trust Clinical Research Facility, under the governance of University Hospital Birmingham NHS Foundation Trust, where manufactured products can be administered to patients in an appropriately staffed and monitored environment.

An objective in 2017 is to get an additional cleanroom suite licensed for potential projects This suite consists of 2 negative pressure isolators (Grade A) located in a Grade B laboratory, sink room (Grade B), change room (Grade B/C), preparation room (Grade C), change room (Grade C/D) linked to the shared unclassified store room.

Processing equipment

- Environment Monitoring System
- Temperature Monitoring System (Tutela) for Fridges, Freezers, Incubators
- Cobe 2991
- CliniMACS
- Prodigy
- 4 x standard CO2 incubators
- Tube sealers, centrifuge, microscope

Analytical equipment

- MACSQuant analyser
- Endosafe PTS Endotoxin Detector
- TECAN Infinite Spectrophotometer
- Microbiology QC
- GMP and process development assays

7.16.3 Licence

MHRA licence for IMPs and an MS specials licence. The facility does not have an HTA licence (at present).

7.16.4 Track record and experience

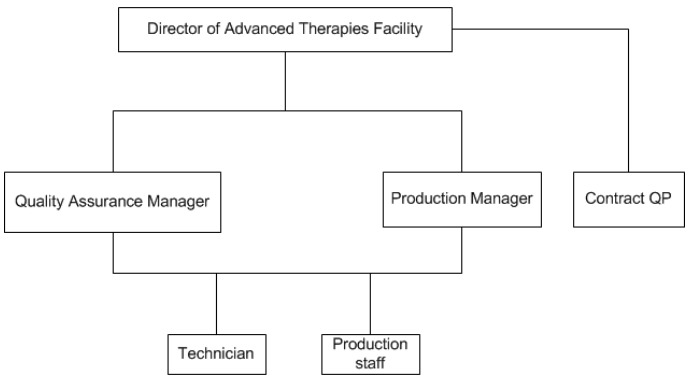
Production for the first clinical trial commenced in June 2016. This involves the manufacture of autologous dendritic cells from patients with hepatocellular carcinoma. The site is also open to a second clinical trial preparing stem cells for release to patients with Acute Respiratory Distress Syndrome.

7.16.5 Personnel

An organogram can be seen in Figure . The facility is regulated by the Advanced Therapies Facility Management Committee which oversees the direction, management, governance and finances.

There is a full time Production Manager, Quality Assurance Manager and technician on site maintaining the Cell Therapy Suite – further technical and production staff is employed on a project by project basis as required. The unit sub contracts a Qualified Person for batch release.

Figure 43 Organogram of organisation structure at University of Birmingham, Cell Therapy Suite



7.16.6 Capacity

The Cell Therapy Suite at the University of Birmingham has the capability to manufacture 2-3 different products simultaneously depending upon the timings and complexities of manufacturing protocols. The forecasted booked capacity is listed below.

2017 – 50%
2018 – 50%
2019 -0%
2020 – 0%

7.17 The University of Manchester Cleanroom Facility

7.17.1 Details

Site address
Core Technology Facility
46 Grafton Street
Manchester M13 9NT

Contact:
Professor Sue Kimber sue.kimber@manchester.ac.uk
Tel: 0161 275 6773
or
Joan Benson joan.benson@manchester.ac.uk
Tel: 0161 275 7436
Web: http://www.marm.manchester.ac.uk/pipeline/gmpfacility/

7.17.2 Facilities at University of Manchester Cleanroom Facility

The facility houses two grade B processing areas each containing 2 x Class II MBSCs; the grade B rooms each has a grade C support/preparation area. A QC testing laboratory is available for environmental monitoring, endotoxin and sterility testing.

Processing equipment

- CO_2 Incubators
- Class II MBSCs
- Centrifuges
- Microscopes
- Heat blocks
- Water baths
- Analytical balance
- LN_2 storage
- Controlled rate freezer
- Controlled temperature storage: ambient to -80°C

Analytical capabilities

- Automated endotoxin testing
- Automated rapid sterility testing (BacT/ALERT® 3D Signature)
- Microbiological and physical environmental monitoring

Figure 44 an example of the facilities at the University of Manchester

7.17.3 Licence

MHRA licence for manufacture of IMPs and a Specials licence. The facility also has HTA and HFEA licences.

7.17.4 Track record and experience

The University of Manchester Cleanroom Facility provides researchers with the ability to translate their research from basic studies and pre-clinical work, to clinical trials, by providing the capacity to generate clinical grade Investigational Medicinal Products (IMPs), Advanced Therapy Medicinal Products (ATMPs) and Specials. GMP derivation of hES cell lines hESCs differentiated to Chondrocytes, for repair of Osteoarthritis, development of a cell/gene therapy treatment for Duchenne Muscular Dystrophy Translation of a novel synthetic polymer nerve conduit for Peripheral Nerve Regeneration.

	Suspension	Adherent	2D	3D
Auto	✓	✓	✓	
Allo	✓	✓	✓	

Human ES Cell	IPS Cell	Cell isolation from donor tissue
✓	✓	✓

7.17.5 Personnel

The facility is headed by a University of Manchester professor who acts as senior management, the cleanroom has 6 staff and 2 consultant QPs.

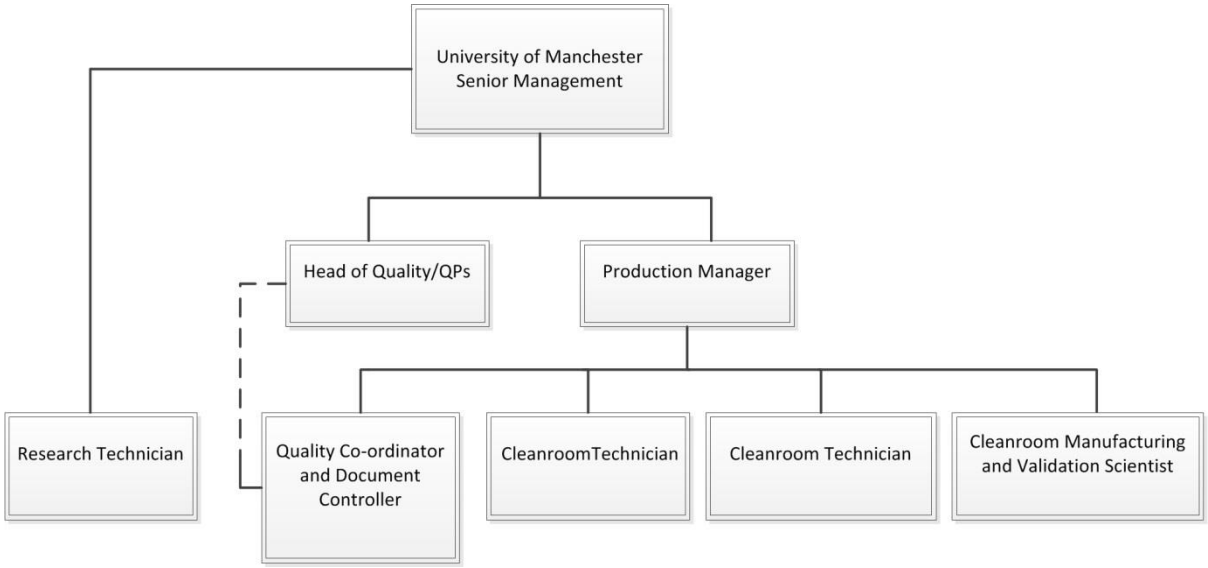


Figure 45 The organogram of the University of Manchester's facility

7.17.6 Capacity

Current and forecasted booked capacity at the facility is listed below:

2017 – 50%
2018 – 25%
2019 – 25%
2020 – 25%

7.18 University of Oxford Clinical BioManufacturing Facility

7.18.1 Details

Address
Clinical BioManufacturing Facility
University of Oxford
Old Rd
Headington
Oxford OX3 7JT

Contact: Eleanor Berrie Eleanor.Berrie@ndm.ox.ac.uk
Tel: 01865 744845
Web: http://www.cbf.ox.ac.uk/home

7.18.2 Facility

Manufacturing suites

- Five grade C rooms in total: one large 51m² room with two MBSCs, two rooms (23m² and 11m²) with one MBSC each, as well as two rooms with isolators: a smaller room of 10m² with a two-port isolator and a larger room of 17.4m² with a 4 glove isolator currently used for fill/finish but could also be used for manufacture.
- One grade D area 22.9m² for preparation, staging and inspection and a through wall pharmaceutical autoclave.

Processing equipment

- 2 x CO_2 shaking incubators
- 2 x static CO_2 incubators
- 4 x Class II MBSCs
- 4-glove isolator
- 2 glove isolator
- 2 ultracentrifuges
- 3 low speed centrifuges
- AKTA pilot

Analytical capabilities

- Endotoxin measurement
- Sterility check
- DNA and protein quantification
- Access to FACS analysis
- Molecular Biological Capabilities (QPCR, PCR, enzyme restriction analysis, sequencing)
- Analytical QC testing for viral vector applications
- Analytical QC testing for residuals

- Other QC testing can be outsourced

Photos showing the finish of the clean rooms can be seen in Figure .

Figure 46 Example photos of Oxford CBF facility

7.18.3 Licence

An MHRA MIA (IMP) licence has been granted which authorises cell therapy products, gene therapy products and many additional manufacturing capabilities. The facility does not currently have an HTA licence. The CBF has prior experience importing IMPs from outside the EU and certifying these to clinical trial in the EU.

7.18.4 Track record and experience

The facility has a great deal of experience with biologics production (recombinant proteins and viruses etc.). Adherent and suspension cell cultures have therefore been used for this purpose. Key staff have experience during previous employment with cell therapy manufacture (including viral transduction). A summary of their experience can be found in Table 13. Personnel at the Oxford CBF have a large degree of experience with viral vector manufacture which is a key component of gene modified cell therapies.

Table 13 Summary of experience for Oxford CBF

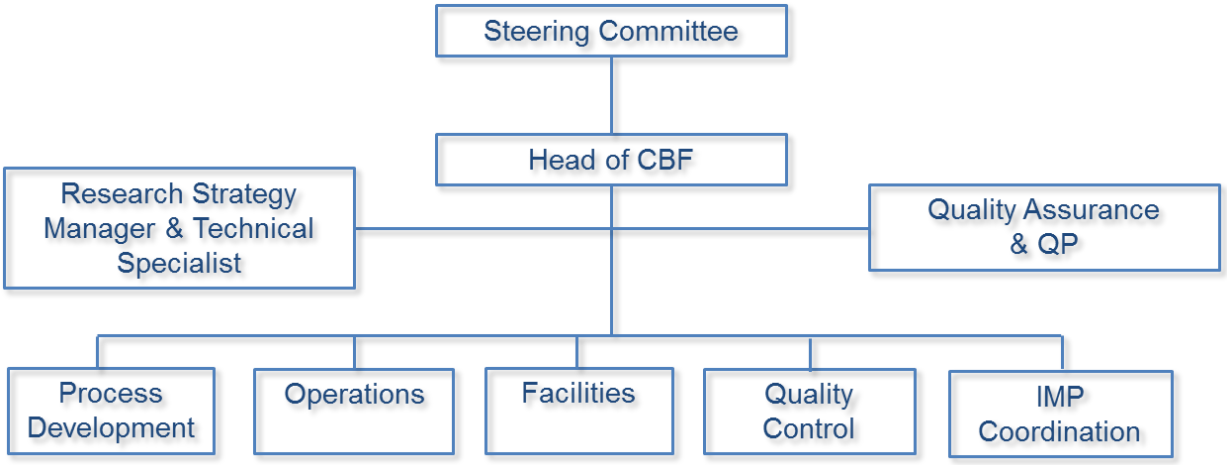
	Suspension	Adherent	2D	3D
Auto				
Allo	✓	✓		

Human ES Cell	IPS Cell	Cell isolation from donor tissue
		Previous Experience

7.18.5 Personnel

In total there are 16 members of staff are working within the facility. The site has one permanent QP onsite and 3 named contract QPs on their licence.

Figure 47 University of Oxford CBF Organogram



7.18.6 Capacity

The facility is currently working at capacity with respect to manufacturing work. The facility has plans for expansion which would mean a greater degree of capacity in the future.

Forecasted booked capacity

2017 – 100%
2018 –50%
2019 – 50%

7.19 Wolfson Gene Therapy Unit

University College London Hospitals NHS
NHS Foundation Trust

7.19.1 Details

Site address

Wolfson Gene Therapy Unit,
UCL Partners Gene Therapy Consortium
Department of Haematology,
University College London Hospitals,
51 Chenies Mews,
London WC1E 6HX

Contact: Professor Robin Ali, Director, UCL Partners Gene Therapy Consortium

Tel: 0207 608 6817 (UCL Institute of Ophthalmology)
0207 679 0703 (UCL Cancer Institute)

Office Address

UCL Partners Gene Therapy Consortium
Department of Haematology, UCL Cancer Institute
University College London
72 Huntley Street
London WC1E 6DD

Contact: Professor Robin Ali, Director, UCL Partners Gene Therapy Consortium
Tel: 0207 608 6817 (UCL Institute of Ophthalmology)

Contact: Professor David Linch, Head, Research Department of Haematology
Tel: 0207 679 6226 (UCL Cancer Institute)

Additional contacts:

WGTU Site Contact: Dr Eugene Arulmuthu, General Manager – Operations & Manufacturing, UCL Partners Gene Therapy Consortium

Tel: 0207 679 0703, 0207 679 6508

7.19.2Facilities at Wolfson Gene Therapy Unit

The Wolfson Gene Therapy Unit's (WGTU) primary purpose is to manufacture gene therapeutic viral vectors under GMP for use in phase I and phase II gene therapy clinical trials in humans. It is not within the remit of the WGTU to produce investigational veterinary products.

WGTU is designed to provide a flexible workspace permitting the production of different types of gene therapy products on a campaign basis. The facility comprised two clean rooms, one to Grade B and one to Grade C operating under negative pressure for Vector Production and Vector Purification operations respectively until Aug 2014. Currently, WGTU have installed a Grade A positive pressure Isolator with integrated Hydrogen peroxide vapour bio-decontamination system in the Vector Purification room and, both Vector Production & Vector Purification clean rooms are being operated to Grade C specifications under positive pressure.

The WGTU GMP unit at 51 Chenies Mews occupies a total area of about 60m^2 and has a clean room suite of 20m^2 with three secure storage areas of about 10m^2 in the basement. The QC laboratory of WGTU in the UCL Cancer Institute at 72 Huntley Street with an area of about 20m^2 is used for testing of in-process and manufactured products. WGTU has validated procedures for the production and purification of recombinant Adeno-Associated Viral (AAV) vectors for gene therapy applications, and sterile filling is has been developed and validated to fill a batch size of 300 vials per day.

General Critical Equipment

- Class II Bio-safety Cabinet (WGTU and QC Lab)
- Positive Pressure 4-Glove Isolator (Grade A)
- Bench-top Prestige Medical Autoclave
- Fridges (WGTU and QC Lab)
- -20 Freezers (WGTU and QC Lab)
- -80 Freezers (WGTU and QC Lab)
- Liquid Nitrogen Freezer
- Integrated Bioquell L3 HPV Gas Generator with Isolator

Production Equipment

- FMS Monitoring System and sensors
- Balances
- Centrifuges
- CO2 Incubators
- AKTA Pilot Purification System
- KrosFlo TFF System
- Microfluidiser
- Crystal M1 Filling Station

Analytical Equipment

- TSCAN Monitoring System and sensors
- Microplate Plate Reader
- Osmometer
- pH Meter
- qPCR Equipment

- Spectrophotometer
- Filter Integrity testing instrument
- Environmental air monitoring & Bioburden testing equipment
- Temperature Dataloggers
- Electrophoresis equipment
- Gel Analysis and documentation system

Figure 48 Example photos of Wolfson's gene therapy unit

7.19.3Licence

Authorisation Holder for MIA(IMP) 17022

University College London Hospitals NHS Foundation Trust
Trust Headquarters, 2nd Floor Central,
250 Euston Road
London NW1 2PQ

Contact Person: **Dr Christopher Holt / Dr Robert Urquhart**
Pharmacy Department, 235 Euston Road, London NW1 2BU

Tel: 0203 447 3028/27

WGTU Site ID: 1802424 under UCLH Authorisation MIA(IMP) 17022 (Sep 2015 - Current)

WGTU Site ID: 1802424 under NHS BT Authorisation MIA(IMP) 25224 (Jan 2011- Feb 2015)

7.19.4Track record and experience

No operations performed with respect to Cell Therapy

rAAV batches manufactured in GMP unit for pre-clinical studies until Feb 2015.
GMP batch of AAV2/5.OPTIRPE65 manufactured for Clinical Trials in Dec 2015.

7.19.5Personnel

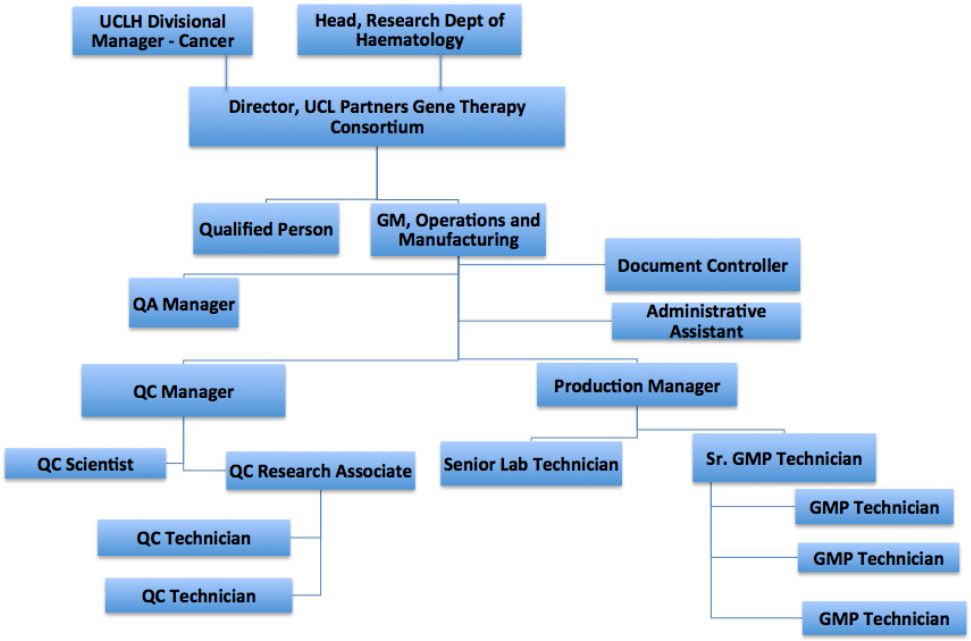


Figure 49 Wolfson's CBF Organogram

7.19.6Capacity

The forecasted booked capacity at WGTU for the next 3 years is listed below:

2017 – 100%
2018 – 75%
2019 – 50%