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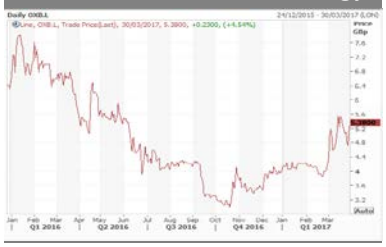
Pharmaceuticals & Biotechnology



Source: Fidessa

Market data	
EPIC/TKR	OXB
Price (p)	5.2
12m High (p)	6.5
12m Low (p)	3.0
Shares (m)	3,088.2
Mkt Cap (£m)	159.0
EV (£m)	178.1
Free Float	65%
Market	LSE

Description

Oxford BioMedica is a UK-based biopharmaceutical company specializing in cell and gene therapies developed using lentiviral vectors, gene-delivery vehicles based on virus particles. In addition to vector development and manufacture, OXB has a pipeline of therapeutic candidates and undertakes innovative pre-clinical R&D in gene-medicine.

Company information

CEO	John Dawson
CFO/elect	Tim Watts/Stuart Paynter
Chairman	Lorenzo Tallarigo
	01865 783 000
	www.oxfordbiomedica.co.uk

Key shareholders

Directors	0.5%
Vulpes	18.9%
M&G	18.1%
Aviva	9.3%
Joy Group	7.6%

Diary

May-17	AGM
Sept-17	Interims

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Oxford BioMedica

Delivering commercial gene-therapy vector

OXB is a specialist gene and cell therapy viral-vector biopharmaceutical company. It offers vector manufacturing and development services, whilst retaining its own proprietary therapeutic candidates. Above service-fees, OXB will receive royalties on commercial products developed with its LentiVector® platform: extensive IP, facilities, and know-how for production and development of lentiviral vectors to generate gene-based therapies. OXB intends to out-license its five clinical candidates and to continue investment in R&D. Bioprocessing royalties are likely to result in significant upside potential in the near future.

- **Strategy**: Oxford BioMedica has four strategic objectives: delivery of process development services which embed its technology in partners' commercial products; commercial manufacture of lentiviral vector; out-licensing of proprietary candidates; and investment in R&D and the LentiVector platform.

- **Revenues:** Bioprocessing and process development command fees-for-service, with process development also incurring upfront, milestone and incentive payments plus licensing income and royalties on commercial products. Out-licensed candidates will deliver licensing fees plus high royalties if successful.

- **Valuation:** An EV/sales multiple of 4x prospective sales for the bioprocessing and process development services is readily justified, which generates a value of £188m. Adding in the risk-adjusted NPV of the potential royalty stream (£46m) suggests a group value of £225m, or 7.5p per share.

- **Risks:** There are inherent risks in clinical trials and commercialisation, particularly in innovative areas such as gene therapy. Oxford BioMedica does not have a controlling stake in commercialisation of partner candidates, and its current strategy is contingent on commercial vector manufacture for partners.

- **Investment summary:** OXB is at a very interesting juncture. Heavy investment in state-of-the-art GMP manufacturing facilities for cell and gene therapies places it on the cusp of generating significant service income and royalties, at a time when it is looking to partner its own clinical candidates. Forecasts for this transformed company suggest that it will turn EBITDA positive in 2017 and become profitable overall at the EBIT level in 2018.

Financial summary and valuation

Year end Dec (£m)	2014	2015	2016	2017E	2018E	2019E
Sales	13.62	15.91	27.78	38.8	47.0	54.0
EBITDA	-9.29	-11.73	-6.78	2.3	6.0	11.4
Underlying EBIT	-10.39	-13.35	-10.45	-2.2	1.5	6.9
Reported EBIT	-10.61	-14.08	-11.32	-3.1	0.5	5.8
Underlying PTP	-10.58	-16.25	-19.44	-7.3	-3.6	1.8
Statutory PTP	-10.80	-16.98	-20.31	-8.2	-4.6	0.7
Underlying EPS (p)	-0.42	-0.48	-0.57	-0.09	0.04	0.22
Statutory EPS (p)	-0.43	-0.51	-0.60	-0.12	0.01	0.18
Net (debt)/cash	13.20	-17.90	-19.05	-25.0	-26.0	-21.8
Capital increase	22.81	0.14	17.50	0.1	0.1	0.1
P/E (x)	-	-	-	-58.8	116.7	23.7
EV/sales (x)	-	-	-	78.8	29.9	15.7

Source: Hardman & Co Life Sciences Research

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Executive summary

Gene-medicine pipeline and bioprocessing services

Oxford BioMedica: specialising in lentiviral vectors…

…for delivery of gene-based medicines

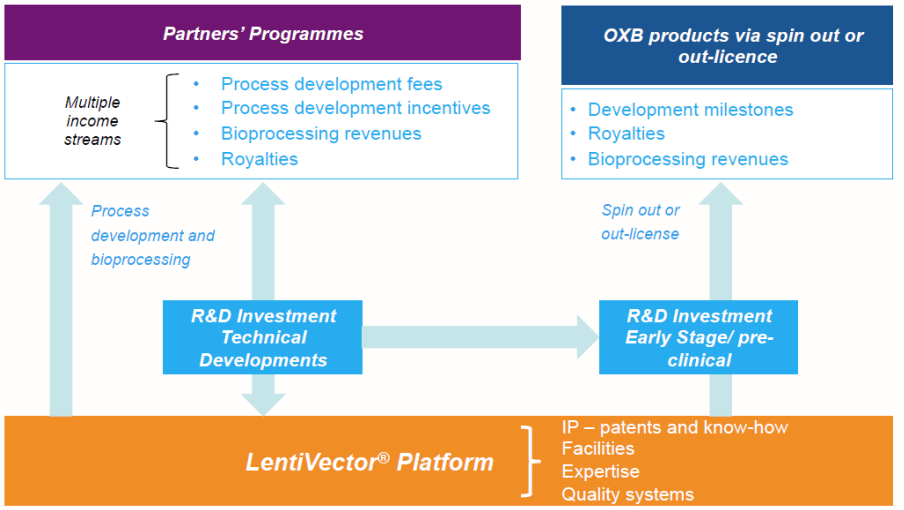
Oxford BioMedica is a biopharmaceutical company specialising in cell and gene therapies delivered with lentivirus-based vectors. The company was founded in 1996 by Oxford academics with expertise in viral vectors: gene-delivery vehicles for gene-based medicines. The company underwent IPO on LSE in 2001. Its LentiVector platform encompasses extensive intellectual property and facilities, which underpin its broad therapeutic candidate pipeline, pre-clinical R&D, and success in providing bioprocessing and process development services for commercial partners.

Focus on bioprocessing and process development…

…and pre-clinical R&D

Management recently updated the company strategy. Clinical asset development will be undertaken by partners who in-license OXB's technology or *via* spin-outs, allowing the company to focus on developing its Lentivector platform and on providing lentivector bioprocessing services for partners. In the future, following regulatory approval and commercialisation by partners, double digit royalties on net sales would become due. Recent investment in manufacturing facilities has greatly increased OXB's manufacturing capacity, positioning it to meet increased demand for commercial supply of lentiviral vector.

Oxford BioMedica business model



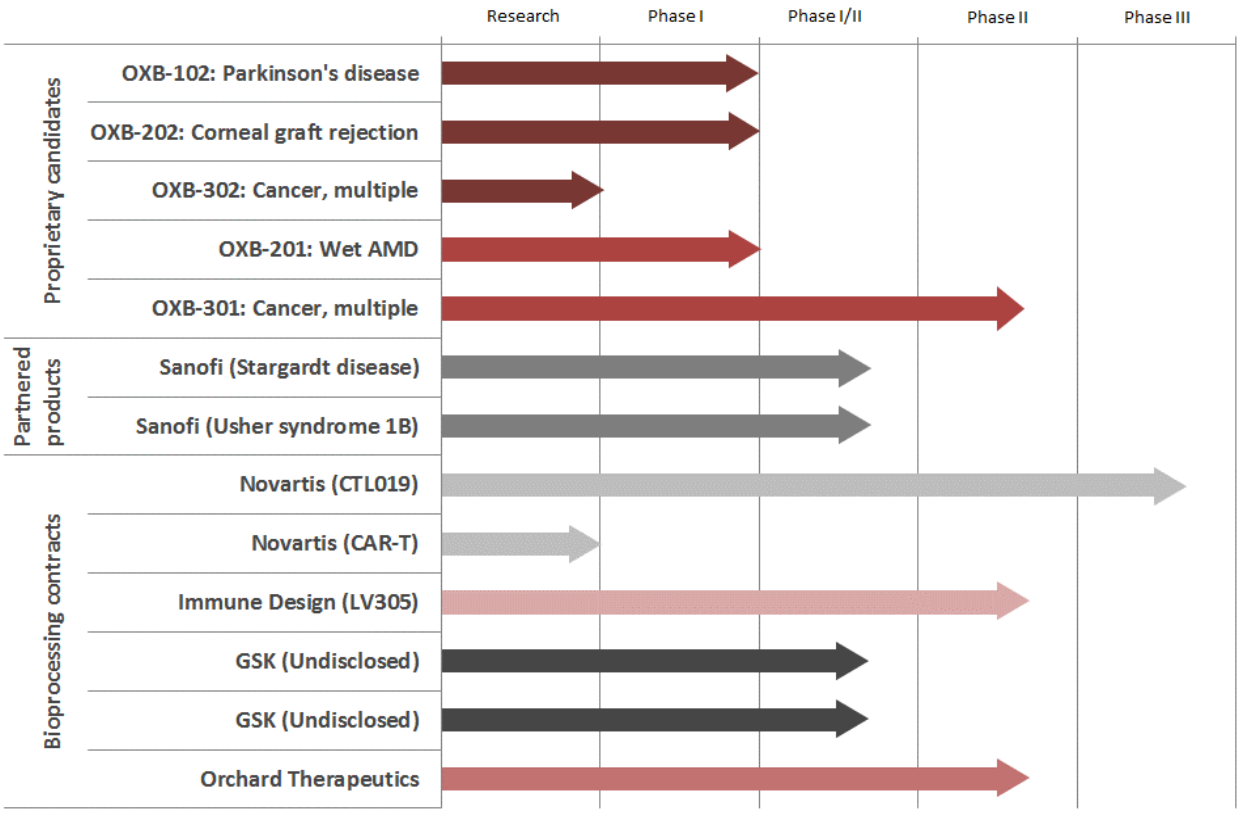
Source: Oxford BioMedica

Business model

Currently, the majority of Oxford BioMedica's revenues are from bioprocessing and process development services e.g. from manufacturing lentiviral vectors for delivery of biopharmaceutical partners' gene and cell therapy candidates. When/if partner candidates reach commercialisation, OXB will receive modest royalties on net sales. In aggregate, OXB's income is categorised into:

- **Service-fees:** for bioprocessing and process development services
- **Additional income:** up-fronts, milestones, incentives, licensing income, and eventually royalties, for bioprocessing and process development services
- **Other income:** Grants and R&D collaborations

Existing Oxford BioMedica assets



Source: Hardman & Co Life Sciences Research

Pipeline and partnerships

One of the major strengths of Oxford BioMedica's business model and updated strategy will be retention of long-term royalties from partner sales of biopharmaceutical products that OXB has been involved in *via* vector process development. These will be in addition to commercial bioprocessing (manufacturing) fees. The company currently has six bioprocessing partnerships in place; none of these are yet commercial therapies, although the Novartis CAR-T product (CTL-019) looks set to receive approval later this year, having had its regulatory submission accepted by the FDA. OXB currently produces vector for its clinical trial programme.

The company has three 'priority' candidates for clinical development. These are a gene-therapy candidate for Parkinson's Disease, technology for genetic modification of donated human corneas to reduce rejection on transplant, and a Chimeric Antigen Receptor-T (CAR-T) cell therapy for treatment of solid tumours. Their development is on hold pending partnership – two gene-based medicines that originated at OXB are currently being developed by Sanofi. The company has restated their commitment to pre-clinical R&D.

Potential royalty stream

As part of our valuation calculations we have assessed the sales potential of OXB's proprietary clinical-stage candidates and of partners' candidates in the most recent bioprocessing/ process development contracts (Novartis and Orchard Therapeutics). These are estimates based on available epidemiological and in-market pricing data, with growth patterns following market authorisation derived from ex-factory sales of comparable biologicals.

Our risk-adjusted royalty stream is worth £46m, or 1.5p per share

The royalty stream (we estimate low single digit for partner sales and low double digit for out-licensed OXB therapies) has the potential to reach in excess of $100m per annum, generating an NPV of $104m/£83m. Risk-adjusting this based on the industry standard probability of biopharmaceutical drug candidates reaching the market, generates an NPV of £46m or 1.5p per share.

Oxford BioMedica royalty summary	
Pre-tax NPV ($m)	$104m
Pre-tax NPV (£m)	**£83m**
Tax rate	20%
Post-tax NPV ($m)	$83m
Post-tax NPV (£m)	**£66m**
Probability of reaching the market	70%
Risk-adjusted NPV ($m)	$58m
Risk-adjusted NPV (£m)	**£46m**
Shares in issue	3,088m
NPV/share (£)	**1.5p**

Source: Hardman & Co Life Sciences Research

Group valuation – Sum-of-the-parts

The above figure is for the royalty stream alone. In the valuation section, we argue that it would be perfectly rational to apply an EV/sales multiple of 3-4x to OXB's bioprocessing & process development services business. The dilemma is finding suitable comparators. Those that have the capability of offering a similar service tend to be part of a multi-national conglomerate whilst most others of a suitable size are not offering exactly the same service as OXB, although the activities of Molmed (MLMD.MI) are relatively similar. Companies involved in the clinical development of CAR-T drugs are more akin to Novartis than to OXB and simply show the market values ascribed to such technologies.

Our sum-of-the-parts valuation equates to 7.5p per share…

…suggesting considerable upside potential

On a sum-of-the-parts basis, we conclude that OXB is currently worth £225m or 7.5p per share, as described in the following table. There is upside potential to this in the event that Novartis confirms positive Phase III outcomes for CTL-019 and also when this product is de-risked by FDA approval, which is expected later in 2017.

Summary valuation	
Oxford BioMedica	**£m**
Bioprocessing (EV/sales 4.0x)	188
Novartis royalty stream – risk adjusted	46
Proprietary portfolio – risk adjusted	10
Group Enterprise Value	**244**
Net cash/(debt)	-19
Market capitalisation	225
Shares in issue (m)	3,008
Valuation/share (p)	**7.5**

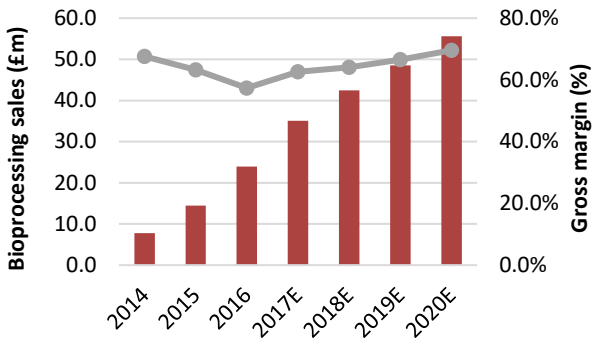
Source: Hardman & Co Life Sciences Research

Investment conclusion

Forecasts indicate that OXB will be EBITDA positive in 2017 and move to overall profitability in 2018

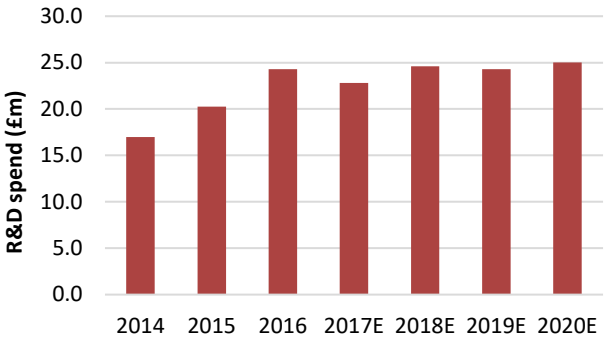
Investment in its state-of-the-art commercial scale manufacturing facilities has transformed the company. Successful completion by Novartis of its Phase III trial of CTL-019 would lead to approval later in 2017, which will be positive for sentiment and lead to valuation uplifts by removing the risk adjustment from the royalty stream. Forecasts suggest that the company will turn EBITDA positive in fiscal 2017 and become profitable overall at the EBIT level in fiscal 2018.

Sales and gross margin



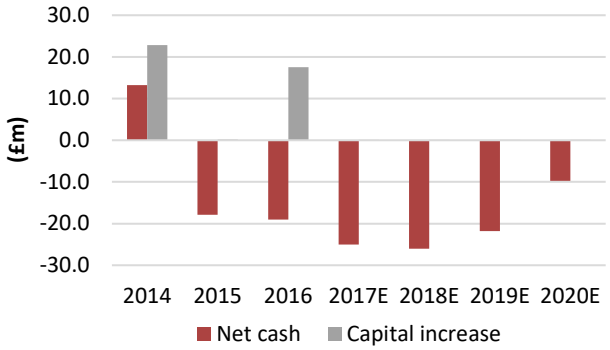
- Oxford BioMedica's sales are from bioprocessing and process development fees, plus additional income such as development milestones
- Royalties will be receivable once partners' therapies reach the market, estimated 2019
- The gross margin has been 60-70% and, although it might dip short term, is likely to trend higher when full operating at full capacity

R&D investment



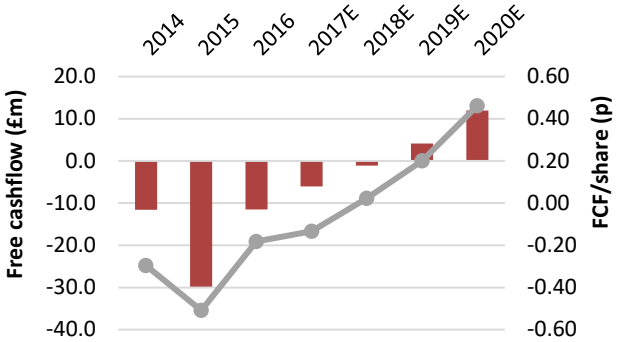
- Recent increased R&D spend has been driven by investment in process development
- Oxford BioMedica intends to out-license/spin-out proprietary candidates: R&D spend will increase only slightly
- Underlying R&D spend on its own discovery programmes is expected to be in the range of £8-10m p.a.

Net cash/capital increases



- At 31st December 2016, Oxford BioMedica had net debt of -£19m, composed of £15.3m cash and £37.1m debt
- During 2016, the company raised new funds around £17.5m in two share issues

Free cashflow



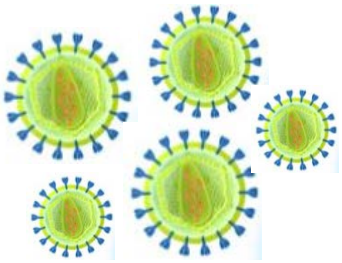
- The company is forecast to become cash positive in 2019 as royalties are received
- 2015 cash flow was impacted by investment in manufacturing facilities to increase GMP bioprocessing capacity to commercial scale

Source: company data; Hardman & Co Life Sciences Research

Overview of Oxford BioMedica

Technology overview

Lentiviral vector



Source: Oxford BioMedica; Hardman & Co

Oxford BioMedica specialises in cell and gene therapies developed using lentiviral vectors. It was the first company to deliver lentiviral vectors to the human eye and brain, breakthroughs achieved with its LentiVector® platform; the company has more than twenty years of vector experience.

Gene and cell therapies address the causes of genetically and cellularly mediated diseases through direct delivery of DNA or RNA to target cells. Delivery is achieved using vectors – in this case lentiviral particles – resulting in expression of therapeutic proteins, potentially for many years following a single treatment. The number of gene and cell therapies in late-stage trials has recently accelerated, thus successful commercial vector manufacture is now critical.

Company history

The LentiVector platform was born from Professors Alan and Sue Kingsman's research at the University of Oxford's Biochemistry Department. In 1995 they founded Oxford BioMedica, which underwent IPO on the Alternative Investment Market (AIM) the following year and on the main LSE in April 2001. Major commercial milestones are outlined below:

OXB major commercial milestones

Milestone	Year
Incorporation of Oxford BioMedica	1995
Approval for first candidate to enter clinical development (TroVax)	2000
First external collaboration agreement (Wyeth, antibody therapy)	2001
Initiation of first Phase I/II study (Prosavin in Parkinson's)	2007
First candidate receives EMA orphan designation (SAR422459)	2009
First IND from FDA (RetinoStat – Phase I/II trial in AMD)	2010
Manufacturing facility acquired in Oxford	2011
MHRA approval for GMP manufacturing	2012
First Phase II trial initiated (TroVax)	2013
Novartis licensing and manufacturing contract	2014

Source: Oxford BioMedica

Strategy

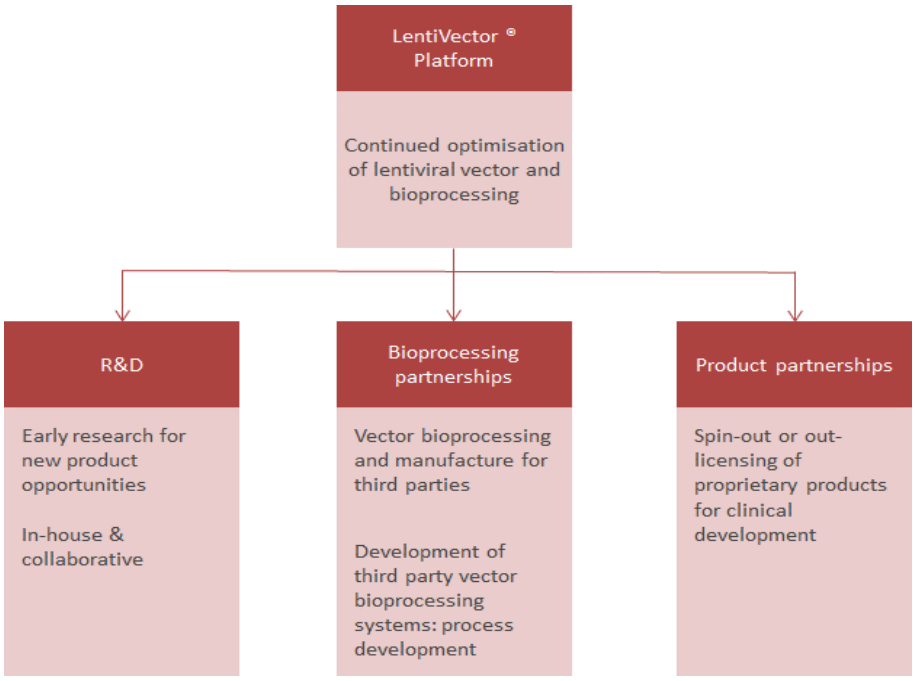
To balance risks to shareholders (from the continued investment required to take proprietary candidates through clinical trials) with creation of value (from bioprocessing and optimisation of the LentiVector platform), in Sep'16 the company announced an update to its strategy. Going forward, clinical development of proprietary candidates will be advanced through transfer to special purpose vehicles (SPVs) or out-licensing to partner organisations. This approach has been successful with two Phase I/IIa gene therapies being developed by Sanofi – the plan now is to out-license/spin-out OXB's other five wholly-owned product candidates.

Business model

This approach will allow OXB to retain its position at the forefront of lentivirus-based vector manufacture, whilst capitalising its scientific expertise for discovery of novel therapeutic candidates. Particular focus is on:

- Optimisation of the LentiVector platform – to increase yield, improve downstream testing, achieve industrial scale-up
- Early-stage R&D – in orphan ocular and CNS diseases, lung, and oncology
- Bioprocessing partnerships – providing vector bioprocessing, batch manufacture, and vector process development expertise
- Product partnerships – clinical development of proprietary candidates *via* spin-out or out-licensing to third parties

OXB business activities



Source: Hardman & Co Life Sciences Research

Value

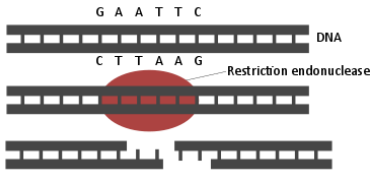
These activities generate value through:

- Increasing the company's intellectual property – e.g. process development for partners may generate IP that is retained by OXB
- Manufacturing revenue – currently per vector batch
- Process development revenue – on the basis of time and materials
- Licensing fees from partners who license OXB's patents or therapeutic candidates – upfront payments, milestone payments, and (future) royalties

Gene editing

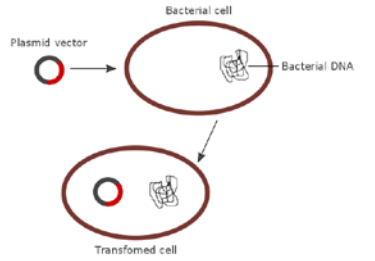
Background

DNA restriction



Source: Hardman & Co Life Sciences Research

DNA cloning



Source: Hardman & Co Life Sciences Research

The biotechnology revolution of the 1970/80s was catalysed by discovery that DNA could be cleaved at specific sites using bacterial restriction endonucleases. Manipulation of these enzymes permitted isolation of select DNA fragments from the genome; using enzymes such as ligases, it became possible to recombine DNA fragments from separate sources. Development of DNA sequencing in 1977 and DNA amplification by Polymerase Chain Reaction (PCR) in 1983 allowed direct identification of a gene's sequence, catalysing modern genetic engineering.

Molecular cloning

Extracted fragments are transported among genetic backgrounds *via* vehicles called vectors. For example, plasmids – individual DNA molecules from bacterial cells – transmit naturally among bacteria *via* processes such as transformation. These can be engineered to carry exogenous DNA.

Bacterial cells are easily transformed with recombinant plasmids in the lab. During culture, bacterial multiplication results in plasmid amplification – a process called cloning. In addition, the bacterial cell machinery can be manipulated to express the recombinant plasmid genes and synthesise the encoded proteins. For example, biosynthetic insulin, first commercially produced in 1982 by Genentech, is manufactured using recombinant *E. coli*.

Modification of mammalian cells

Because of biological barriers to plasmid uptake by mammalian cells, alternative techniques were needed for genetic modification in medical research. Transgenic mice are widely used models of human disease: their creation requires stable transgene expression, a feat first achieved in the late 1970s when viruses were used to transport DNA into the early mouse embryo. In the 1980s, heritable transgene expression in mice was achieved through microinjection of DNA directly into the nucleus of a single embryonic cell.

There are now multiple methods for enhancing the uptake of naked DNA to animal and human cells, broadly categorised into three groups: physical e.g. electroporation to increase cell membrane permeability; mechanical e.g. microinjection with glass needles; and chemical e.g. co-precipitation of DNA and calcium phosphate for uptake by endocytosis. Somatic (non-germ line) cell and gene therapy is permitted subject to regulation but heritable modification of human embryos is illegal.

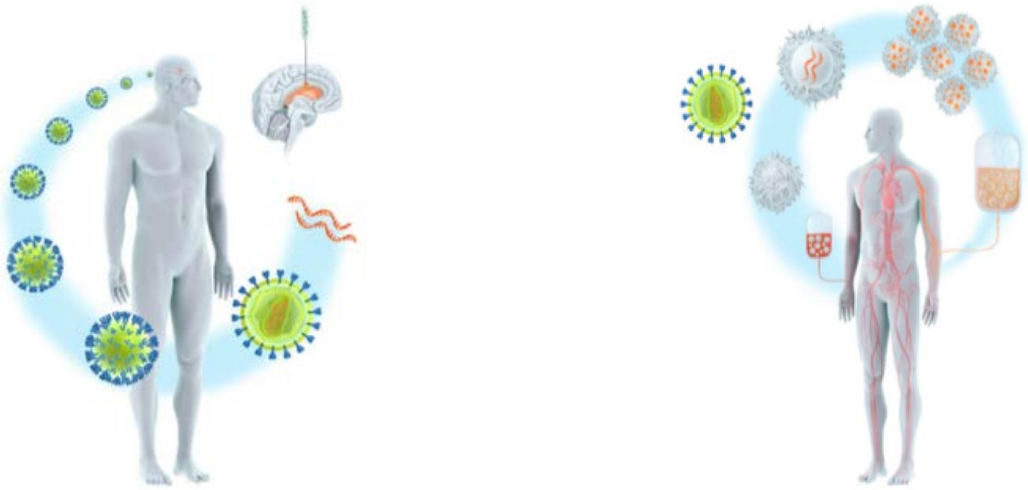
Cell and gene therapy R&D

Key developments

Gene therapy was accelerated from conception in the 1960s to clinical tests within three decades by increasingly sophisticated DNA recombination techniques. The first laboratory experiments to modify human cells with therapeutic genes used calcium phosphate to enhance uptake of the gene for β-globin, a component of haemoglobin under-produced in thalassaemia patients. This led directly to the first use of genetic engineering in a clinical setting.

The principle of gene editing is the same in cell and gene therapies. Recombinant vectors carrying therapeutic nucleic acid (DNA or RNA) are manufactured in a laboratory and inserted to target human cells: *in vivo* in gene therapy, or *ex vivo* in gene-modified cell therapies.

Gene and cell therapies



Gene therapy
***In vivo* gene editing**

Cell therapy
***Ex vivo* gene editing**

Source: Oxford BioMedica

1st cell therapy study…

…at UCLH in 1980

In 1980, a cell therapy study was carried out at UCLH: bone marrow cells were extracted from thalassaemia patients and modified *in vitro* with a β-globin recombinant plasmid for reinfusion into patients. This study had not received ethical permission and was highly criticised. However, it gave advanced therapies public visibility and fast-tracked the necessary regulatory framework.

The following decades saw great progress. The first approved clinical gene transfer took place in 1990: two Severe Combined Immunodeficiency (SCID) patients – who lacked the gene responsible for adenosine deaminase production, ADA – had their T cells modified to carry functional ADA. These T cells persisted for up to 20 years, demonstrating the feasibility of cell therapy as a cure.

Development of advanced therapies: key events

Year	Event (licenced therapy)	Indication	Organisation	Vector	Cells
1980	1st human cell therapy study	Thalassaemia	UCLH, USA	Plasmid	Bone marrow
1990	1st approved gene therapy trial	ADA-SCID	NIH, USA	Retrovirus	T cells
1992	1st stem cell therapy trial	ADA-SCID	HSR-TIGET	Retrovirus	Stem
1999	1st death from vector-associated toxicity	Metabolic disorder	IHGT	Adenovirus	N/A*
2000	1st reported insertional mutagenesis	SCID-X1	Necker Hospital	Retrovirus	Bone marrow
2003	1st human trial lentiviral vector cell therapy	HIV	University of Pennsylvania	Lentivirus	T cells
2008	1st human trial lentiviral vector gene therapy	Parkinson's disease	Oxford BioMedica	Lentivirus	N/A*
2012	1st gene therapy approval (Glybera)	LPL deficiency	uniQure	Adenovirus	N/A*
2016	1st cell therapy approval (Strimvelis)	ADA-SCID	GSK	Retrovirus	Stem

**Gene therapy (in vivo modification)*
Source: Hardman & Co Life Sciences Research; Sheridan 2011, Nat Biotechnol

Adverse events

Viral toxicity…

Unfortunately, adverse events following some trials dented public perception. Widely reported was the death of Jesse Gelsinger in 1999 from his immune reaction against the adenoviral vector used in treating his metabolic disorder. This was the first known death from a gene therapy.

…and insertional mutagenesis in historical trials

A second major complication was revealed in the same period. Insertional mutagenesis, whereby vector-carried DNA is inserted into the wrong chromosomal position, was reported to have resulted in activation of proto-oncogenes in two trials of gene therapy in X-linked SCID. These participants developed T cell malignancies.

Licensed therapies

Four gene/cell therapies currently approved by the EMA…

Increased evidence for efficacy of gene and cell therapy has restored market optimism. There are currently three such therapies with marketing approval by EMA or the US FDA:

…one by the FDA

- **Glybera®** (uniQure) for treatment of severe pancreatitis caused by lipoprotein lipase deficiency – approved 2012 EMA
- **Imlygic®** (Amgen) for treatment of melanoma – approved 2015 EMA and FDA
- **Strimvelis™** (GSK) for treatment for ADA-SCID – approved 2016 EMA
- **Zalmoxis®** (MolMed) for adjunctive treatment of haematological malignancies – conditional approval, 2016 EMA

Cell and gene therapies classified as Advanced Therapy Medicinal Products by EMA

As an example, Glybera's target market is small and there have been few treatments in the four years since approval; however, these drugs are pathfinders that illustrate proof-of-concept for the multiple advanced therapies under development. The EMA classifies these under Advanced Therapy Medicinal Products (ATMPs):

- **Gene therapy medicines** that lead to a therapeutic, prophylactic or diagnostic effect by inserting 'recombinant' genes into the body to treat a variety of diseases, including genetic disorders, cancer or long-term diseases
- **Somatic-cell therapy medicines:** cells/tissues manipulated to change their biological characteristics or cells/tissues not intended to be used in the same essential functions as in the body
- **Tissue-engineered medicines:** cells/tissues that have been modified so they can be used to repair, regenerate or replace human tissue
- **Combined ATMPs:** one or more medical devices combined as an integral part of the medicine e.g. cells embedded in a biodegradable matrix or scaffold

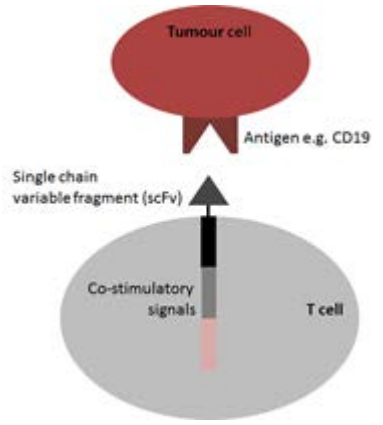
Trials

There were at least 150 trials approved for gene and cell therapies in 2015. The majority of candidate cell therapies are for cancers and most gene therapies in development are for monogenic diseases, particularly in ophthalmology. Of particular relevance is Spark Therapeutics' (Philadelphia, US) Phase III trial of voretigene neparvovec (SPK-RPE65), a gene therapy for inherited retinal dystrophy. Spark has said that it intends to file for BLA in early 2017 – if granted, this will be the first gene therapy for an inherited disorder licensed in the US.

Newer gene editing technologies are also entering clinical development. These techniques include CRISPR-Cas systems, zinc-finger nucleases (ZFNs) and TALENS – one trial delivered the CRISPR-Cas system *in vivo* using a viral vector. These will accelerate gene and cell therapy development for a broader range of indications.

CAR-T Therapy

CAR-T binding a tumour cell



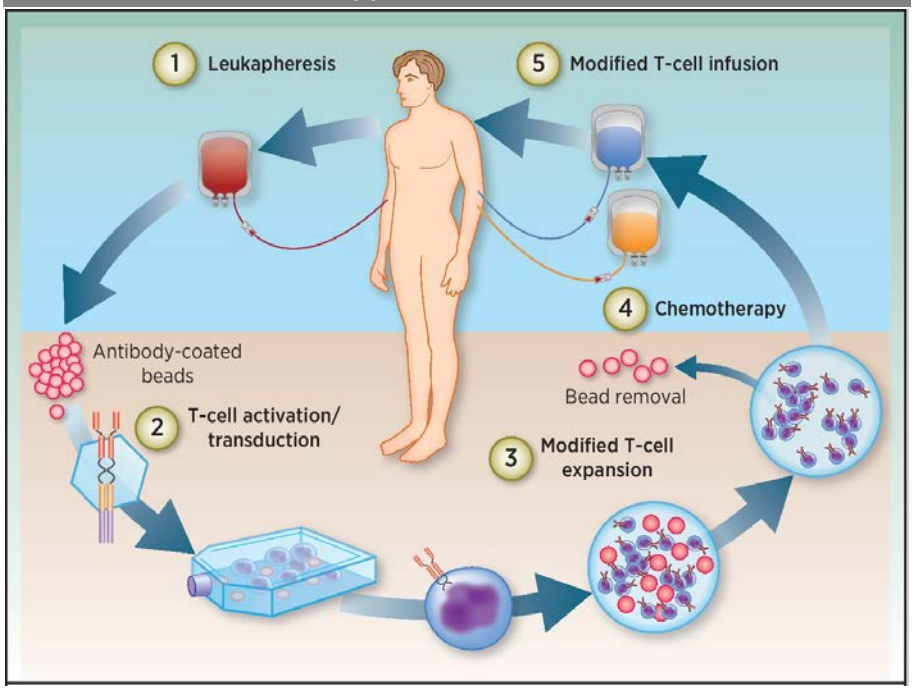
Source: Hardman and Co Life Sciences Research

Most *ex vivo* gene modification therapies are either TCR, stem cell, or Chimeric Antigen Receptor T cell (CAR-T) therapies. CAR-Ts are genetically modified T cells that direct the immune system to recognise cancers by expressing a specific antigen receptor on their surface. The receptor is 'chimeric' because it combines the specificity of an antibody (usually) with additional signalling domains – the recombinant DNA encoding the receptor is delivered to T cells *via* a viral vector. The latest generation CAR-Ts recognise directly antigen on the surface of tumour cells without requiring its presentation *via* MHC on antigen presenting cells.

When CAR-Ts are introduced to the body, they proliferate and generate a cytotoxic immune response against the target antigen if present in the body, or prime the immune system for future recognition by memory T cells. A complication of T cell expansion can be cytokine mediated inflammatory syndromes, which cause symptoms such as fever or renal and respiratory insufficiency. These can be clinically managed, however, so are now rarely fatal in trials.

Delivery of CAR-T therapy requires extraction of autologous cells for transduction. Either the cells themselves must be transported to a cell processing lab and then returned to the treating hospital – requiring cryopreservation – or patients must travel to facilities that can both modify the cells and deliver the therapy.

Treatment with CAR-T therapy



Source: Maus and June 2016

- White blood cells are collected from the patient, usually by leukapheresis
- T cells are isolated (e.g. using antibody-coated beads) and activated
- T cells are shipped to a cell processing facility where they are transduced

- CAR-Ts are expanded, usually in a bioreactor
- The expanded CAR-Ts must be cryopreserved for shipping back to the hospital
- Before the patient can be infused with the CAR-Ts, they have chemotherapy to remove native T cells

Vectors: the basis of cell and gene therapies

Viral-based vectors…

…most common in current trials

The biggest challenge in development, beyond identification of the genetic mediators of disease, is establishing methods for genetic modification (e.g. gene replacement, knock-out, or addition) and for achieving this therapeutically. Successful development is therefore highly dependent on a suitable vector. Key considerations include: targeting specific cells; duration of therapeutic gene expression; and the amount of nucleic acid to be delivered. The vector itself must be genetically modified for safe administration.

In many ways, viral pathogens of humans are ideal vectors. They have evolved to transduce human cells and to possess natural mechanisms for crossing the plasma membrane. Those that naturally integrate into human chromosomes – leading to heritable modification and long-term recombinant gene expression – are a good choice for delivery of therapeutic genes to dividing cells. For treatment of disorders affecting terminally differentiated cells, such as neurons, the vector must transfect non-dividing cells.

Gene therapy vectors

Vector	Example	Natural host	Nucleic acid	Integrates chromo-some	Non-dividing cells	Low toxicity	High gene expression	Low immune-genicity	High genetic load
Plasmids		Bacteria	DNA			■		■	■
Retroviral	Spumavirus: human foamy virus	Human	RNA	■			■		
Lentiviral	Equine infectious anaemia virus (EIA)	Horse	RNA	■	■		■		
	HIV-1	Human	RNA	■	■		■		
Adeno-associated (AAV)	Human parvovirus	Human	DNA		■	■	■	■	
Poxvirus	Vaccinia	Unknown	DNA				■		

Source: Hardman & Co Life Sciences Research

Adeno-associated virus (AAV) vectors and lentiviral vectors (LV) are increasingly being used. Glybera is an AAV vector carrying lipoprotein lipase (LPL) gene that is injected intramuscularly. Lentiviruses, such as HIV-1, are members of the retrovirus family, which infect dividing and non-dividing cells and integrate, making LV efficient for long-term therapeutic gene expression.

Designing lentiviral vectors

The first stage of the lentiviral life cycle – infection – is exploited for delivery of recombinant gene cassettes to human cells. The second stage – replication – is prevented through genetic modification of the wild-type virus during vector design.

Lentiviral vector transduction of human cells

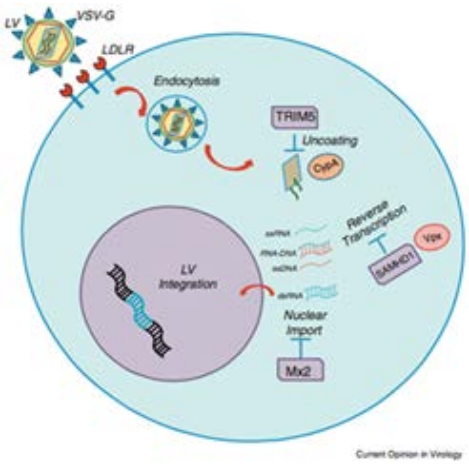
(i) recognition of target cells (*via* surface exposed receptors)

(ii) uptake of LV *via* endocytosis

(iii) reverse transcription of vector RNA into cDNA in the cytoplasm

(iv) vector cDNA translocates the nuclear membrane as part of the pre-initiation complex

(v) integration of vector DNA into the human chromosome

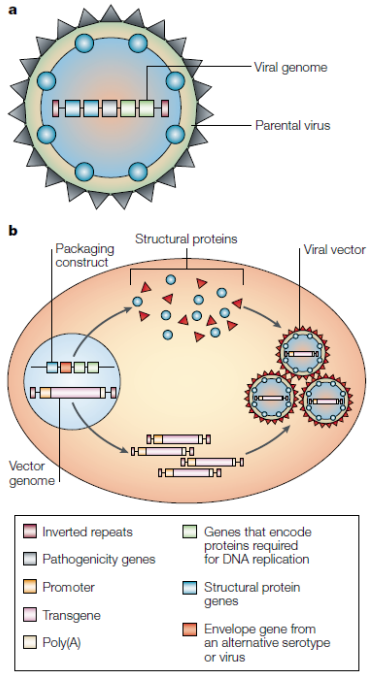


Source: Borsotti 2016; Hardman & Co Life Sciences Research

Split genome packaging for vector manufacture…

…reduces formation of replication-competent lentivirus

Vector construction



Source: Thomas 2003

Preventing viral replication

In addition to the therapeutic gene(s) and sequences needed for expression, safety features must be incorporated in vector design. These include mechanisms for target cell specificity, regulation of therapeutic gene expression, and prevention of adverse effects. The current third-generation minimal LV do not contain the majority of wild-type lentiviral coding regions (<5%[1]). Essential sequences are left in place – for example, those needed for integration of DNA into host chromatin – but those for virion production, and thus replication within the patient, are removed.

To minimise formation of replication-competent lentivirus (RCL) by recombination of viral DNA during vector propagation, the sequence comprising the vector is typically split across three plasmids:

- Vector genome construct – expression cassette
- Packaging construct – necessary genes for viral replication
- Envelope construct – capsid/envelope proteins

All three constructs are used to transfect cell lines in the laboratory, which, when cultured, produce complete vector particles. Homology among constructs is minimised to reduce the chance of recombination. Finally, vectors can be 'self-inactivating', whereby regulatory sequence controlling viral replication is removed.

Specificity

First, pseudotyping of the viral envelope – whereby antigen receptors from different viruses are genetically engineered into one vector – can increase target cell specificity and reduce immune recognition. Secondly, specificity can be increased by modifying the vector to express 'artificial' molecular adaptors, using antibodies or peptide ligands, that bind target cells. Finally, cell-type specific transgene expression can be achieved by incorporating promotors that 'turn on' transgenes in the presence of specific transcription factors.

LV integration patterns are also highly favourable. Inclusion of suicide genes that result in cell destruction in the event of insertional mutagenesis can maximise integration specificity.

[1] Thomas CE, Nature (2003)

Vector manufacture

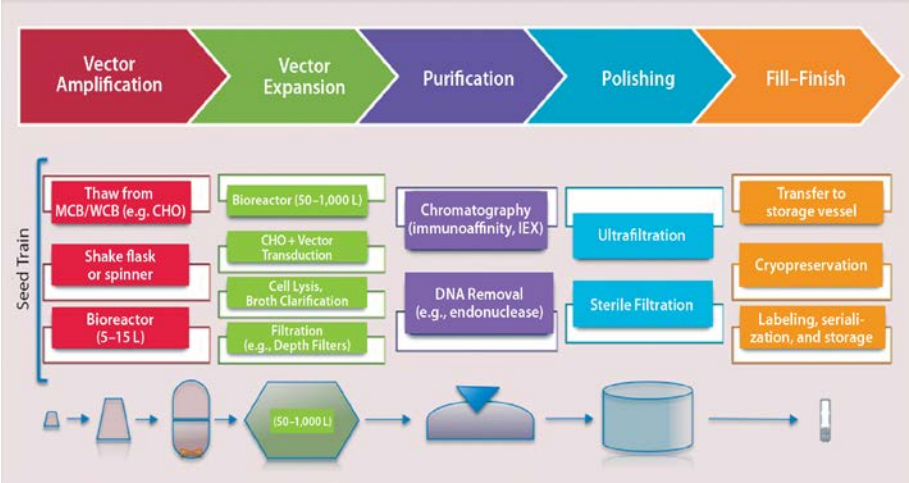
Effective vector bioprocess design is critical for producing safe and efficient vectors. Commercialisation of the multiple cell/gene therapies approaching the market will be dependent on industrial manufacture of viral vectors – i.e. efficient, high titre production of clinical-grade, cGMP vector. This is particularly true for therapies commanding large markets such as the haematological malignancy market. The main manufacturing issues have been in scaling up conventional vector production – most developers outsource bioprocessing to specialist biomanufacturers.

Efficient vector bioprocess design…

…reduces gene therapy COGS

Bioprocessing includes upstream processes e.g. vector amplification/expansion, and downstream processes e.g. purification, quality control, and packaging. Throughout, a major consideration is efficiency since the cost of goods sold (COGS) will drive viability of the therapy in the market. Fetal bovine serum is commonly added to cell cultures in vector production, which is expensive and of limited availability.

Vector bioprocessing



Source: Oxford Biomedica

Upstream processing

Shift towards stable producer cell lines…

…for time and cost efficient commercial manufacture

The main part of the upstream process is transfection and culture of manufacturing cell lines to produce vector particles at high concentration. Uptake of vector plasmids is often facilitated using calcium phosphate, however, for commercial manufacture of cell and gene therapies this method is laborious and costly.

There has been a move towards development of bespoke stable producer cell lines for high volume production. These permanently include all vector components apart from the therapeutic gene construct. Although a considerable investment, vector production is quicker using this method than with transient transfection.

There are, broadly, two approaches to culturing transfected cells: *via* adherent cultures grown in 2D layers in cell factories or *via* cell suspensions in bioreactors. The latter is more amenable to large-scale production, and cell lines adapted to serum-free growth – such as HEK293T lines – are particularly favoured for stirred-tank bioreactors. Bioprocessing considerations include viral sensitivity to shear forces and temperature, which can vary substantially across a culture.

Downstream assays…

…ensure correct vector titres…

…and clinical safety

Downstream processing

To make bulk batches at target titre, vector sub-batches can be combined in sterile downstream processes. Removal of non-functional vector particles increases vector titre (number of transducing units/particles per millilitre) and is essential for safety. Activation of the immune system could result in cytotoxic T-lymphocyte (CTL) responses or cytokine-mediated inflammatory responses, and this is why vector process development runs parallel with clinical development: dose escalation trials necessitate an understanding of the relationship between titre and the immune response. A major focus in gene therapy development is to increase vector potency – so that the same transfection efficiency is achieved at lower titre.

Finally, purification was conventionally achieved by centrifugation. For large-scale manufacture this is inefficient since it can damage vector particles and lower titres. Column-chromatography approaches are now more commonly utilised.

OXB technology

LentiVector® platform

Oxford BioMedica's LentiVector platform combines intellectual property (patents and know-how), materials, and facilities that underlie Oxford BioMedica's proprietary therapeutic candidates and its bioprocessing and process development capabilities. The LentiVector platform is a versatile gene delivery system that uses lentiviral vectors to create cell and gene therapies.

LentiVector platform	
Patent portfolio	>100 patents and patent applications
Know-how	From 20 years of expertise in gene & cell therapy
Facilities	GMP capacity: 2,245m^2 clean room space

Source: Oxford BioMedica

Intellectual property

OXB has >100 patents…

…and >2000m^2 clean room space

Oxford BioMedica's expertise is derived from over 20 years of lentiviral vector and gene therapy R&D. Its intellectual property is protected by an extensive patent portfolio of more than 100 patents and includes extensive know-how. This IP covers technologies across the vector development and manufacturing process, from vector engineering and bioprocessing to downstream assays, along with clinical and commercial product development.

Key patents	
Technology	**Protected until**
3rd generation minimal lentiviral vectors	2018
Vector safety features	2023
Downstream processing of vector	2029
High volume vector manufacture e.g. TRiP system	2034

Source: Oxford BioMedica

Commercial manufacture

Serum-free, suspension bioreactor manufacturing…

…allows commercial lentiviral vector manufacture

The company has developed proprietary processes for manufacturing clinical-grade vectors *via* adherent cultures in cell factories and *via* serum-free suspension culture in 200L bioreactors. It is continuing to develop its technology for large-scale manufacture – it holds patents relating to yield improvement technologies such as the Transgene Repression in vector Production (TRiP) system and for bioprocessing with stable cell platforms such as packaging and producer cell lines. Pilot studies suggest significant improvement in volume (+54% compared to 1st generation process), yield, potency, purity, and efficiency with these processes.

Licensees

OXB has currently a number of licensees that relate to small manufacturing and/or R&D collaborations that are not discussed further in this report:

- GSK holds licences to OXB patents that allow development and commercialisation of candidates based on OXB technology
- MolMed
- Emergent BioSolutions

- Sigma-Aldrich (Merck KGaA)
- Biogen
- Merck & Co
- Pfizer

Advantages

Lentiviral-based vectors can be used to generate both cell therapies – e.g. those requiring modification of haematopoietic stem cells – and gene therapies requiring *in vivo* modification of cells such as neurons. The LentiVector platform has greater capacity than many systems and can accommodate multiple therapeutic genes.

Crucially, the LentiVector platform is designed to overcome the safety and delivery problems associated with earlier generations of vector systems. It delivers genes into cells with high transduction efficiency.

Applications

The LentiVector platform is flexible in its application. It has particular advantages in gene therapies for diseases of the brain and the eye, and can be used to deliver RNA for RNA interference approaches, in addition to coding sequence. The LentiVector platform is also used for manufacture of: immunotherapies such as CAR-T therapy; induced pluripotent stem cells; and emerging therapeutics that use gene editing technologies like CRISPR-Cas. There is therefore a very large potential demand for LV. Finally, the technology can be used as a research tool – e.g. in transgenesis, stem cell manipulation, somatic disease models, target validation, and gene discovery.

Regulatory compliant facilities

In the past year, manufacturing capacity has been greatly accelerated through completion of the Company's expanded facilities. Oxford BioMedica has new state-of-the-art laboratories and three bioprocessing clean rooms (completed Jul'16).

OXB facilities

Location (all Oxford, UK)	Function	Facilities	Regulatory standard	Latest MHRA approval
Harrow House	Bioprocessing	2x clean rooms	cGMP	July 2016
Windrush Court	Headquarters/analytical testing/process development	PCR suite / x3 category 3 laboratories / other laboratories	cGMP	July 2016
Yarnton	Bioprocessing	x1 clean room	cGMP	January 2016

cGMP: current good manufacturing practice
Source: Hardman & Co Life Sciences Research

All facilities are approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for manufacture of bulk drug material for Investigational Medicinal Products (IMPs) and are certified cGMP. The company is therefore fully authorised to release IMPs for use in clinical development.

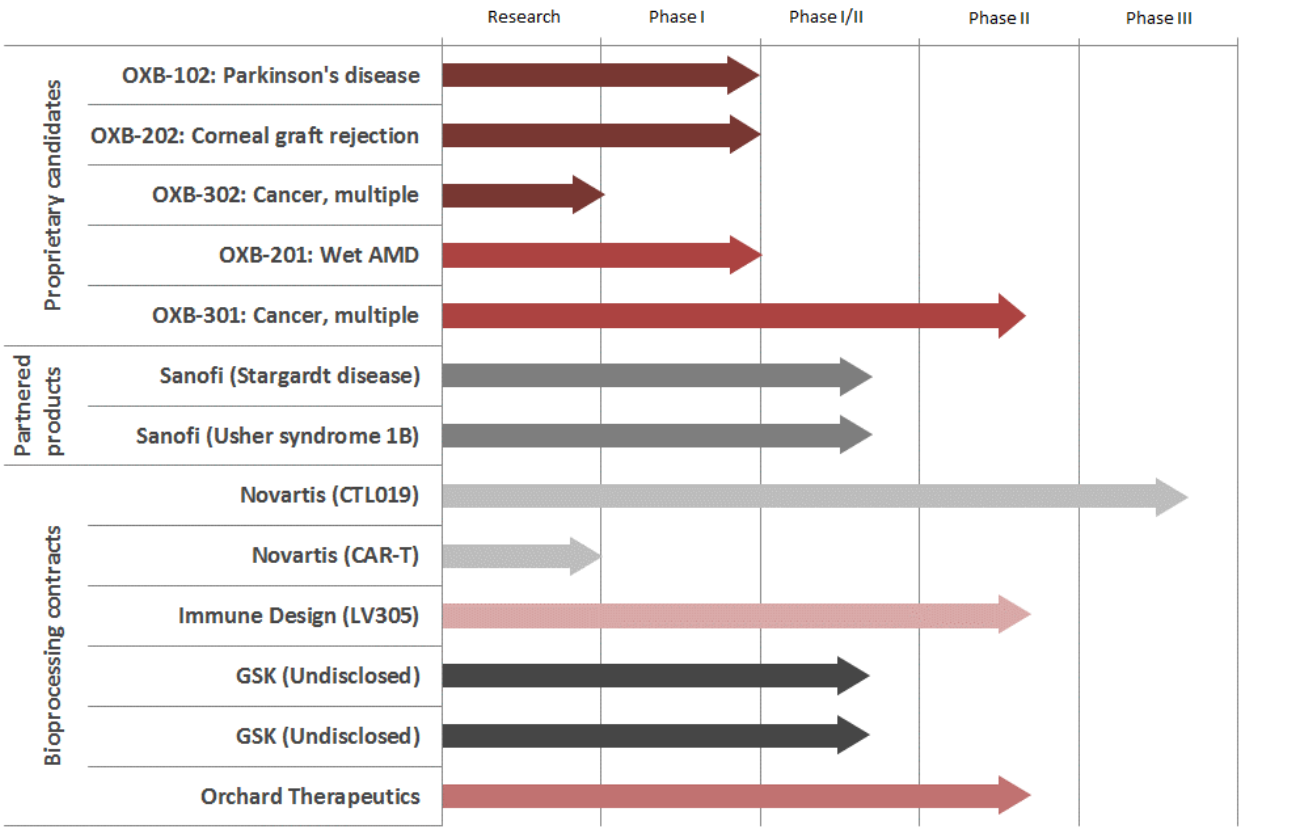
In response to demand for vector from the growing cell and gene therapy market and from the Novartis contract, in 2014 OXB management took the decision to invest in facilities additional to its Harrow House clean room (at full capacity throughout 2015), costing the group approx. £26m. Acquisition and completion of the Yarnton site (leasehold) and Windrush Court was achieved within two years; Yarnton has been supplying Novartis with lentiviral vectors since Jan'16.

The speed with which full certification and expanded facilities was completed is a significant achievement. This has competitively positioned the company to be able to provide partners with a commercial supply of lentiviral vector using its next-generation, large-scale lentiviral vector manufacturing technology.

Pipeline summary

In addition to pre-clinical R&D, OXB is working on 12 candidates. Five are wholly-owned, with three prioritized for spin-out/out-licensing.

Existing Oxford BioMedica assets



Source: Hardman & Co Life Sciences Research

Priority wholly-owned products

OXB-102 – Parkinson's disease

OXB-102 is a candidate gene therapy whose lower potency precursor, OXB-101 (ProSavin), was very promising in Phase I/II trials. The therapy delivers therapeutic genes directly to the brain, increasing dopamine production, which compensates for that lost as a result of the disease. Single treatments could last years.

Parkinson's disease

Parkinson's is a progressive, incompletely understood disease characterised by involuntary tremors and slow and inflexible movement. Symptoms result from reduction of dopamine production as nerve cells in the brain's substantia nigra degenerate. Without sufficient dopamine, nerves communicate sporadically, leading to reduced movement control.

Global point prevalence estimates range from 6-10 million people, including 1.5 million across Europe and the US, and there are likely to be many undiagnosed cases. Most Parkinson's sufferers are over the age of 50, and dementia is common in late-stage disease – dementia is now the biggest cause of death in the UK, and as such there is high and increasing pressure for new treatments.

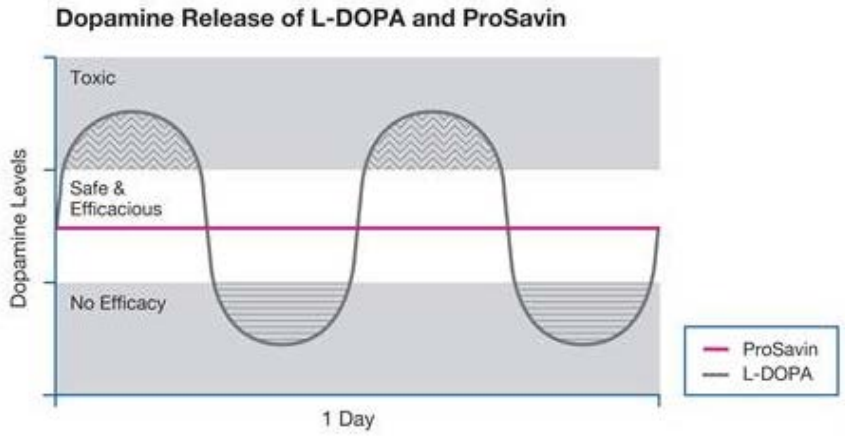
Current standard of care

There is no cure for Parkinson's. Symptoms are managed with a combination of supportive therapies, medication, and sometimes, surgery. Levodopa (L-dopa) has been the gold standard for >40 years: this is an amino acid precursor of dopamine that is administered as a tablet and crosses the blood-brain barrier, leading to intermittent stimulation of dopamine receptors and associated motor complications. It becomes less effective with disease progression since the reduction of dopaminergic neurons decreases drug processing ability. Other medications include dopamine agonists and monoamine oxidase-B inhibitors.

OXB-102 mechanism of action

OXB-102 is designed to overcome the limitations of L-dopa by creating a consistent and long term supply of dopamine through genetic modification of brain cells. It is a lentiviral vector system derived from equine infectious anaemia virus (EIAV) that is injected directly to the striatum, reducing the need for functional dopaminergic cells.

L-dopa v ProSavin: effect on dopamine release



Source: Oxford Biomedica

OXB-102 has three components: the vector genome construct, the packaging construct, and the envelope construct. The vector genome construct contains the three genes that encode enzymes necessary for dopamine production: tyrosine hydroxylase (TH) and cyclohydrolase 1 (CH1), which convert tyrosine to levodopa, and amino acid decarboxylase (AADC) that converts levodopa to dopamine.

OXB-102 vector genome construct

Source: Oxford Biomedica

Development progress

Phase I/II trials (NCT00627588 and NCT01856439) of ProSavin were completed in 2012. Safety, tolerability, and efficacy of bilateral, intra-striatal delivery of ProSavin was assessed in 15 patients with advanced Parkinson's. Three doses from low ($1.9x10^7$ transducing units) to high ($1x10^8$ units) were assessed in separate cohorts, with primary endpoints to identify the number and severity of associated adverse events, and motor responses assessed with the UPDRS scores at six months. The trial was open-label, conducted in two European study sites, and included a 12-month follow up, with a separate follow-up for long-term effects.

The primary endpoints were met, showing ProSavin to be safe, well-tolerated and improving significantly motor function at both timepoints. After 12 months, there had been 54 adverse events – 51 mild, three moderate – most commonly dyskinesia and 'on-off' phenomena. The improvements have been sustained in most patients for at least three years.

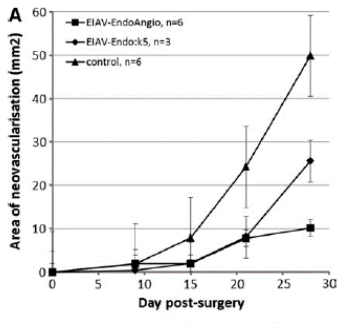
OXB has now completed pre-clinical testing of the more potent vector construct OXB-102, which has higher transfection efficiency. The efficacy arm was completed in 2013, showing potency at least 5x greater than ProSavin. A protocol for a Phase I/II dose escalation study for OXB-102 is with the regulators; however, a partner is needed to carry out this and further trials. Study material has been manufactured.

OXB-202 – Corneal graft

Corneal graft rejection

Corneal transplants are one of the most successful types of tissue transplant performed worldwide, however, many corneal grafts fail because of graft rejection: an immune response to donor tissue. Neovascularization – growth of new blood vessels into the graft – can result in angiogenesis within the cornea, causing it to become increasingly opaque, reducing vision. Most rejection happens 18 months postoperatively, although it can occur even after 20 years. Re-grafting failed transplants is one of the top reasons for corneal transplantation.

Efficacy in pre-clinical models



Source: Oxford BioMedica

OXB-202 mechanism of action

OXB-202, a genetically-modified donated cornea product, is also of high priority for out-licensing for clinical development. A lentiviral vector is used to transform donor corneas with genes for human endostatin and angiostatin, which inhibit angiogenesis into the cornea.

Development progress

A Phase I/II study protocol is expected to be submitted to the regulator in 2017, with patients commencing treatment the same year, if accepted. Focus is initially on US trial sites. Again, this is dependent on successful partnership.

OXB-302 – Solid tumours

OXB-302 is Oxford BioMedica's proprietary CAR-T programme, which is currently completing pre-clinical studies. The 5T4 antigen is prevalent on the surface of solid tumours and metastatic cancer cells, but is less commonly expressed by normal tissues. 5T4 is an exciting target for cancer immunotherapies: discovered by Cancer Research UK, it is included in a variety of therapeutic approaches under development, including in cancer vaccines like Oxford BioMedica's TroVax (OXB-301). OXB-302 is a cell therapy for *ex vivo* modification of autologous T cells with lentiviral vector so that they recognise 5T4 antigen when reintroduced to the body.

OXB-302 development

Two different OXB-302 lentiviral-based vectors have been produced, both of which transduce human peripheral blood mononuclear cells (PBMC). Testing *in vivo* tumour models has demonstrated efficacy, resulting in tumour killing. Clinical testing can begin once the technology is spun-out/out-licensed.

Other candidates

Both OXB-201 and OXB-301 are candidate therapies with potential, however, they require a deal of further development, and as such are not being prioritised for partnership by Oxford BioMedica.

OXB-201 – Wet AMD gene therapy

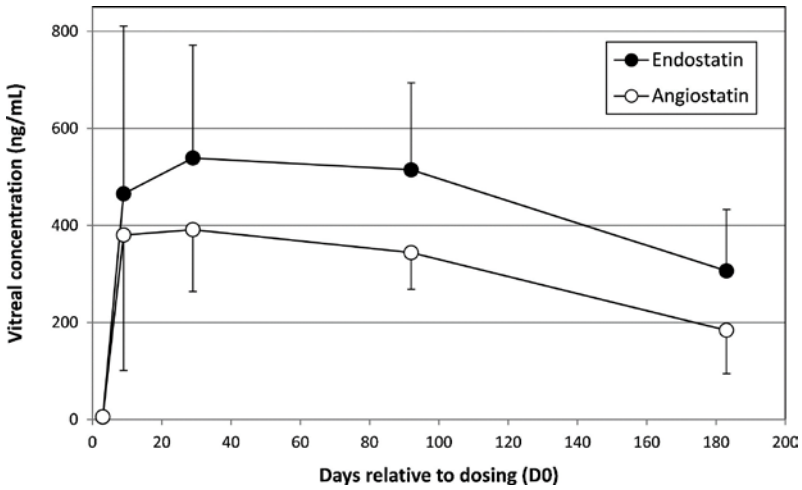
"Wet" Age-related Macular Degeneration (AMD)

The worldwide point prevalence of AMD is 25-30 million people. Wet AMD is an advanced form of AMD, affecting around 10-15% of AMD patients, which accounts for most AMD severe vision loss. It results from disruption to the macular area of the retina (where cone cells are concentrated), which results in angiogenesis as the body attempts to increase oxygen supply to the area. However, the new blood vessels are abnormal and often leak, causing macula scarring and rapid loss of central vision.

OXB-201 mechanism of action

OXB-201 (RetinoStat) is a gene-therapy that acts to treat wet AMD, or a similar condition, diabetic retinopathy, *via* delivery of two genes encoding the anti-angiogenic proteins endostatin and angiostatin. OXB-201 is injected directly to the retina, resulting in modification of local cells that then produce these proteins and prevent vascularisation of the retina. It is the first lentiviral gene therapy to be administered to the human eye.

Long-term effects of OXB-201



Source: Oxford Biomedica

Developmental progress

A Phase I dose escalation safety and tolerability study was completed in May'15, with details published in Oct'16. A total of 21 patients with fibrotic retinas and refractory to anti-VEGF therapy were recruited in the US, with three treated at each of three dose levels, followed by an additional 12 treated at the highest safe dose. Primary

endpoints were met at six months' post-surgery; a secondary endpoint, therapeutic gene expression as measured in aqueous humour samples, was found to be dose-dependent and maintained at 2.5 years in 8 subjects and >4 years in two subjects. Sanofi discontinued their partnership for this candidate following the Phase I trial in 2014. OXB has given this programme lower priority than OXB-102, OXB-202 and OXB-302 for reasons including market opportunity and evidence of efficacy seen to date.

OXB-301 – Solid tumour vaccine

Mechanism of action

OXB-301 is a cancer vaccine that primes the immune system to recognise the 5T4 tumour antigen on the surface of solid tumour cells – as such it is applicable to multiple cancer types including colorectal, renal, and prostate cancer. Unlike other OXB product candidates, OXB-301 (formerly TroVax®) is based on a modified vaccinia viral vector, which has a particularly good safety profile.

Development progress

Clinical development has progressed steadily but slowly, in part due to difficulties in recruiting for trials during the recent accelerated development of cancer immunotherapies. OXB-301 has completed 11 clinical trials to date.

A Phase III trial of TroVax in 700 renal adenocarcinoma patients in 10 countries was completed in 2009. Despite being well tolerated, treatment did not result in enhanced survival relative to placebo and the study did not reach its primary endpoint. Sanofi Aventis returned its rights to TroVax to OXB – to date, development of OXB-301 for this indication has not progressed. The trial did confirm an association between 5T4 antibody responses and enhanced survival, leading to development of the 'immune response surrogate' algorithm, which helps predict 5T4 antibody responses following TroVax treatment. This allows identification of those likely to benefit from TroVax and is used in patient recruitment.

Currently, there are four Phase I/II trials underway in indications such as ovarian cancer. A Phase II mesothelioma study has been completed but with results as yet unpublished. Data released in Feb'17 from a Phase I/II trial in advanced colorectal cancer demonstrated significant anti-5T4 immune responses generated by both low dose chemotherapy and OXB-301. Management has made clear that further Phase III trials would require establishment of a partnership.

OXB pre-clinical research

Green Cross LabCell collaboration

In Jun'16 OXB announced a natural killer (NK) cell-based therapeutics R&D programme in collaboration with Green Cross LabCell (GCLC). GCLC is a South Korean company with a clinically tested platform for producing highly potent and activated NK cells. The combination of this expertise with OXB's LentiVector platform means that initial focus will be on identification of potential CAR-NK candidate oncology therapies, created using lentiviral vectors. GCLC's CEO, Bok-Soo Park, stated that 'OXB is best positioned to accelerate development of these programs'. The parties will share equally the costs associated.

Out-licensed products

Oxford BioMedica has out-licensed two candidates to Sanofi, agreed 2014, for clinical development. OXB will receive development milestone payments and royalties from future sales for both these products. In 2015, OXB transferred the technology for lentiviral vector manufacture for clinical trials to Sanofi, however, OXB still provides advice and clinical analysis of samples following gene therapy.

Sanofi – SAR 422459

Vision: Stargardt disease

Source: Macular Degeneration Support; Oxford BioMedica

Stargardt disease

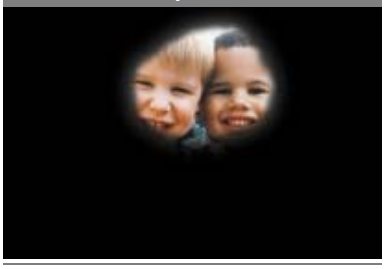
Stargardt disease, also called juvenile macular dystrophy, is a degenerative condition that reduces central vision, usually appearing in adolescence. It is a monogenic recessive disease – mutations in the ABCA4 gene – that results in changes to the macula and is characterised by visible yellow flecks. Prevalence is estimated at around 80-100,000 patients and is the most common form of inherited juvenile macular degeneration, yet there is no approved treatment.

Trials

SAR 422459 is an equine infectious anaemia virus (EIAV)-derived gene therapy that delivers a corrected version of ABCA4 to the retina. It demonstrated efficacy in mouse models of Stargardt disease and was effective for the duration of the study (six months). It is currently in a Phase I/IIa trial, primarily to assess safety and tolerability and secondarily to evaluate its biological activity.

Sanofi – SAR 421869

Vision: Usher syndrome



Source: National Eye Institute, National Institutes of Health; Oxford BioMedica

Usher syndrome

This is a very rare recessive genetic disorder caused by a mutation in any one of at least 11 genes that results in both deafness and blindness. It is incurable. There are three subtypes categorised according to onset and severity of symptoms, which in total affect approximately 30-50,000 people in the US and Europe. A common subtype is type 1B – people are usually born deaf and develop retinitis pigmentosa due to mutation in the gene encoding Myosin VIIA (MYO7A).

SAR 421869 and trials

SAR 421869 is a gene therapy that delivers corrected MYO7A to retinal cells. It is in a currently recruiting Phase I/IIa trial with 18 adult patients; in addition to assessing safety and tolerability, the delay in retinal degeneration will be determined.

Bioprocessing partnerships

Unparalleled manufacturing capacity

Extensive expertise in bioprocessing….

Oxford BioMedica has extensive expertise in bioprocessing and optimising lentiviral vectors, which, combined with its newly expanded facilities, positions the company exceptionally well to provide process development and bioprocessing (GMP-grade vector manufacture) services for clients. These activities require OXB to license its IP to partners for licensing fees in addition to the manufacturing revenue. The Company's gross income is derived from these business activities.

…and process development

Deals may include vector technology 'process development' terms that create new intellectual property for Oxford BioMedica. Of note, the proprietary suspension bioreactor methodology for high-throughput lentivirus production – necessary for commercial manufacture of gene therapies – was developed as part of the Novartis deal. This is strong validation of OXB's service capabilities.

Three bioprocessing deals in place…

…more expected imminently

There are currently three bioprocessing deals in place. Given the number of lentivirus-based cell and gene technologies in late-stage clinical trials, we anticipate that demand for OXB's commercial-scale bioprocessing capability will continue to increase. In particular, the current weakness of sterling is suggestive of an acceleration of demand from Europe and the US.

With Novartis…

Oxford BioMedica's deal with Novartis – announced in October 2014 – includes OXB as the sole manufacturer of lentiviral vector for the CTL-019 (tisagenlecleucel-T) CAR-T programme and includes process development services.

CAR-T programmes

CTL-019 mechanism

This is a CAR-T therapy that targets the CD19 protein, which is only expressed by B cells and their precursors. CD19 is therefore found on the surface of most B cell cancers, such as diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukaemia (B-ALL). Since it is not expressed by haematopoietic stem cells, CAR-Ts that recognise CD19 are very promising in selectively killing cancer cells. In addition to a receptor for CD19, CTL-019 incorporates two signalling domains.

CTL-019 clinical development

Novartis licensed the CTL-019 technology from the University of Pennsylvania in 2012. Latest results from the Phase II ELIANA trial were reported at the 58th American Society of Hematology (ASH) Annual Meeting in December 2016. The trial is evaluating the efficacy and safety of CTL-019 in pediatric and young adults with B-ALL, for which OXB is providing lentiviral vectors expressing CTL-019. The results were very promising, with 82% (n=41) of treated patients achieving complete remission with or without incomplete blood count at three months' post-treatment. Phase II trials are also underway in other indications, for example in 3rd line DLBCL patients in the JULIET trial. Novartis is also undertaking a full Phase III programme, and, although full scientific results have not been published outcomes are assumed to be positive given that the company has submitted it new drug application (NDA) to the FDA.

In March 2017, Novartis announced that the FDA had accepted its Biologics License Application (BLA) filling of CTL-019 for ALL. CTL-019 has breakthrough therapy designation (July 2014) and the recent filing was awarded Priority Review – status designated based on potentially significant improvements in treatment compared to standard applications – which means that the FDA may take action on the application within six months (i.e. by Sep'17). BLA for ALL could, therefore, be expected by end-2017. Novartis expects to file an additional BLA for DLBCL in late 2017[2] and to file for market authorization for both indications in EU later in 2017, having received a Priority Medicines designation from EMA earlier this year.

A second CAR-T

Under the terms of the original 2014 contract, OXB has been providing bioprocessing and process development for a second Novartis CAR-T programme. Although the indication is undisclosed, we note that Novartis has been carrying out exploratory trials in multiple myeloma with BCMA CAR-Ts[3].

Deals

October 2014 contract

Three-year bioprocessing and process development contract with Novartis…

…likely to be extended on market authorisation of CAR-T therapies

The first contract with Novartis for $4m was signed in May'13: in essence this was a process development agreement to gauge feasibility for future work. Success led to the major contracts announced in Oct'14. Under the terms of the three-year agreement:

- OXB manufactures batches of lentiviral vector encoding CTL-019 plus another undisclosed CAR using its cell factory method for Novartis to use in trials
- OXB carries out process development activities for up-scaled manufacturing processes
- Novartis was granted a non-exclusive licence to the LentiVector platform

Income is in the following forms:

- Manufacturing fees per batch of vector produced
- Process development fees – includes milestone payments on delivery of targets (e.g. capacity expansion and yield improvements)
- Upfront payments as licensing income
- Future royalties from sales of CAR-T therapy using OXB vector

The deal was reported to be worth a total of $90 million – $14 million initially including a $4.3m equity subscription – with $76m received over the three years for process development and bioprocessing.

Extension expected

OXB has not yet announced an extension to the bioprocessing part of the deal, which we understand will expire in 2H'17. We assume Novartis will engage OXB as the commercial manufacturer of vector should the therapy receive marketing authorisation: OXB has produced CTL-019 vector throughout trials, so FDA BLA approval would include chemistry, manufacturing, and controls (CMC) regulatory authorisation granted on the basis of OXB's cell factory manufacturing process. This would require OXB facilities to undergo a further inspection.

[2] Novartis Development Update FY2016 (https://www.novartis.com/sites/www.novartis.com/files/q4-2016-ir-presentation-development.pdf)
[3] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500217484.pdf

Novartis "re-integrating" Cell & Gene Therapies unit…

…not likely a blow to commercialisation of CAR-T therapies

In addition, Novartis announced recently that it will be "re-integrating" its Cell & Gene Therapies unit at Morris Plains, NJ – the location for patient cell CAR-T modification – into its Oncology business as part of its immune-oncology strategy. Whilst this superficially could appear to be negative for CAR-T programmes, in our opinion it is likely to suggest an increase in outsourcing of CAR-T bioprocessing to external organisations. With capacity expansion completed, OXB is in place to deliver commercial supply of vector.

With Orchard Therapeutics…

The latest bioprocessing deal (Nov'16) is a 'strategic alliance' with Orchard Therapeutics, whereby OXB will provide bioprocessing and process development services, including an exclusive intellectual property licence. Orchard is a recently incorporated, private, autologous stem cell therapy company that has strong relationships with world-leading private and public healthcare organisations.

Orchard Therapeutics Ltd		
Management position	**Name**	**Most recent/additional affiliation**
SVP Business Operations	Dr Nicolas Koebel	GSK
Chief Manufacturing Officer	Dr Stewart Craig	Sangamo BioSciences
Chief Medical Officer	Dr Andrea Spezzi	GSK
Chief Scientific Officer	Dr Bobby Gaspar	UCL
Chief Regulatory Officer	Anne Dupraz-Poiseau	VCLS

Source: Hardman & Co Life Sciences Research

Orchard's current focus is on serious and life threatening orphan diseases, particularly in children and young adults. Initially, Orchard will use OXB's vectors to manufacture modified autologous stem cells for Phase II/III trials in patients with ADA-SCID, and in early clinical trials in patients with Mucopolysaccharidosis-IIIA (inherited metabolic disorder). Going forward, Orchard will lead global commercialisation of these therapies and of other undisclosed indications.

Under agreement terms, OXB will receive:

- 1.95% equity stake in Orchard
- Licensing fees: royalties on future sales of products covered by the alliance; performance-related milestones e.g. further 1.95% equity stake

With Immune Design…

Immune Design is a clinical stage, listed (Nasdaq: IMDZ) company that is developing immunotherapies. Its partners include Sanofi, Merck & Co, and MedImmune (AstraZeneca).

LV305

OXB continues to provide Immune Design with assistance in release testing of LV305. LV305 is an immunotherapy for *in vivo* treatment or prevention of tumours expressing the NY-ESO-1 antigen. LV305 is administered intradermally – specifically targeting dendritic cells *in vivo*, genetically modifying them to present NY-ESO-1, and therefore, inducing or priming cytotoxic T cell responses against such tumours.

LV305 is currently in at least two Phase I trials for indications including melanoma, sarcoma and ovarian cancer. A Phase II trial is underway to assess the use of CMB305 (which includes LV305) in combination with atezolizumab (TECENTRIQ, Genentech) in patients with sarcoma. Immune Design has received orphan drug designation in US and EU for each component of CMB305 for soft tissue sarcoma.

Contract terms – March 2016

The contract extended in Mar'16 builds on the 2012 process development agreement with Immune Design for development of analytic assays. It includes a non-exclusive, royalty-bearing intellectual property licence from OXB to Immune Design for the use of lentiviral vector-based products. It is our opinion that OXB would be IMDZ' commercial supplier of lentiviral vectors should CMB305 reach the market.

Competitive landscape

At this point we view potential competition to commercial LV manufacture and to OXB-102 (Parkinson's disease) to be of highest importance – the rest of OXB's pipeline is either on hold pending partnership or is in pre-clinical development.

Bioprocessing competition

LV manufacturers

Many Contract Development & Manufacturing Organisations (CDMOs) have specialist cell line capability for viral vector propagation, but few specialise in GMP manufacture of clinical-grade lentiviral vector. The latter is likely to increase since most biopharma companies do not have internal capacity for commercial production and the industry is trending towards specialist outsourcing. OXB is in a very strong position in the global market and is the leader in its niche in the UK.

All ATMP manufacturers with LV processing ability are potential competition. In the table below, focus is on organisations that specify process development services in addition to commercial manufacture. Companies in bioprocessing contracts with clinical ATMP partners are particularly relevant – the closest competitors here are Lonza, MolMed, and Sigma-Aldrich (Merck KGaA). Notably, Lonza supplies Bluebird Bio with LV for CAR-T programmes and MolMed supplies LV for trials sponsored by San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), in addition to its own.

Select GMP clinical-grade LV contract manufacturers

Organisation	Headquartered	Sector	LV based proprietary candidates
apceth Biopharma	Munich, Germany	CDMO	No
Beckman Research Institute	City of Hope – California, US	NPO	Yes
Davis School of Medicine	University of California, US	Public university	Yes
EUFETS	Germany	CDMO	No
Genethon	Paris, France	NPO	Yes
Lonza*	Basel, Switzerland	CDMO	No
Masthercell	Brussels, Belgium	CDMO	Yes
MolMed*	San Raffaele Biotechnology Department – Milan, Italy	Biopharma	Yes
Oxford BioMedica*	Oxford, UK	Biopharma	Yes
PharmaCell	Maastricht, Holland	CDMO	No
St. Jude Children's Hospital	Tennessee, US	NPO	Yes
Sigma-Aldrich (Merck KGaA)	Darmstadt, Germany	Biopharma	Yes
Sirion Biotech	Munich, Germany	CDMO	No
Takara	Japan	CDMO	Yes

N/A: not applicable
**Current supplier for late stage trials (to our knowledge)*
Source: Hardman & Co Life Sciences Research; Merten 2016

Lonza

Lonza is an established Swiss CDMO with global operations, capitalised at CHF11bn (GBP9bn). Within its pharma & biotech business unit it provides a range of development services including custom manufacturing of biopharmaceuticals. It does not derive royalties from these services to our knowledge.

- Supplies Bluebird Bio with LV for CAR-T clinical development

MolMed

MolMed is a clinical-stage biopharmaceutical company that focuses on immuno-oncology. It is headquartered at the San Raffaele Biotechnology Department (DIBIT) in Milan, Italy and is capitalised at €178m (£154m). In addition to proprietary candidates, it produces clinical stage viral vectors and manufactures patient-specific cells modified with LV. One of MolMed's candidates, a bone marrow transplant cell therapy, is in Phase III trials and is under evaluation for EMA conditional marketing authorisation. Notably, the company is in a five-year strategic collaboration with GSK for supply of services and vector – the original collaboration was successful in producing Strimvelis, thus MolMed's commercial manufacturing capabilities have been validated.

- Supplies SR-TIGET and GSK with LV for cell/gene therapy clinical development

Sigma-Aldrich (Merck KGaA)

Sigma-Aldrich was acquired by Merck KGaA (market cap €26bn/£23bn) in 2014 and has been integrated into its life sciences business, Merck Millipore. Merck's life sciences business is one of the largest in the industry, with operations in 66 countries, revenues of €5.7bn and EBITDA at €1.7bn in 2016. Its offerings span the biotech/biopharma production chain, with 300k products including drug therapies. Within Sigma-Aldrich, SAFC is the custom manufacturing business – its Carlsbad, California manufacturing facility has been expanded by Merck in response to increased demand. These are FDA inspected facilities with single use bioreactors allowing for commercial vector production. SAFC manufacturing collaborations were announced prior to the acquisition (e.g. with AGTC) but Merck KGaA collaborations do not appear to have been disclosed.

Cell Therapy Catapult

Within the UK, the Cell and Gene Therapy Catapult has been set up by Innovate UK, the government's innovation agency, 'to drive the growth' of the cell and gene therapy industry. A £55m large-scale GMP manufacturing centre is under construction at the Bioscience Catalyst site in Stevenage, Hertfordshire. The centre will provide manufacturing and office space for a number of companies and centralised GM services. It is due to open in 2Q'17, although there is some way to go to completion. This facility will certainly accelerate vector and candidate manufacturing capacity of companies in this space, but it does not pose a threat to OXB, at least in the short term.

CAR-T competitors

Anti-CD19 therapies

The race to achieve market authorisation for a CAR-T therapy is being closely watched. OXB's considerable investment in manufacturing facilities has banked on a return from royalties and service fees from Novartis' CTL-019 therapy. Novartis recently announced BLA submission for ALL, making it on track to be the first to achieve authorisation for a CAR-T therapy in any market.

CTL-019's main competition is from other anti-CD19 CAR-Ts, since these may be transferable to indications in other B-cell malignancies including CTL-019's primary indication, acute lymphoblastic leukaemia (ALL).

Close on the heels of Novartis is Kite (US): its leading anti-CD19 CAR-T is in Phase II trials for MHL. This CAR-T is also in earlier stage trials for ALL and DLBCL but it is likely

that CTL-019 will be the first CAR-T to receive marketing authorisation for ALL in both US and Europe.

It is worth noting that there are other anti-CD19 CAR-T candidates (e.g. Servier/Pfizer) that utilise allogeneic cells (from donors). If clinically successful, these have the potential to deliver higher returns than autologous therapies because they can be stored for immediate 'off-the-shelf' treatments, considerably reducing COGS. These are at an earlier stage of development because there are greater immunogenicity issues to be overcome.

Clinical CAR-T candidates targeting CD19

Company	Candidate	Phase	Regulatory info	Target	Vector	Primary Indication
Novartis	CTL-019	II	Breakthrough/BLA 1H'17E	CD19 (4-1BB)	Lenti	ALL
	CTL-019	II	N/A	CD19 (4-1BB)	Lenti	DLBCL
Juno	JCAR017	I/II	Breakthrough/PRIME	CD19 (4-1BB)	Lenti	DLBCL
	JCAR014	I/II	N/A	CD19 (4-1BB)	Lenti	ALL/CLL/NHL
Kite	KTE-C19	II	N/A	CD19 (CD28)	Retro	MCL
		I	N/A	CD19 (CD28)	Retro	ALL/DLBCL
Bluebird Bio/Celgene	bb2121	I	N/A	CD19 (CD28)	Lenti	MM
Servier/Pfizer	UCART19*	I	N/A	CD19	TALEN	ALL
Ziopharm/Intrexon	CAR-T	I	N/A	CD19 (CD28, 4-1BB)	Transposon	Lymphoid malignancies

N/A: Not Available
**Allogeneic cell therapy*
Source: Hardman & Co Life Sciences Research

Advanced, but early stage therapies

The Phase II 'ROCKET' trial of Juno therapeutics' JCAR015, which also targets CD19 but is delivered with a retroviral vector, was suspended for the second time in Nov'16 following two further cerebral oedema deaths. Juno had anticipated filing JCAR015 for BLA in 1H'18. In the past, peak market capitalisation of Juno had been $6.4bn (Mar'15) – solely on the potential of unlicensed CAR-T therapies. The share price fell by as much as 50% following news of trial suspension and the company has now announced termination of JCAR015 trials. It should be noted that treatment of many participants with JCAR015 was successful, so the trial deaths really serve as a reminder of the early developmental stage of these therapies. According to Juno, trials of their other CAR-T candidates will continue as planned.

ADA-SCID competition

OXB's latest bioprocessing partner, Orchard, is focused on autologous *ex vivo* stem cell therapies for ADA-SCID (orphan disease affecting around 50 patients in US and UK) and Mucopolysaccharidosis-IIIA. Strimvelis (GSK) is a direct competitor in ADA-SCID; however, MolMed processes the cells in Milan, necessitating patient travel for treatment. Strimvelis COGS are, therefore, likely to be high – we understand that Orchard has an advantage in this respect since its approach includes cryopreservation of the modified cells and transfer to the treating hospital.

Parkinson's disease advanced therapies

Since 2004 there have been at least nine gene therapy trials completed in Parkinson's disease, which showed safety, but not strong efficacy, outcomes. There have been three main strategies. Commonly, AAV vectors are used to deliver dopamine-synthesising enzyme genes; these candidates are furthest through trials. Unlike OXB-102 which delivers all three enzymes needed for dopamine production *via* lentivector, these have to act on orally administered L-dopa since natural conversion declines as disease progresses. OXB's closest competitor in this space is

considered to be Voyager, although the latter's target market is possibly smaller than OXB's given that its efficacy is contingent on concurrent L-dopa therapy.

A second approach – in trials sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH – involves introducing a gene for Glial cell line-derived neurotrophic factor (GDNF) to promote survival of dopaminergic neurons. This is in early trials with primary endpoint data not available until 2025.

The third approach, which reached Phase II trials, acted to modulate neural activity through introduction of the GAD gene. This was not developed once Neurologix (US) filed for bankruptcy in 2012.

Parkinson's disease – gene and cell therapy candidates

Trial sponsor	Partner(s)	Candidate	Phase	Est. primary completion (patients)	Gene(s)	Vector	Administration site (method)
Oxford BioMedica	Pending	OXB-102	I/II pending	N/A	AADC, TH, GCH1	LV	Striatum (injection)
Voyager	Genzyme (Sanofi) California Institute of Technology	VY-AADC01	Ib ongoing	Dec'18 (20)	AADC	AAV	Putamen (infusion)
Jichi Medical University	Takara Bio Inc; Gene Therapy Research Institution	AAV-hAADC-2	I/II ongoing	Oct'17 (6)	AADC	AAV	Putamen (infusion)
National Institute of Neurological Disorders and Stroke		AAV2-GDNF	I ongoing	Jan'25 (100)	GDNF	AAV	Putamen (convection-enhanced delivery)

Source: Hardman & Co Life Sciences Research

Commercial strategy

Updated strategy

Management has emphasised that the company will continue to focus on pre-clinical R&D in addition to bioprocessing and process development partnerships. Clinical development of proprietary candidates is on hold pending spin-out/partnership. At 2016 full-year results, management announced that it expected, among other things, the following progress by the end of 2018:

- New candidates emerging from pre-clinical R&D
- Gene-modified NK cell therapeutic candidate from GCLC research collaboration
- Royalties from CTL-019
- Facilities operating at, or near, capacity (which may increase on further development of manufacturing efficiencies)

Regulatory progress

OXB's facilities are fully certified by the MHRA and are periodically inspected by Novartis as part of the CTL-019 partnership. We understand that award of BLA for CTL-109 would require FDA certification of OXB's facilities – this should be straightforward given Novartis' expertise (*via* Sandoz) in biologicals.

Intellectual property

OXB will continue to add to its IP portfolio through its internal and collaborative R&D and from process development activities undertaken as part of bioprocessing deals. Patents filed early in the company's history will expire this year, but the company is protected by more recent patents and extensive know-how.

Market potential

Quantification of the commercial opportunity for OXB's LentiVector bioprocessing and process development capability is difficult: OXB's manufacturing capacity should increase as bioprocessing efficiency increases; and manufacturing and licensing income is a function of the commercial success of partner therapies and competition from other lentivector manufacturers. We therefore focus on the market potential of Novartis's CTL-019, Orchard's ADA-SCID therapy, and OXB's leading clinical-stage candidates.

Bioprocessing partnerships

CTL-019

Sales of potential CAR-T therapies are difficult to estimate: none are approved, and there are uncertainties in pricing and reimbursement strategies. Strimvelis (cell therapy approved 2016) is priced around €600,000 per treatment, but reimbursement has been agreed only in the one country (Italy) where treatment can be accessed. GSK has agreed to offer a refund if the therapy is unsuccessful. The expense of these treatments may limit their market penetration, particularly in Europe. In estimating OXB's income from CTL-019 vector bioprocessing, we have made the following assumptions:

- CTL-019 BLAs awarded for: paediatric r/r B-ALL and paediatric/adult DLBCL by 2Q'18
- CTL-019 treatment mainly in relapsed/refractory patients with poor prognosis: 10% B-ALL patients and 30% DLBCL patients
- Max 20% penetration of the ALL market in Europe and 30% in US; max 15% penetration of the DLBCL market in Europe and 25% in US by 2025
- Price for single treatment: $600,000
- OXB receives 4% royalties

We estimate that Novartis will achieve sales of $2.05bn per annum from CTL-019 by 2025. OXB could, therefore, receive a total of $82.0m in royalties per annum, in addition to manufacturing revenue.

OXB royalties from CTL-019 partnership

Indication	Geography	Annual prevalence	3rd line cases	Market penetration	Novartis annual sales estimate ($m)	OXB annual Royalties ($m)
Paediatric ALL	Europe	4,000	400	20%	48.0	1.9
Paediatric ALL	US	2,557	256	30%	46.0	1.8
DLBCL	Europe	28,120	9,280	15%	835.0	33.4
DLBCL	US	22,680	7,485	15%	1125.0	44.9

ALL: Acute lymphoblastic leukaemia
DLBCL: Diffuse large B-cell lymphoma
Source: Hardman & Co Life Sciences Research

Orchard

Orchard's genetically-modified stem cell therapy is unlikely to achieve a large market given the rarity of ADA-SCID. However, until GSK develops additional sites for treatment with Stimvelis, Orchard could gain a significant share of the European market e.g. 60%. ADA-SCID causes only around 15 new cases in Europe per year – if priced at $500k, Orchard could make sales of $4.5m pa. In addition to its equity stake, OXB will receive a royalty (estimated 1%) of $45k pa.

Proprietary products

OXB-102

OXB-102 should be in sales by 2030. Time is needed to secure a partner (2H-'17E), complete clinical trials (2028E), and achieve market authorisation. An estimated 610k people over 50 years of age will have Parkinson's in the US, and 1,200k in Europe, by 2030[4]. We estimate that OXB-102 could reach $1.8bn annual sales in EU and US; assuming 10% royalties, OXB will make $181m per annum plus manufacturing fees. This is based on the following assumptions:

- OXB-102 initially used to treat advanced or refractory disease only
- Annual addressable market potentially 36.2k patients (patients progress to advanced disease after 8 years)
- Current treatment options in advanced disease include implant devices that deliver deep brain stimulation (DBS): side effects include seizures. If OXB-102 is demonstrated to have ProSavin's safety profile, it will take market share from these devices, possibly achieving 50% penetration in advanced Parkinson's

[4] Dorsey E.R. et al 2007

- In contrast to autologous cell-based therapies, there is possibility of mass production and reduced COGS – we estimate $100,000 per treatment
- High cost-effectiveness potential given the single treatment (costs for standard Parkinson's disease treatment and after-care are estimated at $25bn pa)

Corneal graft rejection

An estimated 46k corneal transplants are carried out annually in the US. Of these, around 15k are in 'high-risk' patients – those with a high degree of vascularisation in the corneal bed[5] and graft failure rates of 35% after three years. High-risk figures for Europe are around 4k. We assume that OXB-202 would initially be targeted to this market, which, all else being equal could reach 360k patients each year globally.

The uncertainties in quantifying the timing and penetration of this market include:

- tissue bank infrastructure – less established outside Europe and US
- regulatory and operational complexity e.g. local manufacturing facilities needed (viability of donor tissue in storage limited to around 10 days)
- expense of treatments given on a per patient basis
- time needed secure a partner or establish an SPV for clinical development

Assuming 50% penetration rate at peak in US and EU, OXB-202 could be grafted into around 4,300 patients per year. At a price of $20k per cornea, and 10% royalties to OXB, OXB could receive $8.6m annually. This would increase as the product enters additional markets, such as low-risk and first-time corneal grafts.

[5] Parker M. *et al* 2014

Financials & Investment case

Profit & Loss

Revenues

- **Service-fees:** For bioprocessing (manufacturing) and process development services
- **Additional income:** Up-fronts, milestones, and incentives for process development services; licensing income and royalties from bioprocessing and process development partnerships, and from OXB's out-licensed products
- **Other income** (not included in group revenues): Grants and R&D collaborations

OXB has two main revenue streams. First, OXB generates service-fees from bioprocessing and process development activities. The focus is initially on delivering in respect of the Novartis contract, but the company will also take advantage of increased demand from the biopharmaceutical industry for lentiviral vector process development and bioprocessing. This is on a fee-for-service basis.

Secondly, OXB will receive up-front, milestone, and incentive payments for successfully improving yields in process development, and ultimately royalties on net sales of commercial products. Until a reliable royalty stream is reached from substantial and stable sales of drugs using OXB's lentiviral platform, payments will be lumpy year to year. There is a case that such receipts should be treated as 'other income', but for comparative purposes at this stage we treat them the same as OXB, which instead reports only grants and R&D partnering activities as other income.

Revenue summary

Year end Dec (£m)	2014	2015	2016	2017E	2018E	2019E
Bioprocessing + PD	7.80	14.44	23.98	35.07	42.43	48.57
Additional income	6.37	3.54	3.80	3.78	4.58	5.43
Group revenue	**13.62**	**15.91**	**27.78**	**38.80**	**47.00**	**54.00**
Growth rate		+17%	+75%	+40%	+21%	+15%

Source: Oxford BioMedica reports; Hardman & Co Life Sciences Research

Cost of Goods Sold (COGS)

COGS are the direct costs associated with the bioprocessing service. Indeed, a large part of the cost base is from the manufacturing of products for bioprocessing contracts. Therefore, our analysis and forecasts are based on the percentage of these costs against the bioprocessing sales only. In the short-term, until much of the increased capacity becomes utilised, COGS are expected to rise faster than sales, reducing the gross margin. As OXB wins more bioprocessing work, we anticipate COGS to fall as a percentage of sales, and gross margins to increase.

Selling, General & Administration (SG&A)

OXB has only modest direct marketing of its activities at present, so most of the SG&A expense is the corporate overhead. This is currently running at just under £6m per annum. Given that the company intends to run its development projects as separate entities, there is likely to be an increase in personnel to manage its interests, thus SG&A is expected to rise at a rate modestly above inflation.

R&D investment

The recent underlying run rate for OXB's proprietary R&D has been around £10m per annum. However, management has stated its intention to either out-licence its core programmes prior to the start of Phase I/II clinical trials or to spin-out each project to be run as an independent entity with its own external funding. Consequently, proprietary R&D spend is expected to fall only slightly in 2017 and beyond. R&D spend as part of partner process development is likely to remain quite significant and lumpy. The company will, however, continue to invest in pre-clinical development work with the aim of identifying new candidates that can be out-licensed or spun-out.

Profit & Loss account						
Year end Dec (£m)	**2014**	**2015**	**2016**	**2017E**	**2018E**	**2019E**
GBP:EUR	1.24	1.38	1.18	1.18	1.18	1.18
GBP:USD	1.65	1.53	1.35	1.35	1.35	1.35
Bioprocessing + PD*	7.80	14.44	23.98	35.07	42.43	48.57
Additional income	6.37	3.54	3.80	3.78	4.58	5.43
Group revenues	**13.62**	**15.91**	**27.78**	**38.80**	**47.00**	**54.00**
COGS	-4.42	-5.84	-11.84	-14.51	-16.89	-18.04
Gross profit	**9.20**	**10.07**	**15.94**	**24.29**	**30.11**	**35.96**
Gross margin (%)	67.6%	63.3%	57.4%	62.6%	64.1%	66.6%
SG&A	-3.74	-6.01	-5.09	-5.17	-5.47	-5.74
R&D	-16.99	-20.27	-24.30	-22.80	-24.61	-24.29
EBITDA	**-9.29**	**-11.73**	**-6.78**	**2.26**	**5.97**	**11.37**
Depreciation	-0.70	-1.26	-3.34	-4.10	-4.10	-4.10
Amortisation	-0.40	-0.36	-0.34	-0.34	-0.34	-0.34
Other income	1.13	2.86	3.00	1.50	1.50	1.00
Underlying EBIT	**-10.39**	**-13.35**	**-10.45**	**-2.18**	**1.53**	**6.93**
EBIT margin (%)	76.3%	83.9%	37.6%	-5.6%	3.3%	12.8%
Share based costs	-0.22	-0.73	-0.87	-0.97	-1.07	-1.17
Exceptional items	0.00	0.00	0.00	0.00	0.00	0.00
Stat. Operating profit	**-10.61**	**-14.08**	**-11.32**	**-3.14**	**0.47**	**5.77**
Net interest	-0.19	-2.90	-5.81	-5.09	-5.09	-5.08
Forex gain/loss	0.00	0.00	-3.18	0.00	0.00	0.00
Pre-tax profit	**-10.58**	**-16.25**	**-19.44**	**-7.26**	**-3.56**	**1.85**
Exceptional items	0.00	0.00	0.00	0.00	0.00	0.00
Reported pre-tax	-10.80	-16.98	-20.31	-8.23	-4.62	0.68
Tax payable/credit	2.14	3.96	3.67	4.56	4.92	4.86
Underlying net income	**-8.44**	**-12.29**	**-15.78**	**-2.70**	**1.36**	**6.70**
Statutory net income	-8.66	-13.02	-16.64	-3.67	0.30	5.54
Ordinary shares (m)						
Period-end	2,566	2,574	3,088	3,088	3,089	3,090
Weighted average	2,019	2,570	2,780	3,088	3,089	3,090
Fully diluted	2,108	2,670	2,909	3,218	3,219	3,221
U/lying Basic EPS (p)	**-0.42**	**-0.48**	**-0.57**	**-0.09**	**0.04**	**0.22**
Stat. Basic EPS (p)	-0.43	-0.51	-0.60	-0.12	0.01	0.18
U/l Fully-diluted EPS (p)	**-0.40**	**-0.46**	**-0.54**	**-0.08**	**0.04**	**0.21**
Stat. Fully-diluted EPS (p)	-0.41	-0.49	-0.57	-0.11	0.01	0.17
DPS (p)	0.0	0.0	0.0	0.0	0.0	0.0

**PD: Process Development*

Source: Hardman & Co Life Sciences Research

Balance sheet

Loan facility

On 1st May 2015, OXB entered into a loan agreement with Oberland Capital for a $50m facility for expansion of the group's manufacturing facilities. $25m was drawn down immediately and a further $15m was drawn down in September 2015. The loan is repayable no later than 1st May 2022. The loan's essential features are:

- **Coupon:** Cash interest of 9.5% + the greater of 1% or 3-month LIBOR, payable quarterly
- **Royalty:** 0.35% of annual worldwide net sales for a period of 8 years from 1st April 2017 for each $5m drawdown over $30m
- **Exit fee:** The revenue participation may be retired on payment of an exit fee
- **True-up payment:** In the event that the loan is repaid by 1st May 2017, there will be a true-up payment to provide Oberland with a total return of 15%
- **Cash balance:** OXB is required to maintain a cash of at least $10m at all times while this loan is outstanding

Being in USD, the loan is sensitive to exchange rates pertaining to the last day of each reporting period. Weakness of sterling gave rise to a £3.2m translational hit, taken through the financial expense line in the P&L account in 2016. In addition, the company is amortising the likely costs at repayment of the debt which are included as part of the total loans in the balance sheet at the end of the period.

Balance sheet

@31st December (£m)	2014	2015	2016	2017E	2018E	2019E
Shareholders' funds	23.04	10.89	12.62	9.05	9.44	15.08
Cumulated goodwill	0.00	0.00	0.00	0.00	0.00	0.00
Total equity	23.04	10.89	12.62	9.05	9.44	15.08
Share capital	25.66	25.74	30.88	30.88	30.88	30.88
Reserves	-2.62	-14.85	-18.26	-21.83	-21.44	-15.80
Provisions/liabilities	3.46	4.42	3.94	0.00	0.00	0.00
Deferred tax	0.00	0.00	0.00	0.00	0.00	0.00
Long-term loans	1.00	27.26	34.39	37.12	39.85	42.58
Short-term debt	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash	14.20	9.36	15.34	12.11	13.83	20.79
less: Deposits	0.00	0.00	0.00	0.00	0.00	0.00
Invested capital	**13.31**	**33.21**	**34.95**	**34.06**	**35.47**	**36.88**
Fixed assets	8.94	24.40	27.51	25.35	23.09	21.05
Intangible assets	2.11	1.74	1.33	1.00	0.66	0.33
Inventories	1.41	2.71	2.20	3.22	3.90	4.46
Trade debtors	*3.62*	*7.37*	*5.43*	*6.52*	*7.82*	*9.39*
Other debtors	*1.53*	*3.56*	*1.47*	*1.47*	*1.47*	*1.47*
Trade creditors	*-2.79*	*-3.59*	*-2.51*	*-2.51*	*-2.51*	*-2.51*
Tax liability/credit	*2.00*	*2.72*	*3.00*	*3.67*	*4.56*	*4.92*
Other creditors	*-3.52*	*-5.70*	*-3.49*	*-4.65*	*-3.52*	*-2.23*
Debtors less creditors	0.85	4.37	3.90	4.49	7.82	11.04
Invested capital	**13.31**	**33.21**	**34.95**	**34.06**	**35.47**	**36.88**
Net cash/(debt)	**13.20**	**-17.90**	**-19.05**	**-25.01**	**-26.02**	**-21.79**

Source: Hardman & Co Life Sciences Research

Cashflow

- **Depreciation:** The depreciation rate has risen following completion during 2016 of the new manufacturing facilities in Oxford
- **Working capital:** Given that much of OXB's work is on a fee-for service basis, there is no major working capital requirement for the group
- **Net interest:** The actual cash paid on loan interest is lower than the charge to the P&L account because there is no cash payment associated with the amortisation charge accruing
- **Cap-ex:** Completion of Windrush Court facilities is expected to see capital expenditure fall to maintenance levels, estimated at around £2m per annum

Cashflow

Year end Dec (£m)	2014	2015	2016	2017E	2018E	2019E
Trading profit	-10.39	-13.35	-10.45	-2.18	1.53	6.93
Depreciation	0.70	1.26	3.34	4.10	4.10	4.10
Amortisation	0.40	0.36	0.34	0.34	0.34	0.34
Inventories	*-0.73*	*-1.30*	*0.50*	*-1.02*	*-0.68*	*-0.56*
Receivables	*-2.56*	*-5.78*	*4.03*	*-1.09*	*-1.30*	*-1.56*
Payables	*3.37*	*2.98*	*-3.28*	*0.00*	*0.00*	*0.00*
Change in working capital	0.08	-4.09	1.25	-2.10	-1.98	-2.13
Exceptionals/provisions	1.65	0.95	-0.75	-0.75	-0.75	-0.75
Disposals	0.00	0.00	0.00	0.00	0.00	0.00
Other	0.13	0.00	-0.90	0.00	0.00	0.00
Company op cashflow	**-7.43**	**-14.87**	**-5.93**	**-2.70**	**1.26**	**6.36**
Net interest	-0.19	-1.46	-3.21	-5.09	-5.09	-5.09
Tax paid/received	1.64	3.24	4.08	3.67	4.56	4.92
Operational cashflow	-5.98	-13.08	-5.06	-4.12	0.73	6.19
Capital expenditure	-5.58	-16.72	-6.46	-1.94	-1.84	-2.06
Sale of fixed assets	0.00	0.00	0.00	0.00	0.00	0.00
Free cashflow	**-11.56**	**-29.80**	**-11.52**	**-6.06**	**-1.11**	**4.13**
Dividends	0.00	0.00	0.00	0.00	0.00	0.00
Acquisitions	0.00	0.00	0.00	0.00	0.00	0.00
Disposals	0.00	0.00	0.00	0.00	0.00	0.00
Other investments	0.00	0.00	0.00	0.00	0.00	0.00
Cashflow after invests.	**-11.56**	**-29.80**	**-11.52**	**-6.06**	**-1.11**	**4.13**
Share repurchases	-0.23	0.00	0.00	0.00	0.00	0.00
Share issues	22.81	0.14	17.50	0.10	0.10	0.10
Currency effect	0.00	-1.44	-7.13	0.00	0.00	0.00
Loans/cash acquired	0.00	0.00	0.00	0.00	0.00	0.00
Change in net debt	**11.03**	**-31.10**	**-1.15**	**-5.96**	**-1.01**	**4.23**
Hardman FCF/share (p)	-0.30	-0.51	-0.18	-0.13	0.02	0.20
Opening net cash	2.17	13.20	-17.90	-19.05	-25.01	-26.02
Closing net cash	**13.20**	**-17.90**	**-19.05**	**-25.01**	**-26.02**	**-21.79**

Source: Hardman & Co Life Sciences Research

Valuation

Our usual approach to valuing biopharmaceutical companies is to prepare detailed discounted cashflow analyses of each key product in the company's portfolio through to patent expiry to provide the NPV of those cash streams and then to risk-adjust this value based upon long-term industry standards for the probability of the product reaching the market. However, this methodology is inappropriate for Oxford BioMedica given that its strategy is to out-licence/spin-out its putative drug pipeline after establishment of pre-clinical activity and to receive a royalty on eventual sales by its licensee.

Royalties from out-licensed products

Sales potential

We have undertaken our own assessment of the sales potential of each of OXB's development assets based on prevalence, target population, penetration and an assumption on price. Wherever possible, this has been validated against the actual ex-factory sales achieved by a commercially available drug for the same indication from when it was first launched onto the market. OXB would receive modest profit from supply arrangements together with a royalty on net sales.

Royalty stream

Given that the products have been discovered and developed to clinical stage by OXB, we would expect the royalty rate to be ratcheted and in the range of 7-12%.

Risk-adjustment

Risk-adjustment based on well-established industry statistics

Not all the products emanating from OXB's pipeline will reach the market; some will fail in clinical trials on the grounds of safety and/or efficacy, or for commercial/strategic reasons. Therefore, our tried and tested methodology is to risk-adjust the royalty stream to reflect the probability of the product reaching the market. For many years, we have used long-term industry data for these probabilities. However, more recent data suggest that biopharmaceuticals have, in general, slightly better success rates compared to statistics for small molecules. The greatest (positive) impact of this revision occurs at earlier stages of development.

Probability of a putative drug reaching the market

Development Phase completed	Small molecule	Biopharmaceutical
Pre-clinical	1%	2%
Phase I	5%	10%
Phase IIa	20%	35%
Phase IIb	40%	70%
Phase III	80%	85%
Submission to regulators	90%	96%

Source: Hardman & Co Life Sciences Research

OXB's proprietary portfolio

Although there are some products of interest in OXB's proprietary portfolio, these are not the focus of this report. On a risk-adjusted DCF model, because they are at such an early stage of development, they carry only a very small probability of reaching the market. Therefore, other than an overall modest adjustment to our sum-of-the-parts valuation, they have not been included in any significant detail.

Bioprocessing and process development services

Fee-for-service

In the medium term, OXB will generate the majority of its revenues from the bioprocessing service it provides for customers, on which it will make a modest on-cost profit. In addition, it will receive licensing fees and a modest royalty on net sales of the commercial products.

- **Fee-for-service** – income from a diverse, international customer base that provides short-term revenues
- **Licencing revenues/royalties** – long-term income from partners' development and commercialisation of products enhanced by the group's technologies

This part of the business has been valued against some peers that are providing specialist technology through service arrangements with its customers.

Comparative valuation

The difficulty in arriving at a valuation for OXB's integrated service and manufacturing business is that there are few direct comparators. Moreover, where there are examples of companies that compete directly, they tend to be part of much larger organisations offering many services that include bioprocessing, such as Lonza and Merck KGaA.

- **Lonza:** Well-established and experienced manufacturer of biological and pharmaceutical products, capitalised at CHF11bn/$12bn. This Swiss headquartered multi-national company provides a large and diverse range of development services, including custom manufacturing of biopharmaceuticals, chemical syntheses, and organic, inorganic and performance chemicals.
- **Merck KGaA:** Well-established multinational headquartered in Germany with diverse operations in Healthcare, Life Sciences and Performance Materials. OXB would compete with its specialist Biopharmaceutical Manufacturing unit, which is part of the Life Sciences division. This offers a full service from process development through process scale-up for commercial production.

Comparative valuation

Company	Curr	Mkt cap	Net cash	EV	2017 sales	EV/sales
Abcam	GBP	1,677	76	1,601	220	7.3x
Lonza	CHF	10,530	-1,297	11,827	4,300	2.8x
Merck KGaA	EUR	13,454	-11,858	25,112	15,000	1.6x
Oxford BioMedica	GBP	145	-19	164	47.0	3.5x

All figures in local currency. Based on share price at close of business on 27th March 2017
Source: Hardman & Co Life Sciences Research

Given the size and diverse operations of both Lonza and Merck KGaA, a direct comparison with these companies is not realistic. However, they do provide some form of benchmark, as does a company like Abcam. It is easy to argue that the potential growth rate of OXB's bioprocessing business would command a premium in respect of EV/sales comparisons, although not as high as Abcam commands given its long track-record of growth. On this basis, it would be rational to apply an EV/sales multiple of 4-5x to OXB's bioprocessing business service business, especially when it is being validated and underpinned by Novartis. This would imply an EV of ca.£188-£235m based on future sales, just for this part of the business.

Direct comparator

- **MolMed:** The activities of this Italian company are more aligned to those of OXB, although it intends to develop its own products further along the clinical pathway. It is focused on research, development, and clinical validation of novel anti-cancer therapies using cell-based technology that enables bone marrow transplants from partially compatible donors. MolMed also conducts cell and gene therapy projects in collaboration with third parties.

Direct comparator

Company	MolMed	Oxford BioMedica
	MLMD	OXB
Local currency	EUR	GBP
Share price	0.45	4.7
Shares in issue (m)	431.5	3,088.2
Market cap (lc)	194.2	145.1
Mkt cap (£m)	167.4	145.1
Cash	19.7	15.3
Debt	0.0	-34.4
EV (lc)	174.5	164.2
EV (£m)	**150.4**	**164.2**

Prices taken at close of business on 27th March 2017
Source: Hardman & Co Life Sciences Research

Comparative valuation – CAR-T competitors

Earlier in the report (page 30), mention was made of three US-based biotechs all in clinical development with CAR-T drugs targeting CD19 – Bluebird, Juno and Kite. While there are similarities, these three companies have established partnerships and retained commercial rights to their leading clinical candidates. In reality, they are in a similar position to Novartis with CD19 rather than Oxford BioMedica. However, they do highlight the value ascribed to such technologies.

Valuations of CAT-T development companies

Company	Juno	Kite	BlueBird
	JUNO.OQ	KITE	BLUE.OQ
Local currency	USD	USD	USD
Share price	20.9	83.8	74.0
Shares in issue (m)	106.0	54.8	40.6
Market cap (lc)	2,210.5	4,594.8	3,003.7
Mkt cap (£m)	1,769.1	3,995.4	2,611.9
Cash	732.6	414.4	884.9
Debt	0.0	0.0	-121.1
EV (lc)	**1,477.9**	**4,180.4**	**2,239.9**
EV (£m)	1,182.8	3,635.1	1,947.7

Prices taken at close of business on 27th March 2017
Source: Hardman & Co Life Sciences Research

Sum-of-the-parts

Pulling all this together under a sum-of-the parts scenario, and allowing for the fixed asset ownership to first-class HQ and manufacturing facilities, we arrive at the following summary. In the near-term, utilising the new specialised manufacturing capacity will be key. This, in turn, has the potential to drive a very satisfactory long-term royalty stream. These are closely linked and, taken together, on our estimates, represent 96% of the group enterprise value. While we do see value in the LentiVector platform and the proprietary drug candidates that it generates, the very

early stage nature of this business means that most of the NPV is eroded by the low probability of these products reaching the market. In conclusion, Hardman estimates that OXB has a risk-adjusted valuation of 7.5p per share. Further positive news flow from Novartis on CTL109 – successful completion of trials – would change the risk-adjustment and increase the valuation, suggesting that this share price level is likely to be reached relatively quickly. The book value of the GMP manufacturing and HQ fixed assets, £27.5m, is assumed to be inherent in the EV/sales multiple.

Summary valuation

Oxford BioMedica	**£m**
Bioprocessing (EV/sales 4.0x)	188
Novartis royalty stream – risk adjusted	46
Proprietary portfolio – risk adjusted	10
Group EV	**244**
Net cash/(debt)	-19
Market capitalisation	225
Shares in issue (m)	3,008
Valuation/share (p)	**7.5**

Source: Hardman & Co Life Sciences Research

Company matters

Registration

Incorporated in 1995 in the UK, company registration number: 03028927. Originally called Oxford Genetic Therapeutics Ltd, renamed Oxford BioMedica in 1996.

Headquarters:

Oxford BioMedica plc
Windrush Court
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Oxford
OX4 6LT

Tel: +44 1865 783 000

www.oxfordbiomedica.co.uk

Board of Directors

The Board consist of six executive directors and three non-executive directors, including the Chairman. Their representation on the various committees is shown in the following table.

Board of Directors				
Position	**Name**	**Nominations**	**Remuneration**	**Audit**
Chairman	Lorenzo Tallarigo	C		M
Chief Executive Officer	John Dawson			
Chief Financial Officer	Tim Watts			
CFO elect	Stuart Paynter			
Chief Business Officer	Peter Nolan			
Chief Scientific Officer	Kyriacos Mitrophanous			
Chief Technical Officer	James Miskin			
Deputy Chairman	Andrew Heath	M	C	M
Non-executive director	Martin Diggle	M	M	
Non-executive director	Stuart Henderson			C

M = member; C = chair
Source: company reports

Dr Lorenzo Tallarigo – Chairman

Immediately prior to joining Oxford BioMedica, Dr Tallarigo was Chairman of Intercept Pharmaceuticals as well as CEO of Genextra. These positions followed more than two decades at Eli Lilly where he held positions in clinical research, pharmaceutical product management, and latterly, as President of international operations. Dr Tallarigo is a medical doctor by training (University of Pisa, Italy) and holds a Professional Masters Degree from Harvard Business School.

John Dawson – Chief Executive Officer

John has been a member of senior management at Oxford BioMedica since 2008, first as a non-Executive Director, then as CEO from late 2008. From 1996 to 2007, John held senior management positions at Cephalon Inc, including as CFO and Head of Business Development Europe. Prior to Cephalon, John was Director of Finance and Administration of Serono Laboratories (UK) Ltd.

Tim Watts – Chief Financial Officer

Tim joined the OXB Board in 2012 with over 30 years' experience in leading business roles, including in the pharmaceutical and biotechnology sectors. The company has announced that Tim will be leaving the group on 29th September 2017.

Stuart Paynter – Chief Financial Officer elect

OXB has announced that Stuart will be joining the company on 29th August 2017 and will overlap with the current CFO for a month to allow an orderly transition. Stuart is joining from De La Rue plc, where he is Finance Director. He previously worked as Global Head of Audit at Shire (2007-2016). Obtained a BSc in physics at Imperial College, London and qualified as a chartered accountant.

Andrew Heath – Non-Executive Director

Joined the Board in 2010 and appointed Deputy Chairman and Senior Independent Director in 2011. Andrew has experience of the healthcare and biopharmaceutical capital markets and knowledge in marketing, R&D, and business development. Andrew was CEO of Protherics plc from 1997-2008, managing its eventual acquisition by BTG for £220m. Previously, he held senior positions at Aerogen Inc., Astra AB and Glaxo (Sweden).

Martin Diggle – Non-Executive Director

Joined the Board in 2012. He is a founder of Vulpes Investment Management, which manages five funds including Vulpes Life Sciences Fund, Oxford BioMedica's largest shareholder. Martin is an investment professional with over 30 years' experience in investment banking and fund management, including as a partner and director of UBS Brunswick.

Stuart Henderson – Non-Executive Director

Joined the Board in 2016. Previously, he was partner at Deloitte, where he was Head of European Healthcare and Life Sciences. Prior to this, he was partner at Arthur Andersen, also specialising in life sciences and biotechnology. Stuart has extensive experience in audit and transaction support and has worked with all aspects of life science businesses from start up to multinational, as well as reporting accountant on numerous IPO and Class 1 transactions. A former director of the Babraham Institute and sits as an observer on the board of OneNucleus, the Life Sciences trade body for Cambridge and London.

Financing history

The company listed on AIM in December 1996. In April 2001, OXB moved onto the main market of the London Stock Exchange and concomitantly, raised approximately £33m of new capital @ 55 pence per share fund its R&D programmes.

Over the years, the company has undertaken 10 significant share issues at a range of share prices (2p to 60p), raising total new capital of around £180m. The company has also received some non-equity funding in the form of grants to progress some pre-clinical development work. While this does represent a chequered history, investors should be focusing on the transformation that has taken place over the last two to three years since signing the Novartis deal. At the time of writing, this had reached a very exciting stage given the news that Novartis has already filed CTL-019 with the FDA and received notification that the regulator has accepted this BLA filing as being complete and ready for assessment. Approval later this year is expected to result in significant upside potential as described earlier.

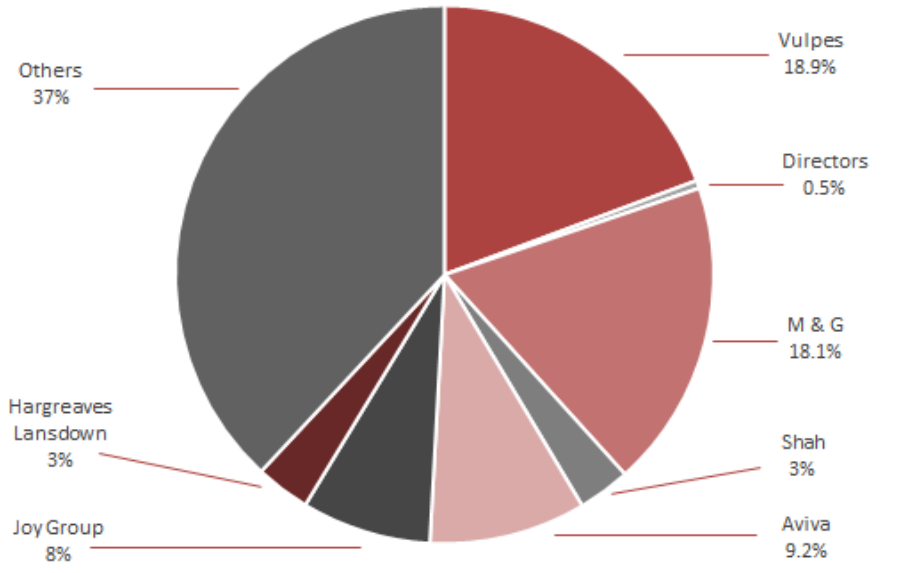
Oxford BioMedica – Financing history						
Comment	**Date**	**Shares (m)**	**Price (p)**	**Raised (£m)**	**Shares o/s (m)**	**Valuation (£m)**
	1999				57.0	
Placing @38p	Jan-00	13.7	38.0	5.2	151.3	57.5
Issue of new ordinary shares @60p	Aug-00	14.6	60.0	8.8	166.4	99.8
Placing & Open offer @55p	Mar-01	59.8	55.0	32.9	227.5	122.2
27-for-50 Rights issue @17p	Oct-03	129.8	17.1	22.2	383.7	65.6
Placing, Subscription & Open offer @25p	Nov-05	120.3	25.0	30.1	492.8	123.2
Placing & Open offer @5p	Dec-10	394.7	5.0	19.7	944.9	47.2
Placing & Open offer @2.5p	Jun-12	463.4	2.5	11.6	1,408.2	35.2
Placing & Open offer @2p	May-14	1,078.4	2.0	21.6	2,494.6	49.9
Novartis deal	Oct-14	70.8	3.8	2.7	2,565.4	97.5
Placing @6.3p	Feb-16	128.4	6.3	8.1	2,702.9	170.3
Placing & Subscription @3p	Sep-16	383.4	3.0	11.5	3,088.0	92.6
Total	**Mar-17**		**5.2**	**179.4**	**3,088.2**	**159.0**

Source: Company reports

Share capital

Oxford BioMedica has 3,008.2 million Ordinary shares in issue, 0.5% held by the Directors and 18.9% held by Vulpes Investment Management. The group had 128.4m options outstanding at the end of September 2016.

Key shareholders



Source: company reports; Hardman & Co Life Sciences Research

Share price performance

Source: Thomson Reuters

Risks

The risk profile of Oxford BioMedica has changed significantly over the last three years. The company has moved from high-risk and capital intensive pharmaceutical R&D to a specialist service provider, with the catalyst for this change being the supply agreement with Novartis.

Manufacturing service

Considerable investment in its new state-of-the-art commercial scale manufacturing facilities positions OXB amongst only a handful of companies worldwide that can provide this service. There is big demand for both small-scale (for research and clinical trials) and large-scale (commercial quantities) GMP production of cell-based gene therapies and, given the specialist nature, even the pharmaceutical majors are willing to outsource such work.

In the short-term, there are three risks for OXB. First, the approval of CTL-019 is completely out of the company's hands, both the success/failure of the regulatory process and the timing of it, although the BLA does have fast-track designation which puts the approval on a six month process with the FDA. Secondly, although OXB supplied Novartis with all of its clinical trial material for CTL-019, to our knowledge there is no contract in place presently for material supply for commercialisation. It is inconceivable that Novartis would turn to an alternative supplier at this late-stage in the process. Therefore, we believe that a new deal is currently being negotiated. The announcement by Novartis that the FDA has accepted the BLA for review does increase the pressure for this to be resolved.

Thirdly, having invested in its GMP facilities, OXB is not currently using these to their full capacity. On the one hand, agreement with Novartis for commercial supplies would greatly increase capacity utilisation and improve efficiency; on the other hand, a supply agreement with Novartis coupled with the deal to supply Orchard could see full capacity utilisation reached relatively quickly, especially if OXB was to conclude a small number of further deals. However, this would be a good problem to have as it would imply that OXB is running profitably and generating cash, thereby providing it with the financial resources to invest in enlarging the manufacturing capacity.

Proprietary assets

The decision to seek partners to out-license OXB's proprietary R&D pipeline reduces risk and cost. However, it can take considerable time to conclude such deals and there can be no guarantee of success, given the industry standard rate of attrition in clinical trials. Spinning out and/or out-licensing these assets would also result in a loss of control of their development.

Glossary

ALL	Acute lymphoblastic leukaemia
ATMPs	Advanced Therapy Medicinal Products
BLA	Biologics License Application
CAR-T	Chimeric Antigen Receptor T cell
CLL	Chronic lymphocytic leukaemia
CMC	Chemistry, manufacturing, and controls
cGMP	Current Good Manufacturing Practice
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medical Agency
FDA	US Food and Drug Administration
MHRA	Medicines and Healthcare products Regulatory Agency
LV	Lentivirus-based Vector
MCL	Mantel Cell Lymphoma
MM	Multiple Myeloma
NHL	non-Hodgkin Lymphoma
Plasmid	Typically a small circular DNA strand from a bacterium that can replicate independently of chromosomes, used in genetic engineering
Recombination	Process of forming new combinations of DNA by exchanging DNA sequence among DNA molecules
Somatic cell	Non-germ line cell
TALEN	Transcription Activator-Like Effector Nucleases
Transduction	Introduction of foreign genetic material into cells using viral vectors
Transgene	Gene introduced to one organism from another of a different species
Transfection	Insertion of exogenous DNA into animal cells (usually refers to non-viral methods)
Transformation	Genetic alteration of a cell through incorporation of exogenous DNA, causing transient or stable genetic changes. Often refers to uptake of plasmids by bacteria.
UPDRS	Unified Parkinson's Disease Rating Scale

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