Cell and Gene Therapy GMP Manufacturing in the UK:
Capability and Capacity Analysis March 2016
Contents
1 Executive summary ............................................................................................................... 7
2 Introduction and methodology .......................................................................................... 11
3 Glossary of terms .............................................................................................................. 12
4 High level summary of data ................................................................................................ 13
  4.1 UK GMP cell therapy manufacture ............................................................................. 13
    4.1.1 High level summary ............................................................................................... 13
    4.1.2 Classification of clean rooms ............................................................................... 16
    4.1.3 Summary of track record and experience ............................................................... 17
  4.2 UK Gene Therapy Manufacture .................................................................................... 19
    4.2.1 High level summary ............................................................................................... 19
    4.2.2 Summary of track record and experience ............................................................... 23
  4.3 Geographic locations of cell therapy and gene therapy facilities .................................. 25
5 Future Capacity and Expansion .......................................................................................... 26
  5.1 Expansion of existing organisations .............................................................................. 26
  5.2 New sites ....................................................................................................................... 26
  5.3 Large-scale commercial supply capacity ...................................................................... 26
6 Manufacturing Organisations ............................................................................................. 28
  6.1 Cancer Research UK Biotherapeutics Development Unit ............................................. 28
    6.1.1 Details ....................................................................................................................... 28
    6.1.2 Facility ....................................................................................................................... 28
    6.1.3 Licence ....................................................................................................................... 29
    6.1.4 Track record and experience .................................................................................... 29
    6.1.5 Personnel .................................................................................................................. 30
    6.1.6 Capacity .................................................................................................................... 31
  6.2 Cellular Therapeutics Ltd (CTL) .................................................................................. 32
    6.2.1 Details ....................................................................................................................... 32
    6.2.2 Facility ....................................................................................................................... 32
    6.2.3 Licence ....................................................................................................................... 33
    6.2.4 Track record and experience .................................................................................... 33
    6.2.5 Personnel .................................................................................................................. 33
    6.2.6 Capacity .................................................................................................................... 34
  6.3 Biomedical Research Centres (BRC) GMP Unit at Guy’s and St Thomas’ .................... 35
    6.3.1 Details ....................................................................................................................... 35
    6.3.2 Facility ....................................................................................................................... 35
    6.3.3 Licence ....................................................................................................................... 36
    6.3.4 Track record and experience .................................................................................... 36
    6.3.5 Personnel .................................................................................................................. 37
    6.3.6 Capacity .................................................................................................................... 37
  6.4 Imperial College London, John Goldman Centre for Cellular Therapy ........................ 38
    6.4.1 Details ....................................................................................................................... 38
    6.4.2 Facility ....................................................................................................................... 38
6.4.3 Licence ................................................................................................................. 38
6.4.4 Track record and experience ......................................................................................... 39
6.4.5 Personnel ....................................................................................................................... 39
6.4.6 Capacity................................................................................................................ .......... 40

6.5 Rayne Cell Therapy Suite (RCTS) and The Wellcome Trust / BRC Clinical Research Facility and Cell Therapy Unit (CTU) at King’s College London ......................................................................................... 41
6.5.1 Details ................................................................................................................. ............ 41
6.5.2 Facility ................................................................................................................ ............. 41
6.5.3 Licence ................................................................................................................. .......... 42
6.5.4 Track record and experience ......................................................................................... 42
6.5.5 Personnel ............................................................................................................... ........ 43
6.5.6 Capacity................................................................................................................ .......... 44

6.6 NHS Blood and Transplant (NHSBT) ........................................................................ 45
6.6.1 Details ................................................................................................................. ........... 45
6.6.2 Facilities at Speke ................................................................................................. ..... 46
6.6.3 Licence ................................................................................................................. ........... 47
6.6.4 Track record and experience .......................................................................................... 47
6.6.5 Personnel ............................................................................................................... ........ 48
6.6.6 Capacity................................................................................................................ .......... 48
6.6.7 Facilities at the Clinical Biotechnology Centre, Langford ............................................ 49
6.6.8 Licence ................................................................................................................. ........... 51
6.6.9 Track record and experience .......................................................................................... 51
6.6.10 Personnel ............................................................................................................... ........ 51
6.6.11 Capacity................................................................................................................ .......... 51
6.6.12 Facilities at Birmingham ............................................................................................... 52
6.6.13 Licence ................................................................................................................. ........... 52
6.6.14 Track record and experience .......................................................................................... 52
6.6.15 Personnel ............................................................................................................... ........ 52
6.6.16 Capacity................................................................................................................ .......... 52

6.7 Roslin Cell Therapies Cellular Therapy Facility (Scottish Centre for Regenerative Medicine) .......................................................................................................................................... 53
6.7.1 Details ................................................................................................................. ........... 53
6.7.2 Facilities at Roslin Cell Therapies ................................................................................. 53
6.7.3 Licence ................................................................................................................. ........... 55
6.7.4 Track record and Experience .......................................................................................... 55
6.7.5 Personnel ............................................................................................................... ........ 56
6.7.6 Capacity................................................................................................................ .......... 57

6.8 Scottish National Blood Transfusion Service (SNBTS) Cellular Therapy Facility (Scottish Centre for Regenerative Medicine) ........................................................................................................ 58
6.8.1 Details ................................................................................................................. ........... 58
6.8.2 Facilities at SNBTS ................................................................................................. ..... 58
6.8.3 Licence .......................................................................................................................... 59
6.8.4 Track record and experience ....................................................................................... 59
6.8.5 Personnel ....................................................................................................................... 60
6.8.6 Capacity.......................................................................................................................... 60
6.9 Cellular Therapies, Great Ormond Street Hospital .......................................................... 61
6.9.1 Details ............................................................................................................................ 61
6.9.2 Facility ........................................................................................................................... 61
6.9.3 Licence ........................................................................................................................... 62
6.9.4 Track record and experience ....................................................................................... 62
6.9.5 Personnel ....................................................................................................................... 63
6.9.6 Capacity.......................................................................................................................... 63
6.10 Moorfields Eye Hospital, Cells for Sight Cell Research Unit ........................................... 64
6.10.1 Details ............................................................................................................................ 64
6.10.2 Facility ........................................................................................................................... 64
6.10.3 Licence ........................................................................................................................... 65
6.10.4 Track record and experience ....................................................................................... 65
6.10.5 Personnel ....................................................................................................................... 65
6.10.6 Capacity.......................................................................................................................... 65
6.11 Moorfields Eye Hospital, Cells for Sight Cell Research Unit ........................................... 66
6.11.1 Details ............................................................................................................................ 66
6.11.2 Facility ........................................................................................................................... 66
6.11.3 Licence ........................................................................................................................... 67
6.11.4 Track record and experience ....................................................................................... 67
6.11.5 Personnel ....................................................................................................................... 67
6.11.6 Capacity.......................................................................................................................... 67
6.12 Newcastle Biomedicine Cellular Therapy Facility ............................................................ 68
6.12.1 Details ............................................................................................................................ 68
6.12.2 Facility ........................................................................................................................... 68
6.12.3 Licence ........................................................................................................................... 69
6.12.4 Track record and experience ....................................................................................... 69
6.12.5 Personnel ....................................................................................................................... 69
6.12.6 Capacity.......................................................................................................................... 70
6.13 University of Oxford Clinical BioManufacturing Facility .............................................. 71
6.13.1 Details ............................................................................................................................ 71
6.13.2 Facility ........................................................................................................................... 71
6.13.3 Licence ........................................................................................................................... 72
6.13.4 Track record and experience ....................................................................................... 72
6.13.5 Personnel ....................................................................................................................... 72
6.13.6 Capacity.......................................................................................................................... 73
6.14 Royal Free Hospital London, Centre for Cell and Gene Tissue Therapeutics ................. 74
6.19.6 Capacity.................................................................................................................. 94
6.20 Wolfson Gene Therapy Unit .......................................................................................... 95
   6.20.1 Details ................................................................................................................... 95
   6.20.2 Facilities at Wolfson Gene Therapy Unit.............................................................. 95
   6.20.3 Licence .................................................................................................................. 97
   6.20.4 Track record and experience.................................................................................. 97
   6.20.5 Personnel ............................................................................................................. 98
   6.20.6 Capacity.............................................................................................................. 98
7 Conclusions ..................................................................................................................... 99
1 Executive summary

The Cell and Gene Therapy Catapult continues to review the status of MHRA MIA(IMP) licenced GMP manufacturing in the UK and publish on an annual basis. The report, now in its third year, is designed to collect evidenced-based information and provide an overall picture of the capability and capacity of UK MHRA-licenced cell and gene therapy manufacturing facilities. The review was initiated in 2013 and has been continued following a request in the government response to recommendation of an annual stocktake by the House of Lords 2013-14 inquiry into Regenerative Medicine. Previous year’s reports can be viewed at https://ct.catapult.org.uk/our-approach.

This survey, and its predecessors, have been dominated by facilities who are available to industry and academe through various contract or joint venture mechanisms. There is, however, a small but growing number of facilities who are not available to the general market and have been, or are in the process of, being built specifically for proprietary manufacturing purposes. These company-specific facilities shall be tracked throughout the coming year and reported on in the 2017 annual survey.

UK GMP Cell and Gene Therapy Manufacturing 2016

A snapshot of the nation’s GMP cell and gene therapy manufacturing resource for 2016 is captured in Figure 1. Over the last year, the network has grown from 18 to 22 GMP manufacturing facilities, supplying over 4300m² of licensed total cleanroom space (one company making products for their own clinical trials declined to take part in the survey). Over 50% of the total cleanroom operational space is dedicated to gene-therapy (>2400m²) whilst the cell therapy footprint is ~1900m². Over 90% of the gene therapy capacity is commercially owned space; which is in stark contrast to commercial cell therapy organisations, which account for less than 10% of the total cell therapy footprint. The remainder of the total cleanroom space is distributed between UK academia and the NHS. The network of facilities is supported by a 391 strong workforce with a diverse track record for a range of skills and technologies.

Figure 1 Snapshot of the UK GMP Cell and Gene Therapy Industry 2016
A list categorising all the facilities analysed in this review can be found below. The four new additions for 2016 are shown in **bold** and one transferred licence marked with an *:

**MHRA-licenced 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 – Speke
- Royal Free Hospital, CCGTT
- Scottish Centre for Regenerative Medicine (Roslin Cell Therapies and SNBTS)
- 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-licenced multifunctional cell and gene therapy manufacturers**
- Cancer Research UK, Biotherapeutics Development Unit
- King’s College London Cell Therapy Unit, Clinical Research Facility¹
- Kings College London, Rayne Cell Therapy Suite²
- University of Oxford, Clinical Biomanufacturing Facility

**MHRA-licenced gene therapy manufacturers**
- Bioreliance Ltd
- Cobra Biologics, Keele
- NHSBT – CBC Langford
- Oxford Biomedica, Harrow House, Oxford²
- **Oxford Biomedica, Yarnton, Oxford²**
- Wolfson Gene Therapy Unit

*University of Manchester GMP facility supersedes Intercytex Ltd in this report following transfer of MIA(IMP) licence from Intercytex Ltd, because of this the GMP facility at the University has been classed as a pre-existing facility rather than a new addition

**UK GMP Cell Therapy Manufacturing 2016**

During 2015/2016, a network of 16 facilities supplying ca. 1900m² cleanroom space met the demands of a buoyant cell therapy manufacturing sector. The growth seen over the last 12 months, including 5 additional cleanrooms and 39 jobs (see Figure 2), was mainly attributed to the addition of a newly MHRA-licenced site at NHSBT Birmingham and the inclusion of the University of Manchester’s footprint in this year’s analysis. The latter was not available to the market last year whilst MIA(IMP) licence transfer from Intercytex Ltd took place. Spare capacity levels across the 16 facilities varied between 0-50%, but on average remained low for the second year in a row at 24%, and equated to ca. 400m² of actual free cleanroom space. Sustained low spare capacity demonstrates the continued strong demand for cell therapy manufacturing space, but also highlights the potential risk of manufacturing demand exceeding available manufacturing capacity in the short-medium term. In mitigation, a number of manufacturing facilities have considerable planned expansion projects on the horizon to boost existing cleanroom space by an estimated ca. 1000m²; this is in addition to the Cell and Gene Therapy Catapult Manufacturing centre, which remains on track to deliver a step

¹ Combined for analysis in section 4 of the review
² Combined for analysis in section 4 of the review
change in large-scale manufacturing capacity delivering 2292m² of cleanroom space over two production floors within a 7200m² building footprint.

**Figure 2 UK GMP Cell Therapy Manufacturing Sector Growth 2015/2016**

**UK GMP Gene Therapy Manufacturing 2016**

Gene therapy production in the UK continued to thrive in 2016 as shown in Figure 3. Three new dedicated-gene therapy facilities were added to the review, doubling the number of listings to 6. Oxford Biomedica opened a second independent manufacturing site in Yarnton, Oxford. The other two new listings were pre-existing facilities at Bioreliance Ltd and the Wolfson Gene Therapy Unit. Bioreliance Ltd, an established viral vector manufacturer, scaled back a large client project in 2015 returning operational capacity to the market place, whilst the Wolfson Gene Therapy Unit completed a licence variation application in September 2015 and was granted MIA(IMP) authorisation under University College London Hospital. In addition to the footprint growth associated with new facility listings, increase in resources including the 31% rise in full time personnel was in part a reflection of the 3-fold increase in demand for gene therapy services reported at Cobra Biologics and on-going expansion projects at Oxford Biomedica. Even with the additional footprint, average spare capacity at the facilities dipped to 16% for 2016 equating to ca. 200m² of actual free cleanroom space (excluding Oxford Biomedica). However, average availability is anticipated to rise over 3-fold for 2017 to 53%, increasing free cleanroom space to ca. 1000m² (excl. Oxford Biomedica) which will help support the very rapid rise in recent demand within the sector.

**Figure 3 UK GMP Gene Therapy Manufacturing Sector Growth 2015/2016**
Future Outlook

Analysis of the technical capability of all the facilities was very positive, showing that the UK manufacturing sector covered the sphere of current cell and gene therapy manufacturing requirements. Most of the facilities specialising in cell therapy manufacture were located in the NHS or UK academia. The majority of these facilities have been established to enable the translation of academic research into clinical trials. This shows that the UK has a strong manufacturing base to facilitate the translation of early phase research into the clinic. In contrast to cell therapy production, the manufacture of viral vectors and plasmid DNA for gene modification processes is predominantly driven by commercial organisations.

The large-scale Cell and Gene Therapy Catapult manufacturing centre currently being constructed, has not been included in this analysis. This £55 million investment will be operational by the middle of 2017 and will allow companies to manufacture, at large (phase III) and commercial scales, both cell and gene therapies in a segregated flexible environment. This 7200m² manufacturing centre will provide a step change in large-scale and commercial cell and gene therapy manufacturing capability for the UK and complement the existing early phase network. This will join-up the translational landscape in the UK allowing therapies to move from basic research, into the clinic and finally to commercial production.

The extensive expansion in gene therapy production already witnessed in 2015/2016 plus the considerable planned GMP cell therapy expansion highlights the growth in cell and gene therapies in the UK. The combination of world leading research, the network of early phase clinical manufacturing centres, substantial commercial gene therapy capacity and the large-scale Cell and Gene Therapy Catapult manufacturing centre mean that the UK is well positioned within the global cell and gene therapy industry. This manufacturing centre will further stimulate the growth of the industry within the UK and also the attraction of inward international investment.
2 Introduction and methodology

The Cell and Gene Therapy Catapult, established in 2012, is an independent centre of excellence with a remit to advance the growth of the UK cell and gene therapy industry, by bridging the gap between scientific research and full-scale commercialisation. A key component of this is to ensure that the UK has a strong and competitive manufacturing base for cell and gene therapies.

Through conducting a UK-wide GMP manufacturing survey, national resource and spare manufacturing capacity can be identified, and a basis for decisions about future infrastructure investment needs developed. 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 this data was published in April 2014 and has been subject to annual review every successive March since.

The aim of the report is to collect and summarise information on each of the MHRA-licenced manufacturing sites in the UK with current spare GMP capacity. An overview of the technical and quality capabilities at each of the facilities, alongside predictions of their available operational capacity can then be compiled. Key questions posed to the facilities as part of the survey are outlined below:

- What types of cell/viral vector/plasmid DNA manufacturing processes does the site handle?
- What types of processing equipment does the site have available?
- What grade/number of clean rooms, MBSC and isolator technology does the site have?
- What licences does the site have?
- How many staff does the site employ and what is the distribution between production, QC and QA?
- How many parallel projects and products can the site deal with?

For annual reviews conducted in 2015-2016, all facilities listed in the preceding report were contacted for updates with regards to their capability and capacity. In addition adverts were communicated via the Cell and Gene Therapy Catapult website and social media, and the EudraGMDP database (http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do) was reviewed to gather information on any potential new facility listings for the report. A summary of the changes made to the facility listings for 2016 are documented in Table 1.

Table 1 Changes to facility listings for the 2016 UK GMP Manufacturing Capability and Capacity Report

<table>
<thead>
<tr>
<th>Transferred listing</th>
<th>Organisation/facility name</th>
<th>Contact name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Manchester – successful transfer of MIA(IMP) and Specials licences from Intercytex Ltd</td>
<td>Joan Benson</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New listing</th>
<th>Organisation/facility name</th>
<th>Contact name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHSBT Birmingham</td>
<td>Jon Smythe and Phil Jenkin</td>
</tr>
<tr>
<td>2</td>
<td>Oxford Biomedica (2nd independent site at Yarnton)</td>
<td>Alex Lewis and Simon Simpkins</td>
</tr>
<tr>
<td>3</td>
<td>Bioreliance Ltd</td>
<td>Andrew Holt</td>
</tr>
<tr>
<td>4</td>
<td>Wolfson Gene Therapy Unit</td>
<td>Eugene Arulmuthu</td>
</tr>
</tbody>
</table>
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 High level summary of data

4.1 UK GMP cell therapy manufacture

4.1.1 High level summary

A snapshot of the nation’s GMP cell therapy manufacturing resource for 2016 is captured in Figure 4. A network of 16 GMP manufacturing facilities are in place, 4 of which have multifunctional cell and gene therapy production capabilities. The facilities supply nearly 1900m² of licensed total cleanroom space between them for the manufacture of cell therapies (ca. 1700m² in the hands of UK academia and the NHS and ca. 200m² commercially owned). The sector has an extremely positive outlook with numerous planned expansion projects on the horizon. The extensions, scheduled to come online in 2017/2018 (detailed in section 5.1), aim to increase current licenced cleanroom space by an estimated 1000m².

Figure 4 Snapshot of the UK’s Cell Therapy Manufacturing Resource 2016

A comparison of the UK’s current capability and capacity for cell therapy manufacture, compared to data reported in the 2014 and 2015 reports, is shown in Figure 5.
Growth for the sector continued in 2015/2016, with the addition of a new facility listing for NHSBT Birmingham. The NHSBT site in Birmingham completed the MHRA-licence approval process in Q1 2016, with licencing for cell therapy IMP manufacture commencing in April 2016. Aside from the number of cell therapy listings increasing to 16 for 2016, Intercytex Ltd’s 2015 facility listing was superseded by the University of Manchester’s GMP facility in 2016. Intercytex Ltd was not included in the detailed capability and capacity analyses of the 2015 report, whilst the facility refocused its activities from contract manufacturing to product development, and initiated transfer of its MHRA MIA(IMP) and Specials licences to the university. The successful transition of Intercytex Ltd’s licences to the University of Manchester was confirmed for 2016 and the university was included in all analyses for this year’s annual review.

The newly licenced facility at NHSBT Birmingham and pre-existing resources at the University of Manchester’s GMP facility accounted for the total increase in number of cleanrooms available for cell therapy manufacture and the majority increase in number of full time personnel employed within the sector for 2016. Newly-created personnel posts were also recorded at Guy’s and St Thomas’ Hospital GMP Facility, the University of Newcastle Biomanufacturing Facility and the Rayne Cell Therapy Suite at King’s College London. One of the largest increases observed for 2015/2016 was the number of part time personnel employed in the sector. The majority of the 60% increase was reported by the Cellular Therapy Laboratories at Great Ormond Street Hospital, with the number of posts at the facility increasing from 8 to 30 in the space of a year. Considerable
recruitment at the unit was required to meet the demands of the increased numbers of products being manufactured and increases in clinical trials.

As highlighted in Figure 6, the average availability of manufacturing capacity at the centres, which can be contracted out externally or utilised for internal projects, rapidly declined during the 2014-2015 period from 45% to 26%. The decline was negligible during 2015-2016, and spare capacity began to plateau at 24%, equating to ca. 400m² of actual free cleanroom space. Nevertheless, the low level of spare capacity for 2016 suggests that the centres remain busy as cell therapies continue to enter clinical trials. This trend will be investigated further following publication of the Cell and Gene Therapy Catapult’s annual Preclinical and Clinical Databases later in the year, https://ct.catapult.org.uk/preclinical-database, https://ct.catapult.org.uk/clinical-trials-database.

A degree of operational capacity will be returned to the marketplace when current projects at the facilities reach the end of their project lifecycle; over a quarter of manufacturing sites reported an increase in spare capacity for 2016. This trend is predicted to continue into 2017 and average availability anticipated to rise to 34%, however free cleanroom space will only marginally increase to ca. 600m² for cell therapy manufacturing operations.

The sustained demand for manufacturing services in 2016 necessitates the continued growth of operational cleanroom space within the UK. This is required to alleviate potential short to medium term deficits in available capacity, which could otherwise impede clinical trial manufacture. Numerous expansion projects aiming to increase the existing total cleanroom footprint and the opening of the Cell and Gene Therapy Catapult large-scale manufacturing centre in mid-2017 will provide crucial growth for the industry, and continue to support prospective cell therapies.

Figure 6 Spare capacity trends 2014-2016 (plus projected 2017 availability)

N.B Projected 2017 spare capacity at University of Oxford CBF is 100% due to future expansion plans
4.1.2 Classification of clean rooms

Table 2 summarises the classification of cleanrooms available in cell therapy manufacturing facilities across the UK. Small changes in the number and classification of cleanrooms were observed for 2016. The re-classification of 3 x grade B cleanrooms to grade C was approved at the University of Oxford CBF following MHRA inspection, 3 x grade B cleanrooms were newly licenced for IMP cell therapy manufacture at NHSBT Birmingham and 2 x grade B cleanrooms were bought online at the University of Manchester following the successful transfer of MIA(IMP) and Specials licences from Intercytex Ltd.

The table highlights that there is a very flexible facility offering by the UK for processing via both open systems (grade B clean rooms with grade A MBSCs) or within closed systems/isolators in lower classification suites. This highlights the UK’s dynamic capability for cell therapy manufacture using a variety of processing types.

Table 2 Number and classification of clean rooms across UK GMP Cell Therapy Manufacturing facilities in 2016 (2015 figures are shown in brackets)

<table>
<thead>
<tr>
<th>Grade of clean room</th>
<th>Grade B</th>
<th>Grade C</th>
<th>Grade D</th>
<th>Isolators within a classified area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of rooms</td>
<td>36 (34)</td>
<td>18 (15)</td>
<td>16 (16)</td>
<td>22 (22)</td>
</tr>
</tbody>
</table>
### 4.1.3 Summary of track record and experience

Figure 7 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. A number of facilities broadened their track records since 2015. Both the Royal free Hospital CCGTT and Cancer Research UK BDU gained track records in iPS and hESC cells respectively, and NHSBT Speke extending its operations to include 2D culture systems (2015 track record not shown). It is promising to see that as a national resource, the current UK capability covers the whole technology sphere of current cell therapy manufacturing requirements.

Figure 7 Summary of UK GMP cell therapy process experience 2016

---

**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 incl. any necessary testing; Cell from donor – handling primary tissues and cells; iPS – generation of induced pluripotent stem cells from donor tissue; hESC – generation 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.

---

Table 3 shows a summary of the capacity, capability and availability of the manufacturing organisations. Again the table highlights that the UK has a strong and diverse manufacturing base to support early phase clinical development for a wide variety of different manufacturing processes and product types.
Table 3 GMP Cell Therapy capability and availability summary at UK organisations for 2016

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Parallel products (open/closed)</th>
<th>Capability</th>
<th>Availability 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Auto suspension</td>
<td>Allo suspension</td>
</tr>
<tr>
<td>Cancer Research UK, BDU</td>
<td>2</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cellular Therapeutics Ltd</td>
<td>6 (4/2)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Guy’s &amp; St Thomas’ Hospital, GMP Facility</td>
<td>4 (1/1)*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Imperial College London, John Goldman Centre for Cellular Therapy</td>
<td>4 (4/0)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Kings College London, RCTS and CRF</td>
<td>4</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NHSBT - Speke</td>
<td>2 (1/1)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Roslin Cell Therapies</td>
<td>4</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SNBTS</td>
<td>DoP</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>University College London, GOSH Cellular Therapy Laboratories</td>
<td>5</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Moorfields Eye Hospital, ATMP Manufacturing Unit</td>
<td>2</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>University of Newcastle Biomanufacturing Facility</td>
<td>9</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Oxford Clinical BioManufacturing Facility</td>
<td>DoP</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Royal Free, CCGTT</td>
<td>7 (7/0)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>University of Bham, CTS</td>
<td>2 DoP</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>University of Manchester</td>
<td>2-3</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NHSBT Birmingham</td>
<td>3</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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
4.2 UK Gene Therapy Manufacture

4.2.1 High level summary

4.2.1.1 Dedicated gene therapy production facilities

MHRA-licenced biotechnology facilities specialised in the manufacture of viral vectors and/or supporting plasmid DNA for *in vivo* and *ex vivo* cell modification purposes were a new addition to last year’s GMP manufacturing survey.

A snapshot of the nation’s GMP gene therapy manufacturing resource in 2016 is captured in Figure 8. A network of 6 GMP manufacturing facilities are in place, supplying over 2400m² of licensed total cleanroom space between them for the manufacture of gene therapies (ca. 2300m² owned by commercial organisations and ca. 200m² controlled by UK academia and the NHS).

Figure 8 Snapshot of the UK’s GMP Gene Therapy Resource 2016

A comparison of the UK’s current capability and capacity for dedicated gene therapy manufacture, compared to data reported in 2015, is shown in Figure 9.
Abundant growth was experienced by the dedicated gene therapy manufacturing sector for 2016. The number of gene therapy specialists captured for 2016 doubled to six. The 3 new facility listings comprised; the opening of a second fully independent GMP manufacturing site for Oxford Biomedica, and the inclusion of 2 pre-existing facilities; Bioreliance Ltd and the Wolfson Gene Therapy Unit.

Oxford Biomedica announced in January 2016 that it had received approval from the MHRA to manufacture bulk drug product for Investigational Medicinal Products at the organisation’s newly commissioned facility in Yarnton, Oxford. The Yarnton site provides an additional 560m² operational cleanroom space to support the organisation’s own proprietary programmes and current/prospective strategic partnerships. Bioreliance Ltd, a long established viral vector manufacturer, recently scaled back a large client project which consumed 100% of the company’s Glasgow facility’s operational capacity. As a result the facility has spare capacity that is progressively being made available to the market place once again. The Wolfson Gene Therapy Unit, originally licenced under NHSBT MIA(IMP), completed an application for variation in September 2015 and was granted authorisation to manufacture IMPs under University College London’s MHRA licence.

The inclusion of 3 new facility listings in 2016 was accompanied by a considerable 78% increase in the number of manufacturing cleanrooms available for gene therapy manufacture. Of the 14 new cleanrooms listed for 2016, 4 were newly created at the OXB Yarnton site and are contained within a single-product run suite. The additional 10 cleanrooms were pre-existing at Bioreliance Ltd, operated at Grade B with Grade A laminar flow hoods for open manipulations, and the Wolfson Unit.
The number of full time personnel employed within the sector was also subject to sizeable growth over the year, with a 31% increase. Aside from pre-existing positions at Bioreliance and the Wolfson Unit, 23 of the 52 newly listed positions were attributed to recruitment drives at both Cobra Biologics and Oxford Biomedica. Increases at Cobra Biologics were a direct consequence of the reported three-fold increase in demand for their gene therapy manufacturing services during 2015. The site anticipates that recruitment will need to continue in 2016 to meet this demand. The strong increase in staff numbers at Oxford Biomedica reflect the on-going expansion projects currently taking place at the organisation.

Figure 10 highlights the spare capacity levels at dedicated gene therapy manufacturing sites for 2015-2016 and projected availability in 2017. Spare capacity at the Oxford Biomedica sites has not been incorporated in the figures, since capability and capacity at the organisation is available for strategic partnership rather than contract manufacturing. Average availability dipped from 30% in 2015 to 16% in 2016 at the remaining organisations, delivering approximately 200m² of actual free cleanroom space. Despite returning to the marketplace for 2016, operational capacity at Bioreliance Ltd remains low initially as the site scales back a large client project and gradually increases availability. Projected average spare capacity is anticipated to rise over 3-fold in 2017 and average 53%, opening up ca. 1000m² cleanroom space across 3 CMOs (NHSBT CBC Langford, Cobra Biologics and Bioreliance Ltd).

Figure 10 Spare capacity at UK GMP Gene Therapy Manufacturers (plus projected 2017 availability)
Facilities dedicated to the manufacture of gene therapies remain predominantly commercial organisations. This contrasts with the cell therapy sector, which is primarily located within UK academia and the NHS.

On the whole, commercially driven, dedicated gene therapy manufacture remains buoyant in 2016, and the combination of on-going expansion projects, return of established manufacturers to the market place and increased demand for services provide a very optimistic outlook for the UK's gene therapy industry which is essential as global demand remains high.

### 4.2.1.2 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 sections 6.1, 6.5 and 6.12 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 and jointly described in section 6.5.

Figure 11 Summary Data for Multifunctional Cell and Gene Therapy Facilities 2016 (2015 data inset)
### 4.2.2 Summary of track record and experience

Figure 12 shows a breakdown of the types of gene therapies and cell culture systems that the facilities with gene therapy capabilities are experienced in (includes dedicated and multifunctional gene therapy facilities). The return of Bioreliance Ltd to the market place has strengthened the nation’s resource for GMP gamma retro-virus and adenovirus manufacture, and although the company doesn’t have a track record in AAV or lenti-virus manufacture, capability is available at the facility.

Analysis of the combined technical capabilities of the facilities is very encouraging. The manufacture of GMP-grade lentivirus and gamma-retrovirus, two of the main viral vectors used in current *ex vivo* gene modification processes, are supported by the majority of facilities listed. Other key viral vectors: adenovirus, AAV, and the manufacture of supporting plasmid DNA are also covered.

**Figure 12 Summary of UK gene therapy facility process experience 2016**

Table 4 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 2016 and beyond, whilst Oxford Biomedica continues to undergo an extensive expansion project. The opening of the UK Cell and Gene Therapy manufacturing centre in 2017 will further enhance the existing viral vector manufacturing network and facilitate the large scale manufacture and initial commercial supply of gene therapies.
Table 4 GMP Gene Therapy capability and availability summary at UK organisations

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Capability</th>
<th>Availability 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parallel</td>
<td>Suspension</td>
</tr>
<tr>
<td></td>
<td>products</td>
<td></td>
</tr>
<tr>
<td>Cancer Research UK</td>
<td>1</td>
<td>✓</td>
</tr>
<tr>
<td>Kings College London, RCTS and CRF</td>
<td>4</td>
<td>✓</td>
</tr>
<tr>
<td>NHSBT – CBC Langford</td>
<td>2</td>
<td>✓</td>
</tr>
<tr>
<td>Oxford Clinical BMF</td>
<td>DoP</td>
<td>✓</td>
</tr>
<tr>
<td>Cobra Biologics</td>
<td>4-5</td>
<td>✓</td>
</tr>
<tr>
<td>Oxford Biomedica, Harrow House and Yarnton</td>
<td>DoP</td>
<td>✓</td>
</tr>
<tr>
<td>Bioreliance Ltd</td>
<td>8</td>
<td>✓</td>
</tr>
<tr>
<td>Wolfson Unit</td>
<td>1</td>
<td>✓</td>
</tr>
</tbody>
</table>

Key: DoP – dependent on process; PE – previous experience
4.3 Geographic locations of cell therapy and gene therapy facilities

The map shown in Figure 13 highlights the diverse geographical spread of sites across the UK, with a clear cluster around the Greater London area (8 facilities). 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 13 Location of MHRA-licenced cell and gene therapy manufacturing sites within the UK

Map data ©2016 GeoBasis-DE/BKG (©2009), Google
5 Future Capacity and Expansion

Annual reviews of the data repository are important to identify facility expansions, increase in personnel numbers and track records and the opening of new facilities. They act as an annual stock-take of regenerative medicine manufacturing capacity in the UK, as recommended by the House of Lords in the 2013-2014 Regenerative Medicine report.

As a forward looking statement a description of upcoming expansions of existing facilities or newly licenced sites has been outlined below.

5.1 Expansion of existing organisations

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 ~300m² 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/early 2018.

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 will start Q1/Q2 2016 and completion will be towards the end of 2018, creating an additional 697 m² of space for the organisation.

The Rayne Cell Therapy Suite at King’s College London is building a new suite of cleanrooms, which are anticipated to boost vector production capacity between 2-3 fold. The additional 80m² of cleanroom space is scheduled to be available in 2017.

Oxford Biomedica continues to undergo an extensive expansion project. Following the opening of a second independent facility in Yarnton in November 2015, which bought with it a further 560m² cleanroom space for the organisation, a third GMP single-product suite will be bought online in Q2 2016 taking operational cleanroom space at the original Harrow House facility up to 1200m².

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 2017 review.

5.2 New sites

NHSBT currently have two sites licenced to manufacture IMP cell therapies at Speke and Birmingham. An additional site in Filton (Bristol) is in the process of obtaining licences for IMP cell therapy manufacture and is due to be inspected by the MHRA in April 2016. Further details regarding progress with licence approval will be provided when available in the 2017 review.

To our knowledge no other new MHRA-licenced cell or gene therapy manufacturing sites are due to come online in 2016/2017, however please contact gmp@ct.catapult.org.uk if you have any information regarding new facilities that we are currently not aware of.

5.3 Large-scale commercial supply capacity

One of the barriers to the growth of the cell and gene therapy industry is the ability to grow cells reliably and cost effectively at scale. During 2013, the Cell and Gene Therapy Catapult, identified the lack of large-scale facilities as one of those obstacles to the translation of research into commercially
viable products. The UK is strongly positioned for early clinical phase manufacturing and the large scale capacity centre will help in growing a UK based global industry.

In 2013, The House of Lords Science and Technology Committee, recommended the building of manufacturing facilities to support the scale-up of treatments in mid-to-late stage of development. The UK Government committed up to £55m to the creation of a world-leading manufacturing facility in March 2014 to meet this business need.

The manufacturing centre, which is currently being constructed and will be managed by the Cell and Gene Therapy Catapult, will open in mid-2017 and be used by companies for the manufacture of late phase clinical trial and initial commercial supply of advanced therapeutic medicinal products including cell and gene therapies. The novel concept of the facility is of great interest for Biotech and Pharma companies as it enables them to have a flexible manufacturing solution without the capital investment of an own build. Companies are also attracted by the idea that the capabilities and services of the Cell and Gene Therapy Catapult, including process and analytical development as well as regulatory support are accessible.

The senior site leadership team for the manufacturing centre has been recruited under the experienced guidance of the Director of the Manufacturing Centre James Biggins and the Director of Quality Jon Halling. The team is presently establishing robust operational and quality systems that will guarantee GMP compliant manufacturing of multi products from different companies within the facility and is developed in close relationship together with the MHRA. These systems will also enable the collaborating companies to interface their quality system whilst retaining their IP and control.

The manufacturing centre is a unique global business proposition based in the UK that will provide national and international developers with a stepping-stone into the EU, US and other growing international markets. It will:

- Enable the growth of organisations by reducing/spreading the costs and risks of establishing and running a specialist manufacturing facility;
- Provide approx. 7200m² of total space that will enable up to 12 firms to simultaneously, but separately, manufacture different therapies within a secure, compliant facility, developed in close relationship with the medicines regulator;
- The space will be used as a series of segregated modules, operating at Grade B downgradeable to C or D over two production floors. Per floor, this shall deliver a total clean room footprint of 1146m² and a total controlled environment footprint supporting multi-product cleanroom function of 1647m²;
- The centre will also have warehousing, dispatch and QC facilities;
- Allow firms to make their products for pivotal clinical trials leading to further investment in UK manufacturing;
- Allow consistent and reliable transport of products into the EU within 24hrs, from its location in Stevenage with an established, cost effective pharmaceutical manufacturing workforce;
- Accelerate global expansion opportunities by reducing their cost and increasing speed of expansion using a flexible, replicable clean room design; and
- Accommodate multiple processing methodologies, including viral vectors, stem cells and tissue engineering within the same facility.
- The centre will be MHRA licensed to support worldwide product compliance
6 Manufacturing Organisations

6.1 Cancer Research UK Biotherapeutics Development Unit

6.1.1 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

6.1.2 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 in process of being 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 CO₂ 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

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
- Stability Cabinets
- Sterility Test Isolator

Photos showing the finish of the clean rooms can be seen in Figure 14.

*Figure 14 Example photos of CR UK BDU facility*

### 6.1.3 Licence
MHRA licence for IMPs has been granted, currently does not cover cell therapy products, but the intention is to apply for a license amendment in 2016 and add cell therapy products. The site does not have an HTA licence.

### 6.1.4 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, and various Hybridoma cell lines). Technology transfer of a manufacturing process for expansion of human embryonic stem cells and their differentiation into dendritic cells is on-going with the intention to commence GMP manufacture in the summer of 2016. A summary of staff experience can be found in Table 5.

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 5 Summary of experience for CR UK BDU

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>iPS Cell</th>
<th>Cell isolation from donor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>✓ Previous experience</td>
</tr>
</tbody>
</table>

6.1.5 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 15.

Figure 15 CR UK BDU Organogram
6.1.6 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.

The main bottleneck limiting further increases in capacity appear to be staff numbers. A second bottleneck defined as space within process development labs to run through the process prior to GMP manufacture was also identified.

A concept design study was completed in 2015 to evaluate potential plans for facility expansion.

Standard methodology to plan capacity and occupancy are used and updated monthly. Available capacity is described below.

2016 – 0%
2017 – 0%
2018 – 50%
2019 – 100%
6.2 Cellular Therapeutics Ltd (CTL)

6.2.1 Details

**Address**
Cellular Therapeutics Ltd
48 Grafton Street
Manchester M13 9XX

**Contact:** [info@cellulartherapeutics.co.uk](mailto:info@cellulartherapeutics.co.uk)
Tel: 0161 606 7278
Web: [www.cellulartherapeutics.co.uk](http://www.cellulartherapeutics.co.uk)

6.2.2 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. An example cleanroom at Cellular Therapeutics Ltd can be seen in Figure 16

**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)

**Analytical equipment**
- Flow cytometer
- Microbiology QC
- GMP and process development assays
Figure 16 Example of clean room at the Cellular Therapeutics Unit

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

6.2.4 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

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPS Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2.5 Personnel
An organogram for CTL can be found in Figure 17. 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.
6.2.6 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 us to manufacture between 60 and 100 complex ATMP products per year.

Available capacity:

2016 – 40%
2017 – 35%
2018 – 45%
2019 – 70%
6.3 Biomedical Research Centres (BRC) GMP Unit at Guy’s and St Thomas’

6.3.1 Details
Address
NIHR Guy’s and St Thomas’ Biomedical Research Centre
BRC GMP Unit
Clinical Research Facility
15th Floor, Tower Wing
Guy’s Hospital
Great Maze Pond
London SE1 9RT

Contact: Chris Fisher Christopher.fisher@gstt.nhs.uk
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

6.3.2 Facility
Guy’s and St Thomas’ BRC 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. Examples of cleanrooms at the facility can be seen in Figure 18.

Processing equipment
- 3 x Rigid four-glove Grade A isolators
- Incubators
- Controlled-rate freezer
- Rocking platforms
- 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
6.3.3 Licence
MHRA licences for IMPs and Specials; HTA licence for procurement, donor testing and processing.

6.3.4 Track record and experience
Experience with autologous T cells and autologous Treg cells at the facility. A summary of the experience can be found in Table 7.

Table 7 Summary of experience for Guy’s and St Thomas’

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
<th>Previous Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td>Previous Experience</td>
<td>Previous Experience</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>iPS Cell</th>
<th>Cell isolation from donor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Experience</td>
<td>Previous Experience</td>
<td>Previous Experience</td>
</tr>
</tbody>
</table>
6.3.5 Personnel
Two members of staff are permanently employed in the CRF 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. Three advanced therapy production scientists and an 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 19 Organogram of Guy’s and St Thomas’ CRF

6.3.6 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 spare capacity can be found below.

2016 – 20%
2017 – 20%
2018 – 20%
2019 – 20%
6.4 Imperial College London, John Goldman Centre for Cellular Therapy

6.4.1 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

6.4.2 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 20 Example of clean room at John Goldman Centre for Cellular Therapy
No photographs provided.

6.4.3 Licence
MHRA Licences to manufacture IMPs and Specials. HTA licences have also been awarded for various operations.
6.4.4 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 8.

Table 8 Summary of experience for John Goldman Centre for Cellular Therapy

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>iPS Cell</th>
<th>Cell isolation from donor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

6.4.5 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 21.

Figure 21 Organogram of John Goldman Centre for Cellular Therapy
6.4.6 Capacity
The centre has two independent suites each with two grade B rooms enabling up to four simultaneous projects. The spare capacity over the next few years is indicated below.

2016 – 25%
2017 – 20%
2018 – 20%
2019 - 20%
6.5  Rayne Cell Therapy Suite (RCTS) and The Wellcome Trust / BRC Clinical Research Facility and Cell Therapy Unit (CTU) at King’s College London

6.5.1  Details

Address
King’s College London,
The Rayne Institute,
123 Coldharbour Lane,
London SE5 9NU

Contact: Farzin Farzaneh Farzin.farzaneh@kcl.ac.uk
Tel: 020 7848 5902/2900
Web:http://www.kcl.ac.uk/lsm/research/divisions/cancer/research/sections/haemat/oncology/services/celltherapysuite.aspx

6.5.2  Facility
The RCTS premises contains 40m² 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 CTU facility has a floor area of 420m² and is separated into three suites. The Cell and Gene Therapy (CGT) suite contains two independent grade D areas complete with isolators. Each area is designed to handle separate products. Production runs in The Cell and Gene Therapy Suite 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 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
- CO2 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 – normal
- Multi laser/coulor FACSCanto and LSR Fortesa Analysers
- FACSARia cell sorting
6.5.3 Licence
The RCTS facility holds MHRA licences for MIA(IMP) and Specials. In addition it also has an 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 facilities.

6.5.4 Track record and experience
The organisation has experience with dendritic cells for a variety of different indications, donor 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 9 Summary of experience for the Rayne Cell Therapy Suite and the Cell Therapy Unit

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell isolation from donor tissue</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.5.5 Personnel
There are twelve permanent members of staff at the RCTS and the Cell and Gene Therapy component of the Cell Therapy Unit. The current list of staff include:

Lucas Chan......................... Head of Manufacture
Rebecca Pru......................... Head of Quality
Joti Bhalla ......................... Quality Manager
Cristina Trento...................... Research Fellow – QA/QC
Yuqian Ma............................. Research Fellow
Sabine Domning....................... Research Fellow
Alexandra Anderson............... Research Assistant
Katarzyna Wolanska-Hajduk.. Research Assistant
Maeve McEnery....................... Research Assistant
Sarah O’Mahoney.................... Research Assistant
Mai-Mai Fung ......................... Research Assistant
Hedieh Shirazi....................... Research Assistant
Majahar Sayed....................... Research Assistant
David Darling......................... Process Development
Wendy Collicott..................... QA/QC (Pharma-Resolution)
David Farrer......................... Ext. QP (Pharma-Resolution)
Farzin Farzaneh..................... Internal QP/DI/ Director
### 6.5.6 Capacity

The RCTS and the CGT 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.

- 2016 – 40%
- 2017 – 50%
- 2018 – 60%
- 2019 – 70%
6.6 NHS Blood and Transplant (NHSBT)

6.6.1 Details

NHS Blood and Transplant (NHSBT) has three sites with MHRA Manufacturer’s Authorisation for IMPs covering cell and gene therapies. In addition, there are a further five laboratory sites with HTA licences (one of which has future plans to add MHRA 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](mailto: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](mailto: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](mailto:phil.jenkin@nhsbt.nhs.uk)
**Tel:** 0121 278 4147

**Additional contacts:**

**Contact:** Teresina Pinnington, Business Development Manager,
[teresina.pinnington@nhsbt.nhs.uk](mailto:teresina.pinnington@nhsbt.nhs.uk)
**Tel:** 07889 304615

**Contact:** Dr Jon Smythe, Head of Cellular and Molecular Therapies, [jon.smythe@nhsbt.nhs.uk](mailto:jon.smythe@nhsbt.nhs.uk)
**Tel:** 01865 38 7967
**Web:** [http://www.nhsbt.nhs.uk](http://www.nhsbt.nhs.uk)
6.6.2 Facilities at Speke
The NHSBT Speke facility has two grade B rooms with Class II MBSC dedicated to the manufacture of cell therapies. There is also an additional grade B room and a grade C room shared with the NHSBT Tissue Services department. The department also has a dedicated QC laboratory.

Processing equipment
- Class II cabinets
- CO₂ 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
6.6.3 Licence
The Speke site has a MHRA licence for IMPs and a HTA licence.

6.6.4 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 10 Summary of experience for NHSBT

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Human ES Cell</td>
<td>IPS Cell</td>
<td>Cell isolation from donor tissue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓
6.6.5 **Personnel**
The NHSBT site in Speke has six dedicated staff for IMP manufacture.

Figure 25 Organogram of NHSBT, Speke site

6.6.6 **Capacity**

2016 – 10%
2017 – 10%
6.6.7 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 26 Examples of clean rooms and equipment at NHSBT (CBC site)
6.6.8 Licence
The CBC site has a MHRA licence for the manufacture and importation of molecular IMPs.

6.6.9 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.

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

Figure 27 Organogram of CBC site

6.6.11 Capacity
CBC can process two products in parallel with a capacity of up to 15 to 20 products per year, depending upon scale. Current available capacity is shown below:

2016 – 40%
2017 – 80%
6.6.12 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.

Processing equipment
- Class II cabinets
- CO₂ 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

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

6.6.14 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.

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

6.6.16 Capacity
2016 – 33%
2017 – 33%
6.7 Roslin Cell Therapies Cellular Therapy Facility (Scottish Centre for Regenerative Medicine)

6.7.1 Details

Roslin Cell Therapies, a subsidiary of Roslin cells, is situated within the Scottish Centre for Regenerative Medicine (SCRM). Roslin Cell Therapies shares the Cellular Therapy Facility with the Scottish National Blood Transfusion Service at SCRM.

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

Daria Olijnyk-Dallis, Business Development Executive
Tel 0131 658 5189

Web: www.roslincells.com

6.7.2 Facilities at Roslin Cell Therapies

The Roslin Cell Therapies processing area is divided throughout the 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 (for both Roslin Cell Therapies and SNBTS) are shown in Figure 28. 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

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

Roslin Cell Therapies is located close to a number of MHRA licenced contract testing facilities who provide a full range of testing capabilities.

Cell/Product Storage:
- Statebourne Vapour Phase LN₂ Storage Vessels
- Mechanical -150 °C Freezers
6.7.3 Licence

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

6.7.4 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 proceed in the right direction and the right standards 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

The Cell Therapy Development Team have many years’ experience of translating academic cell therapy protocols to GMP, process development and the associated documentation required for GMP manufacturing.
Table 11 Summary of experience at Roslin Cell Therapies

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>IPS Cell</th>
<th>Cell isolation from donor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

6.7.5 Personnel
Roslin Cell Therapies currently has 32 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 28.

Figure 29 Organogram of Roslin Cell Therapies
6.7.6 Capacity

The amount of spare capacity currently forecast at the facility can be seen below.

2016 – 50%
2017 – 50%
2018 – 50%
2019 – 100%
6.8 Scottish National Blood Transfusion Service (SNBTS) Cellular Therapy Facility (Scottish Centre for Regenerative Medicine)

6.8.1 Details

SNBTS is situated within the Scottish Centre for Regenerative Medicine (SCRM).

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

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

Contacts
Prof. John Campbell: Associate Director, Research, Development and Innovation
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

6.8.2 Facilities at SNBTS

The SNBTS manufacturing area is divided into 2 suites consisting of:

Manufacture:
2 grade B processing rooms + 2 Grade A MSCs in each.
1 Grade C clean room + 1 Grade A MSC – tissues and closed processes
1 Grade C shared support area

Characterisation & QC:
Controlled non classified GMP cell analysis room, including Flow Cytometry and Cell enumeration

Plans are also underway for the development of a new purpose built National Centre for the SNBTS, anticipated to be operational from late 2017/early 2018. The state of the art facility will have fully validated Grade A, B, C and D operating space providing extensive manufacturing capacity.
Processing Equipment:
- 2x GE Excellerex 10L bioreactor
- 2x CliniMACS plus
- 2x CliniMACS prodigy
- 8x Cell culture incubators
- Centrifuges
- 2x Controlled rate freezer (Planers)
- Closed system cell processing – TSCD, Tube sealers

Analytical Equipment:
- FACS Canto II
- Sysmex haematology analyser
- Evos imaging microscope (x3)

Cell/Product Storage:
- 2x Statebourne Vapour Phase LN₂ Storage Vessels

See Figure 28 for images of example clean rooms at SNBTS (within the SCRM). SNBTS is located close to a number of MHRA licenced contract testing facilities who provide a full range of testing capabilities.

6.8.3 Licence
SNBTS holds individual HTA licences, MHRA MIA (IMP) and Manufacturer’s Specials licences for the facility.

6.8.4 Track record and experience
SNBTS currently produces 5 different cellular therapy products, under appropriate HTA, MHRA specials or MIA (IMP) licences. These are CD133+ autologous stem cells, EBV-specific cytotoxic T cells, and corneal epithelial stem cells, autologous macrophage therapy for cirrhosis (MATCH trial), endothelial cell product for vascular repair.

SNBTS has extensive cell therapy translational research laboratories at SCRM which are involved in the final translation of several other novel cell therapy products and have access from early 2017 to additional controlled facilities at the new SNBTS National Centre. This contains an additional suite of cleanrooms for cellular therapy (1x Grade C and 1x Grade B, in addition to ~300m² Grade D space for closed manufacturing consisting of flexible ‘pods’ and Grade A isolators.

Table 12 Summary of experience at SNBTS

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allo</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell</td>
<td></td>
<td>Cell isolation from donor tissue</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.8.5 Personnel
SNBTS employs 11 full time team members and receives extensive R&D and QA support from wider SNBTS. The organogram for SNBTS is shown in Figure 30.

Figure 30 Organogram of SNBTS

6.8.6 Capacity
The amount of spare capacity currently forecast at SNBTS is as follows

2016 – 10%
2017 – 5%
2018 – 10%
2019 – 20%
6.9 Cellular Therapies, Great Ormond Street Hospital

6.9.1 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

6.9.2 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
6.9.3 **Licence**
MHRA licence for IMP and specials. The facility is also licenced by the HTA.

6.9.4 **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 13 Summary of experience for GOSH Cellular Therapies

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auto</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Allo</strong></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
6.9.5 Personnel
The unit is organised under a chief pharmacist with an aseptic services manager, a quality assurance manager and a contract QP.

Figure 32 Organogram of Cellular Therapies at GOSH

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

2016 – 10%
2017 – 10%
2018 – 30%
2019 – 30%
6.10 Moorfields Eye Hospital, Cells for Sight Cell Research Unit

6.10.1 Details

**Address**
UCL Institute of Ophthalmology
11-43 Bath Street
London, EC1V 9EL, UK

**Contact:** Julie Daniels [j.daniels@ucl.ac.uk](mailto:j.daniels@ucl.ac.uk)
**Tel:** 0207 608 6893
**Web:** [http://www.ucl.ac.uk/cells-for-sight/cell-therapy](http://www.ucl.ac.uk/cells-for-sight/cell-therapy)

6.10.2 Facility
The facility is split into two grade B manufacturing areas. The smaller area contains one MBSC and one CO₂ incubator. The larger area contains three MBSCs and three CO₂ incubators.

**Processing equipment**
- 4 x Class II MBSCs
- 4 x CO₂ incubators
- Fridges and freezers

**Analytical equipment**
- 2 x Microscopes
- Microbiological incubators

*Figure 33 Example of clean room at Cells for Sight*
6.10.3 Licence
The facility has an MHRA licence for IMP manufacture, a Specials licence and a HTA licence.

6.10.4 Track record and experience
The main area of experience involves both allogeneic and autologous manufacture of limbal stem cell cultivation on a scaffold. There is also manufacturing experience with retinal pigmented epithelial cells derived from human ES cells.

Table 14 Summary of experience for Cells for Sight

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.10.5 Personnel
The facility employs production and quality managers a contract QP and one technician. Additional staff are supplied by the client/PI.

Figure 34 Organogram of Cells for Sight

6.10.6 Capacity
The organisation indicated that they were capable of running greater than 3 open process products per year.

2016 – 50%
2017 – 50%
2018 – 50%
2019 – 50%
6.11 Moorfields Eye Hospital, Cells for Sight Cell Research Unit

6.11.1 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

6.11.2 Facility
The facility is split into two grade B manufacturing areas. The smaller area contains one MBSC and one CO2 incubator. The larger area contains three MBSCs and three CO2 incubators.

Processing equipment
- 4 x Class II MBSCs
- 4 x CO2 incubators
- Fridges and freezers

Analytical equipment
- 2 x Microscopes
- Microbiological incubators

Figure 35 Example of clean room at Cells for Sight
6.11.3 Licence
The facility has an MHRA licence for IMP manufacture, a Specials licence and a HTA licence.

6.11.4 Track record and experience
The main area of experience involves both allogeneic and autologous manufacture of limbal stem cell cultivation on a scaffold. There is also manufacturing experience with retinal pigmented epithelial cells derived from human ES cells.

Table 15 Summary of experience for Cells for Sight

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auto</strong></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Allo</strong></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>IPS Cell</th>
<th>Cell isolation from donor tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

6.11.5 Personnel
The facility employs production and quality managers a contract QP and one technician. Additional staff are supplied by the client/PI.

Figure 36 Organogram of Cells for Sight

6.11.6 Capacity
The organisation indicated that they were capable of running greater than 3 open process products per year.

2016 – 50%
2017 – 50%
2018 – 50%
2019 – 50%
6.12 Newcastle Biomedicine Cellular Therapy Facility

6.12.1 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

6.12.2 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)
- CO₂ incubators
- Refrigerated centrifuges
- Caridion Cobe 2991 cell processing equipment
- Water baths
- Blood warmer
- CliniMACS Plus
- Miltenyi Prodigy

Analytical equipment
- Microscope
- FACS
- PCR Thermocycler

Figure 37 Example of clean room at Newcastle Biomedicine Cellular Therapy Facility
6.12.3 Licence
MHRA licence for manufacture of IMPs and “Specials”. The facility also has a HTA licence.

6.12.4 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.

Table 16 Summary of experience for Newcastle Biomedicine Cellular Therapy Facility

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human ES Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPS Cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.12.5 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 38.

Figure 38 Organogram of Newcastle Biomedicine Cellular Therapy Facility
6.12.6 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 available capacity at the facility for the next four years is listed below:

2016 – 40%
2017 – 30%
2018 – 30%
2019 – 30%
6.13 University of Oxford Clinical BioManufacturing Facility

6.13.1 Details

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

Contact: Sarah Moyle sarah.moyle@ndm.ox.ac.uk
Tel: 01865 744845
Web: http://www.cbf.ox.ac.uk/home

6.13.2 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 CO₂ shaking incubators
- 2 x static CO₂ 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 39.

Figure 39 Example photos of Oxford CBF facility

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

6.13.4 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 17 Summary of experience for Oxford CBF. 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 17 Summary of experience for Oxford CBF

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human ES Cell</th>
<th>IPS Cell</th>
<th>Cell isolation from donor tissue</th>
<th>Previous Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.13.5 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.
6.13.6 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.

2016 – 0%
2017 – 100 - 200%
2018 – 200%
6.14 Royal Free Hospital London, Centre for Cell and Gene Tissue Therapeutics

6.14.1 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

6.14.2 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 41.
6.14.3 Licence
MHRA MA(IM) MS 11149 / HTA licence 11016

6.14.4 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 18 Summary of experience at CCGTT

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allo/Auto</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human ES Cell</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>iPS Cell</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.14.5 Personnel
The structure of personnel at the facility can be seen in Figure 42.
6.14.6 Capacity
The amount of spare capacity currently forecast can be seen below.

2016 – 10%
2017 – 10%
2018 – 10%
2019 – 10%
6.15 University of Birmingham, Cell Therapy Suite

6.15.1 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: c.j.steele@bham.ac.uk
Tel: 0121 414 7668

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

6.15.2 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.

Processing equipment
- Environment Monitoring System
- 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
6.15.3 Licence
MHRA licence for IMPs and an MS specials licence. The facility does not have an HTA licence (at present).

6.15.4 Track record and experience
The unit is a new facility and will commence production in September 2015. Initial projects at the facility will include the production of the autologous dendritic cells, and process validation for this project is currently being performed at the unit. The site has also received training to become part of the Athersys trial preparing stem cells for release to patients with ARDS. This trial is expected to open at Birmingham in the first quarter of 2016.

Table 19 Summary of experience at University of Birmingham CTS

<table>
<thead>
<tr>
<th>Allo/Auto</th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human ES Cell</td>
<td>✅</td>
<td>✅</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>iPS Cell</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Cell isolation from donor tissue</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

6.15.5 Personnel
An organogram can be seen in Figure 43. 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
6.15.6 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.

2016 – 50%
2017 – 50%
2018 – 50%
2019 -100%
6.16 The University of Manchester Cleanroom Facility

6.16.1 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/support/gmpfacility/
www.manchester.ac.uk

6.16.2 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. All project work conducted at the facility must be a collaboration with the university.

**Processing equipment**
- CO₂ Incubators
- Class II MBSCs
- Centrifuges
- Microscopes
- Heat blocks
- Water baths
- Analytical balance
- LN₂ 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 Example cleanrooms at University of Manchester

6.16.3 Licence

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

6.16.4 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.

Experience at the facility includes:

- 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

Table 20 Summary of experience at University of Manchester

<table>
<thead>
<tr>
<th></th>
<th>Suspension</th>
<th>Adherent</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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

6.16.5 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 Key personnel at University of Manchester Cleanroom Facility
6.16.6 Capacity

Available spare capacity at the facility is listed below:

2016 – 0%
2017 – 50%
2018 – 75%
2019 – 75%
6.17 Cobra Biologics

6.17.1 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

6.17.2 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 240 employees (92 based in UK). Cobra has a commercially licenced fill / finish and secondary manufacturing facility and supplies commercial products to Europe and the rest of the world. The company routinely produces a wide range of bio-therapeutics ranging from plasmid DNA, viral products, microbial and mammalian proteins and have been manufacturing GMP batches for over 15 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.

An example of a GMP cleanroom at Cobra Biologics is shown in Figure 46.
6.17.3 Licence
All of Cobras’ facilities are cGMP licenced 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.

6.17.4 Track record and experience
Cobra has 15 years of experience as a contract manufacturer providing services for gene therapy. In the UK the main gene therapy site is designed for BLS-2 handling. The company has worked with over 50 customers and produced over 80 GMP batches for customers in Europe, North America and Asia in Phase I to Phase III clinical trials.

Over the last 15 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 small quantities of 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.
6.17.5 Personnel
Key personnel working in the gene therapy facility in Cobra Biologics, Keele, UK are shown in the organograms below

Figure 47 Key production personnel at Cobra Biologics, Keele facility

Figure 48 Key analytical personnel at Cobra Biologics, Keele UK
6.17.6 Capacity
The availability at the Keele facility for the next 4 years is listed below:

2016 – 20%
2017 – 80%
2018 – 100%
2019 – 100%
6.18 Oxford BioMedica

6.18.1 Details

Site addresses

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

Yarnton manufacturing facility
Oxford Biomedica (UK) Limited
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

6.18.2 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. In November 2015, our existing facility at Harrow House, Cowley was supplemented by a new facility in Yarnton, situated on the outskirts of Oxford. Purposefully designed around the Groups’ current and future state lentiviral vector processes, the 560m²/6,028ft² of extra clean room space at Yarnton future-proofed the Groups’ manufacturing capabilities. The Yarnton and Harrow House facilities are operated independently, thereby providing a robust dual supply strategy for our own products and those of our partners. The production clean room areas are supported by an additional ~1100m² providing warehouse, QC, office, utilities and fallow space.

Processing equipment:

- ÄKTA Ready liquid chromatography systems
- Microbiological Safety Cabinets
- CO₂ incubators
- Centrifuges
- -150°C, -80°C and -20°C freezers
• Peristaltic pumps
• Filter integrity testers

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 CO₂ 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 49.

Figure 49 Example cleanroom and support areas at Oxford BioMedica

An extensive expansion plan is ongoing at Oxford BioMedica; the total operational clean room area in Q1 2016 is 950m² and, with additional suites reaching operational status in the first half of 2016, will reach 1,200m² in upstream and downstream processing areas across multiple independent suites and sites.

6.18.3 Licence
Oxford BioMedica is MHRA licensed for IMP manufacture
6.18.4 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.

Upon completion of the ongoing expansion plan, in addition to the current capacity, Oxford BioMedica’s facilities will be able to accommodate production in 3D packed bed technologies and in 200L single-use stirred-tank bioreactors.

6.18.5 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 Business Officer (CBO). Batch release is performed by the Qualified Person (QP) who also manages the QC micro function and QA officers.

6.18.6 Capacity

Current capacity at the start of 2016 is 950m² of cleanroom processing space. Further capacity expansion at the Groups’ Harrow House facility is scheduled for completion in H1 2016 (1,200m²) which will provide a third independent suite designed to house our next generation suspension processes.
6.19 Bioreliance Ltd

6.19.1 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

6.19.2 Facilities at Bioreliance Ltd

BioReliance has a long established facility for:

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

The facility based in Glasgow is shown in Figure 50. BioReliance has 8 cleanrooms, all 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.
6.19.3 Licence

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

FDA Facility establishment Identifier: 3005343934

6.19.4 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.

6.19.5 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.

6.19.6 Capacity

Available capacity at the Glasgow site is forecast as follows:

2016 – 5%
2017 – 50%
2018 – 50%
2019 – 50%
6.20 Wolfson Gene Therapy Unit

6.20.1 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

6.20.2 Facilities 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 60m² and has a clean room suite of 20m² with three secure storage areas of about 10m² in the basement. The QC laboratory of WGTU in the UCL Cancer Institute at 72 Huntley Street with an area of about 20m² 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
Images of the WGTU are shown in Figure 51

Figure 51 Example cleanrooms at Wolfson Gene Therapy Unit

6.20.3 Licence

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)

6.20.4 Track 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.
6.20.5 Personnel

An organogram showing personnel structure at the WGTU is shown in Figure 52.

Figure 52 Personnel structure at WGTU

6.20.6 Capacity

The spare capacity at WGTU for the next four years is listed below:

2016 – 0%
2017 – 0%
2018 – 25%
2019 – 50%
Conclusions

The nation’s GMP cell and gene therapy manufacturing landscape continues to flourish for 2016, as evidenced by the sustained high demand for manufacturing capacity, newly licenced cell and gene therapy manufacturing sites and extensive cleanroom expansion plans.

The UK has a strong research base in cell therapies and this is supported by a network of early phase GMP manufacturing centres. In total 16 facilities have been highlighted in 2016, with current capability and capacity to manufacture cell therapies to licensed GMP. A number of these facilities have significant expansion plans over the next year or two, to meet the demands of the burgeoning industry. Gene therapy capabilities within the UK have expanded considerably, underpinned by a small number of commercial organisations and a small established academic base.

The centres are highly experienced and their combined knowledge and track-record covers the sphere of current requirements for cell and gene therapy manufacture. A wide variety of equipment is available at the sites to support this proficiency. Most experience centres around manufacture using ‘open systems’ either in grade A/B environments or in isolators. Some facilities do have experience of working with ‘closed systems’.

The facilities are spread fairly evenly across the UK (Oxford, Speke, Keele, Birmingham, Bristol, Manchester, Newcastle, Glasgow and Edinburgh), with a significant cluster in and around central London.

Most of the cell therapy facilities are located in the NHS or UK academia; the exception being Cellular Therapeutics and Roslin Cell Therapies, who are commercial organisations. In contrast, gene therapy facilities are predominantly commercial and operate at a larger scale and capacity.

For the second year in a row spare capacity at cell therapy manufacturing sites remained low. Availability at the centres must be monitored closely over the coming years, as it is integral for prospective growth within the sector. Numerous expansion projects aim to mitigate the reduction of current spare capacity, and reflect the ever expanding nature of the UK cell therapy manufacturing sector. Spare capacity at gene therapy centres also declined, however the expected progressive return of operational capacity to the market place by the facilities in 2017 will help cope with the current and predicted increase in demand.

This report will continue to track the spare operational capacity at market-accessible manufacturing sites and will be a useful tool to help map future manufacturing requirements, when used in combination with the annual Preclinical and Clinical Databases also published by The Cell and Gene Therapy Catapult.

The UK Cell and Gene Therapy Catapult Manufacturing Centre, which is on track to be operational in 2017, will complement this existing network. This centre will provide a step change in capacity for cell and gene therapy manufacture in the UK. It will complete the translational picture for the UK, allowing transfer from the research stage into the clinic and finally to later phase trials and commercial manufacture.

The combination of the high quality research taking place in UK academia, the network of early phase manufacturing centres, substantial commercial viral vector capacity and The Cell and Gene Therapy Catapult large-scale manufacturing centre will mean that the UK remains a very attractive location for the global cell and gene therapy industry.