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Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**OXB**
Price (p)	12.0
12m High (p)	12.3
12m Low (p)	3.9
Shares (m)	3,107.7
Mkt Cap (£m)	372.9
EV (£m)	392.1
Free Float	63%
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	Stuart Paynter
Chairman	Lorenzo Tallarigo
	01865 783 000
	www.oxfordbiomedica.co.uk

Key shareholders

Directors	0.4%
Vulpes	18.7%
M&G	18.0%
Aviva	6.7%
Hargreaves Lansdown	3.9%

Diary

Mar-18	Finals

Analysts

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Oxford BioMedica

Bioverativ deal – establishes structure

Oxford BioMedica (OXB) is a specialist advanced therapy lentivirus-based vector biopharma company. It offers vector manufacturing and development services and is developing its own proprietary drug candidates. In addition to LentiVector® service contracts, OXB will receive royalties on commercial therapies developed with its platform. This deal structure was established with Novartis for Kymriah™, the first approved CAR-T therapy, and has now been followed by a collaboration and licence agreement adopting a similar structure with Bioverativ Inc (BIVV), for the development and potential clinical supply of vector to treat haemophilia.

- **Strategy**: OXB has four strategic objectives: delivery of process development services that 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.

- **Bioverativ deal:** OXB has signed a collaboration and licence agreement with BIVV for the development and potential manufacture of vectors for haemophilia gene therapy. OXB received $5m up-front and is eligible to receive milestone payments of up to $100m, thus establishing a 'normal' deal structure.

- **Bioverativ:** BIVV is a US-based specialist haemophilia and rare blood disorders biopharma company. However, as announced in January, it is in the process of being acquired by Sanofi for $11.6bn. 2017 sales were $1.1bn from two approved drugs. Its pipeline includes lentivirus-based gene therapies for haemophilia.

- **Manufacture:** Although OXB has made significant investment recently in manufacturing facilities, this deal, together with existing supply deals with Novartis and Orchard Therapeutics, will utilise most of OXB's capacity, such that any further deals are likely to require an increase in manufacturing capacity.

- **Investment summary:** OXB is at a very interesting juncture. Heavy investment in state-of-the-art GMP manufacturing facilities for production of gene therapy vector has resulted in supply agreements with Novartis and Bioverativ, on top of existing partnerships, positioning the group on the road to significant bioprocessing service income, milestones, and royalties.

Financial summary and valuation

Year-end Dec (£m)	2014	2015	2016	2017E	2018E	2019E
Sales	13.62	15.91	27.78	38.80	47.00	54.00
EBITDA	-9.29	-11.73	-6.78	0.01	7.95	9.42
Underlying EBIT	-10.39	-13.35	-10.45	-4.42	3.51	4.98
Reported EBIT	-10.61	-14.08	-11.32	-5.39	2.45	3.82
Underlying PBT	-10.58	-16.25	-16.26	-9.27	-0.93	0.55
Statutory PBT	-10.80	-16.98	-20.31	-10.23	-1.99	-0.62
Underlying EPS (p)	-0.42	-0.48	-0.45	-0.16	0.12	0.17
Statutory EPS (p)	-0.43	-0.51	-0.60	-0.19	0.09	0.13
Net (debt)/cash	13.20	-17.90	-19.05	-19.22	-16.48	-12.21
Capital increase	22.81	0.14	17.50	0.10	0.10	0.10
P/E (x)	-	-	-	-	99.7	71.6
EV/sales (x)	-	-	-	-	49.3	41.6

Source: Hardman & Co Life Sciences Research

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Deal with Bioverativ

Collaboration and licensing agreement

In February 2018, Oxford BioMedica entered into a collaboration and licensing agreement with the US-based biotechnology company Bioverativ Inc. OXB will perform process development to transfer its LentiVector platform to BIVV's investigational gene therapy programmes for treatment of haemophilia A and B. This approach has been extensively validated in OXB's 11 partnership agreements – including development and supply of lentivirus-based vector for the first FDA approved gene therapy, Novartis's CAR-T therapy, Kymriah.

Terms

Major new deal worth up to $105m

The agreement grants BIVV a licence to OXB's LentiVector platform and industrial-scale manufacturing technology in return for $5m up-front, plus potential milestones of up to $100m. This will ensure that OXB's technology is embedded within BIVV's investigational haemophilia gene therapies, resulting in a royalty payable on sales, should any products be commercialised.

Process development for Bioverativ's haemophilia gene therapy programmes

The deal does not include a completed clinical supply agreement given that the therapy is only at the pre-clinical development stage. It does, however, include the potential for OXB to supply BIVV's clinical programmes should they take place. We presume that OXB would be the sole supplier of vector to BIVV on a successful outcome.

Comparison of OXB's Novartis and Bioverativ deals

Term	Novartis deal 1	Novartis deal 2	Novartis deal 2 extension	Bioverativ
Type	Collaboration	Collaboration/licensing	Manufacturing	Collaboration/licensing
Year	2013	2014	2017	2018
Duration	1 year	3 years	3-5 years	
Upfront	N/A	$14m	$10m	$5m
Milestones, incentives, service payments	$4m	$76m	$90m min	$100m max (regulatory and sales milestones)
Process development	Yes	Yes	Yes	Yes
Clinical supply	Yes	Yes	Yes	**Potential**
Commercial supply	No	**No**	Yes	No
Royalty	No	Yes	Yes	Yes

Source: Company announcements; Hardman & Co Life Sciences Research

Risks

Milestones

Attempting to accurately forecast the timing and value of individual BIVV milestone and bioprocessing payments at this point in time is difficult because of the risks inherent in clinical and commercial development. There is little doubt that translation of OXB's LentiVector technology to BIVV's gene therapy will be successful; however, there are safety and efficacy hurdles to overcome in clinical trials. A benchmark for success is hard to come by: competitors' gene therapies for haemophilia are in Phase I/II and III, and there is only one gene therapy for an inherited disorder licensed in the US market – Luxterna (Spark Therapeutics) for certain types of blindness, based on adeno-associated virus (AAV) vector – which was approved very recently, on 19th December 2017.

The average probability of a biopharmaceutical drug at the same stage of development as the BIVV programme reaching the market is only one percent. For a gene therapy, however, the probability is likely to be far higher, as they are designed specifically against genes that are causally related to the target indication. Such therapies are estimated to be twice as likely to successfully reach the market[1]. The difficulty for a gene therapy in a larger indication is more likely to come from safety issues revealed in late stage trials involving large numbers of patients, when compared to conventional small molecule drugs.

Probability of a putative drug reaching the market

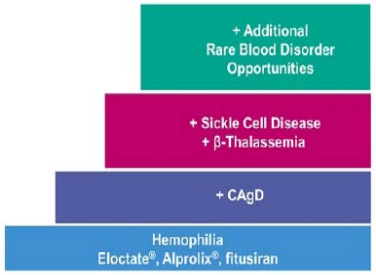
Development phase completed	Small molecule	Biopharmaceutical
Pre-clinical	0.1%	1%
Phase I	5%	10%
Phase IIa	20%	35%
Phase IIb	40%	70%
Phase III	80%	85%

Source: Hardman & Co Life Sciences Research

Sanofi acquisition

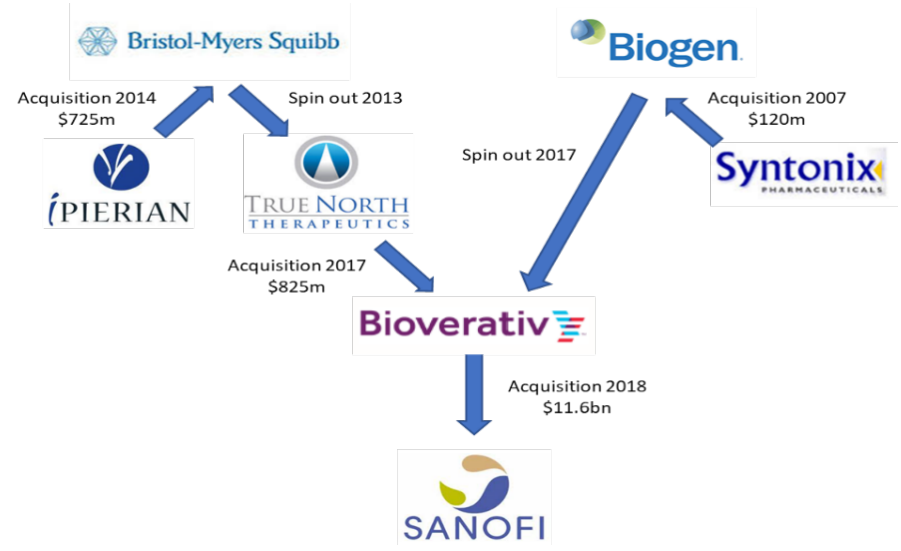
Sanofi is set to acquire BIVV in a deal worth $11.6bn, as announced on 22nd January and unanimously approved by both boards. It is expected to close within three months. We do not perceive this to be a risk to OXB's involvement in process development for BIVV's gene therapy programmes, because its haemophilia assets are highly relevant to Sanofi's strategy in rare diseases (under Sanofi Genzyme, based in Cambridge, MA), particularly in non-malignant haematology markets. BIVV's haematology offering is complementary to Sanofi's Fitusiran, a Phase III investigational therapy for haemophilia based on RNA interference (RNAi), whereby the expression of particular genes is inhibited by targeting messenger RNA molecules. Sanofi obtained the global rights to Fitusiran from its collaboration with Alnylam Pharmaceuticals in early 2018. In turn, Sanofi's commercial reach, particularly in emerging markets, will expand access to BIVV's two marketed factor replacement haemophilia therapies.

Non-malignant haematology*



**Sanofi expanding haematology presence over time*
Source: Sanofi

Flow of Bioverativ's haemophilia IP and technology



Source: Hardman & Co Life Sciences Research

[1] Nelson MR, et al. *The support of human genetic evidence for approved drug indications.* Nature Genetics 2015 (47):8

The haemophilia market

The disorder

14 core gene involved in blood clotting cascade…

…mutations in Factors VIII and IX cause haemophilia A and B, respectively

Haemophilia is a rare bleeding disorder caused by mutations in genes encoding proteins involved in the coagulation (blood clotting) cascade. There are 14 core genes involved in the cascade including those coding for Factor VIII (F8) and Factor IX (F9), which are located on the X chromosome. Mutations in the F8 gene cause haemophilia A and those in F9 cause haemophilia B, with abnormal or deficient proteins produced that prevent proper coagulation. Monogenic (single-gene) genetic disorders are the ideal target indications for gene-therapies.

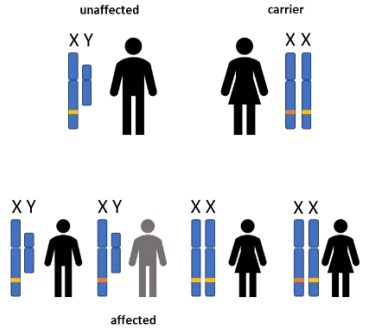
Severity

Depending on the mutation, certain levels of active clotting factor may be produced: patients with <1% active factor are diagnosed with severe haemophilia; 1-5%, moderate haemophilia; and 5-40%, mild haemophilia[2]. Complications of moderate and severe haemophilia include progressive joint damage and conditions such as intracranial haemorrhage due to the 'bleeds' that occur spontaneously or following mild trauma.

Prevalence

Approximately 181,000 people are currently diagnosed with haemophilia worldwide, of which 83% have haemophilia A; the majority is male because of the inheritance patterns of the disorder. The F8 and F9 genes are located on the X chromosome, which in males (XY chromosomes) is always inherited from their mother (XX chromosomes). The mutations are recessive, meaning that, in females, a mutation in one chromosome can be compensated by a copy of the normal gene on the other. Since males have only one X chromosome, if they inherit the mutation from a carrier mother, they will certainly have the disorder. Haemophilia can also develop spontaneously, as is the case in one third of sufferers. In total, the population is estimated at 331,000[2] but individuals may not be diagnosed until a major bleed occurs following an event such as surgery.

Recessive X-linked disorders



X and Y: X and Y chromosomes
mutated gene in orange
Source: Hardman & Co Life Sciences Research

Therapeutic market

Prophylactic treatment

Hardman & Co estimates that the global market for haemophilia drugs is currently worth $9.9bn. This is mainly repeat sales of replacement clotting factors that are given intravenously. In mild cases, treatment is usually as needed, but depending on severity, prophylactic therapy is recommended, which requires infusions multiple times per week.

The global haemophilia market was worth $9.9bn in 2017…

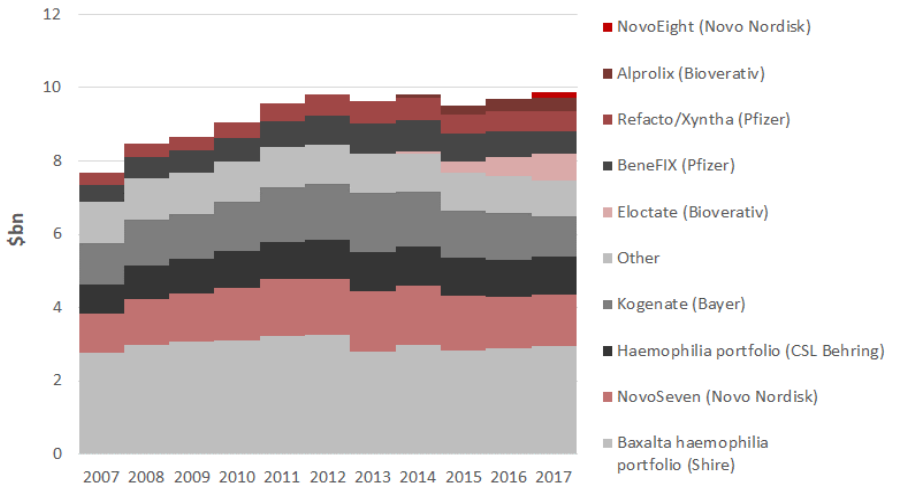
…but changing dynamics suggest that it has only grown 0.1% p.a. over the last five years

In recent years, new, extended half-life (EHL) recombinant factor products have entered the market. These remain in the bloodstream for longer, meaning fewer injections for patients and that a single dose can generally control a bleed.

A major setback to all replacement factor treatments is the development of 'inhibitors', which are antibodies against the replacement factors. This makes treatment less or in-effective and is very serious. Although inhibitor development can be treated using immune tolerance induction therapy, it is very expensive and requires highly specialised care.

[2] Sanofi presentation 'Sanofi to Acquire Bioverativ' published 22nd January 2018.

Ex-factory sales of haemophilia therapies



Source: Hardman & Co Life Sciences Research

Entry of EHL factor therapies is altering the market

Market dynamics

Existing growth drivers include improved diagnosis and access to therapies in developing countries, adoption of EHL therapies, which are more convenient for prophylactic and acute treatment, and improved survival of male haemophiliacs.

Recent estimates refer to growth in the market of around 7% annually[2]. Neither the period of time nor the therapeutic segment is stated, but the figure probably refers to growth in sales of the newer therapies, since it contrasts with our own estimate that the total market has remained flat in the last five years (0.1% CAGR). Taken together, this would be consistent with cannibalisation of sales of conventional therapies by those of more expensive, but less frequently used, EHL factor therapies. Based on our assumptions, even without the entry of expensive, potentially curative gene therapies, the market will grow an estimated ca.3.5% over the next five years (2017-22) to ca.$12.0bn.

Global haemophilia market

Product	Description	Marketer	2014 $m	2017 $m	2020 $m	CAGR 2014-17	CAGR 2017-20
Baxalta portfolio	Haemophilia	Shire	2,984	2,957	3,138	-0.3%	2.0%
NovoSeven	Recombinant Factor VII	Novo Nordisk	1,628	1,396	1,274	-5.0%	-3.0%
Kogenate/Kovaltry	Recombinant Factor VIII	Bayer	1,473	1,108	950	-9.1%	-5.0%
CSL Behring	Haemophilia	CSL Behring	1,064	1,023	1,086	-1.3%	2.0%
Eloctate	Anti-haemophilic factor (VIII)	Bioverativ	58	725	925	131.5%	8.5%
BeneFIX	Coagulation Factor IX	Pfizer	856	604	586	-11.0%	-1.0%
Refacto/Xyntha	Anti-haemophilic factor	Pfizer	631	551	534	-4.4%	-1.0%
Alprolix	Coagulation Factor IX	Bioverativ	76	365	401	68.7%	3.2%
NovoEight	Recombinant Factor VIII	Novo Nordisk	0	167	184	-	3.2%
Other	Haemophilia	Miscellaneous	1,045	985	890	-2.0%	-3.3%
Global market			**9,815**	**9,881**	**11,101**	**0.2%**	**4.0%**

Source: Hardman & Co Life Sciences Research

Manufacturers

BIVV is a US biotechnology company with around 450 employees and headquartered in Waltham (MA). It has two marketed products, both of which are EHL clotting factor therapies, Eloctate (Elocta in Europe) for haemophilia A and Alprolix for haemophilia B. Launched in the US in 2014, these represented the first major advancement in haemophilia in about 20 years. They have since been approved in Europe (in 2015 and 2016, respectively), where they are marketed by SOBI.

Both of BIVV's marketed medicines are highly differentiated recombinant Fc fusion products. This means that Factor VIII or IX is fused with the Fc region of IgG1 antibody to form a single molecule that is produced using human cell lines. Phase IV trials are underway to investigate the efficacy of these products in patients with inhibitors. With global sales of $1.1bn in 2017, their success has stolen market share from conventional factor replacement therapies, resulting in a burst of consolidation and licensing activity in the market. For example, Shire (SHP) bought Baxalta (ex-Baxter) in 2016 for $32bn, acquiring the EHL treatment Adyvonate in the process. This contributed to sales of $3.0bn for Shire's haematology business in 2017. Bayer occupies a large portion of the market too; following US approval of Kovaltry in 2016, its haemophilia sales were estimated to be $1.1bn in 2017. CSL Behring also won approval for a third-generation EHL product called Afstyla in 2016, which contributed to full-year sales of $1.0bn for its haematology business in 2017. In February 2018, Novo Nordisk submitted licensing applications for an EHL therapy for haemophilia A in both the US and Europe.

BIVV has also a development pipeline of rare blood disorder therapeutic candidates that includes gene therapies for haemophilia A and B, and gene editing therapies for sickle cell disease and β-thalassemia.

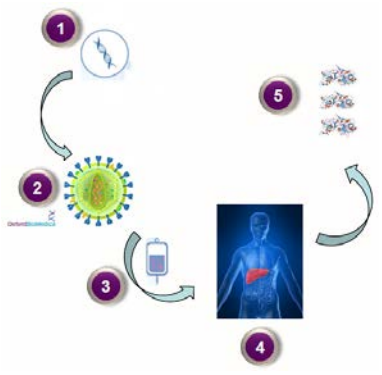
Gene therapy for haemophilia

BIVV – OXB deal

Haemophilia gene therapy programmes

OXB will be carrying out process development to progress to clinical trials BIVV's haemophilia A and B gene therapy candidate therapies, programmes being carried out in collaboration with the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) in Milan. The technology is based on SR-TIGET's lentiviral gene transfer expertise, which underlies multiple developmental gene-therapies.

Haemophilia gene therapy



Source: Oxford BioMedica

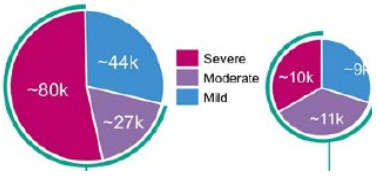
The therapy is in pre-clinical development; it is Hardman & Co's assumption that the deal has been timed to give the collaborators about one year for technology transfer prior to first-in-man trials. This will involve, predominantly, adaptation of OXB's existing LentiVector platform technology so that vector specifically and selectively targets hepatocytes (liver cells) and carries the sequences for Factor VIII or IX expression. Given that the vector will be administered *in vivo*, immunogenicity will be reduced by modifying the antigens that are expressed on its envelope; OXB has prior experience of *in vivo* gene-therapies with its proprietary, clinical-stage gene therapy for Parkinson's Disease, OXB-102. Of the three constructs used to generate vector producing cell lines, we presume only the vector genome and envelope constructs will need modifying. BIVV's expertise in haematology will underpin formulation and clinical administration.

Therapeutic hypothesis

The genes encoding Factors VIII and IX will be transferred to hepatocytes using modified lentivirus-based vectors that are either directly injected into the liver or systemically introduced for relocation to the liver. The hepatocytes will produce the recombinant factor, potentially indefinitely. The major advantage of lentivirus-based vectors (as opposed to AAVs) is that the therapeutic gene is integrated into the human chromosome, so in dividing cells – like hepatocytes – the therapeutic gene is copied to daughter cells along with the rest of the human genome. This would represent a potential 'cure' and render conventional factor-replacement unnecessary. Moreover, because the protein would be produced by the patient's own cells, issues with development of inhibitor would likely be overcome[3].

Potential market

Prophylaxis patient segments



Haemophilia A **Haemophilia B**

Source: Sanofi

Note that the gene therapy would not be inherited by children of treated patients. An estimated 400 babies are born each year with haemophilia in the US alone. Gene therapy in paediatric haemophilia patients is a particularly exciting prospect, given that it would prevent the development of complications such as arthritis. The value proposition for reimbursement is thus particularly high in paediatrics.

Initially, however, it is expected that the therapy will be targeted to those with severe disease and with inhibitors. The 'severe' patient segment comprises around 53% of the existing haemophilia market, or ca. $5bn of annual sales. Given that the annual cost of treating a single patient is around £100,000 in the UK, and that the price of a gene therapy is likely to be at least double this (Luxterna is priced at $425,000 per eye), we would expect the market to grow dramatically in the next five or so years as gene therapies for haemophilia are approved and adopted. There would then be erosion of the 'severe patient' prophylactic market segment as the need for conventional therapies reduces at a faster rate than the number of severe patients increases.

Competitive landscape

There are two companies with clinical-stage gene therapies for haemophilia, in addition to BIVV: the biotechnology company Spark Therapeutics (Philadelphia, PA) and BioMarin (San Rafael, CA), which has six marketed products. Both of these programmes are at a later stage of development than BIVV's; they are, however, based on AAV vectors, which have distinct disadvantages when compared with lentivirus-based vectors for *in vivo* modification of dividing cells. Re-dosing with an AAV-based therapy would be complicated by the immunity acquired in the original application. We discuss different vector types in detail in our initiation note on OXB: 31.03.17-delivering-commercial-gene therapy-vector.pdf.

Clinical gene therapy programmes for haemophilia

Company	Programme(s)	Haemophilia	Phase	Clinical trials*
Spark Therapeutics	SPK-8011	A	I/II	Two ongoing in adult males with haemophilia
	SPK-9001 (with Pfizer)	B	I/II	Three ongoing in adult males with haemophilia
BioMarin	Valoctocogene roxaparvovec	A	III	Three ongoing in adult males with severe haemophilia

**clinicaltrials.gov*

Source: Hardman & Co Life Sciences Research

[3] Annoni A et al. *Liver gene therapy by lentiviral vectors reverses anti-factor IX pre-existing immunity in haemophilic mice.* EMBO Mol Med. 2013 (5)

Outlook

Partnering strategy

OXB appears to be moving towards a more commercial process for its licensing activities, learning from its experience in biopartnering, e.g. with Novartis, where OXB was not named as the guaranteed commercial provider of vector for CTL019 in their second deal, leaving some uncertainty until it was extended shortly prior to the approval of Kymriah. Furthermore, the rate of new deals may well increase now that its industrial-scale manufacturing has been established, and it is at the stage where transfer of the LentiVector platform technology to investigational gene-therapies is relatively fast, representing almost a 'plug-and-play' process for integration of different therapeutic genes.

Manufacturing capacity

OXB could secure further deals in the next 12 months, for example if its partner Orchard Therapeutics receives approval for its investigational ADA-SCID programme, which is currently in a pivotal trial. Additional deals will require headcount and facilities investment and increases in manufacturing capacity, for example as the company moves even beyond 200L bioreactor cell culture. Longer term, additional facilities may be needed as the company moves towards larger volume bioreactors.

Scalability of bioreactors

Source: Sartoriusi

Forecasts

2017 full year results are due in March 2018. No significant changes have been made compared to our previous published forecasts (September 2017). However, three factors have been taken into account. First, our costs have been increased to reflect the increase in personnel needed to deliver vector to Novartis and BIVV. Secondly, we have included the up-front receipt of $5m for the BIVV deal in fiscal 2018. No allowance has been made currently for future increases in headcount and capital expenditure in 2018 and 2019 that are likely needed in order to deliver the services behind these two projects. Thirdly, forecasts have been adjusted from constant currency to reflect actual average US$ exchange rates: average for P&L and period-end for balance sheet.

Summary financials

- **EBITDA:** Increasing the costs in 2017 has brought EBITDA down by around £2.4m to £0m for the full-year.
- **Other income:** The $5.0m/£3.6m BIVV up-front is a single payment in 2018 and the £3m Innovate grant is accrued over three years starting in fiscal 2018.
- **Cash:** The net debt position at 31st December 2017 is now forecast at -£19.2m, an increase of around £2.5m compared to previous forecasts.

Forecast summary

Year-end Dec (£m)	2014	2015	2016	2017E	2018E	2019E
GBP:USD	1.648	1.529	1.354	1.289	1.289	1.289
Profit & Loss:						
Bioprocessing + PD	**7.80**	**14.44**	**23.98**	**35.1**	**42.4**	**48.6**
Additional income	6.37	3.54	3.80	3.8	4.6	5.4
COGS	-4.42	-5.84	-11.84	-17.5	-19.3	-20.8
Gross profit	9.20	10.07	15.94	21.3	27.7	33.2
Gross margin (%)	0.68	0.63	0.57	55%	59%	61%
SG&A	-3.74	-6.01	-5.09	-6.4	-6.9	-7.4
R&D	-16.99	-20.27	-24.30	-22.1	-23.3	-23.3
EBITDA	-9.29	-11.73	-6.78	0.0	7.9	9.4
Other income	1.13	2.86	3.00	2.8	6.1	2.5
Underlying EBIT	-10.39	-13.35	-10.45	-4.4	3.5	5.0
EBIT margin (%)	0.76	0.84	0.38	-0.1	0.1	0.1
Net interest	-0.19	-2.90	-5.81	-4.8	-4.4	-4.4
Pre-tax profit	-10.58	-16.25	-16.26	-9.3	-0.9	0.5
Tax payable/credit	2.14	3.96	3.67	4.4	4.7	4.7
Underlying net income	-8.44	-12.29	-12.59	-4.8	3.7	5.2
Weighted av. shares (m)	2,019	2,570	2,780	3,096	3,108	3,109
Underlying EPS (p)	-0.4	-0.5	-0.5	-0.2	0.1	0.2
Fully diluted EPS (p)	-0.4	-0.5	-0.4	-0.1	0.1	0.2
Balance sheet:						
Share capital	25.66	25.74	30.88	30.9	30.9	30.9
Reserves	-2.62	-14.85	-18.26	-24.0	-21.2	-17.1
Provisions	3.46	4.42	3.94	0.0	0.0	0.0
Debt	1.00	27.26	34.39	32.6	35.0	37.4
less: Cash	14.20	9.36	15.34	13.4	18.5	25.2
Invested capital	**13.31**	**33.21**	**34.95**	**26.1**	**26.2**	**26.0**
Net cash/debt	13.20	-17.90	-19.05	-19.2	-16.5	-12.2
Cashflow:						
Operating profit	-10.39	-13.35	-10.45	-4.4	3.5	5.0
Change in working capital	0.08	-4.09	1.25	-1.4	-1.1	-1.1
Tax & interest	1.45	1.79	0.87	-1.2	-0.4	-0.2
Operational cashflow	**-7.43**	**-14.87**	**-5.93**	**2.9**	**4.9**	**6.4**
Capital expenditure	-5.58	-16.72	-6.46	-1.9	-1.8	-2.1
Free cashflow	**-11.56**	**-29.80**	**-11.52**	**-0.3**	**2.6**	**4.2**
Acquisitions	0.00	0.00	0.00	0.0	0.0	0.0
Share issues	22.81	0.14	17.50	0.1	0.1	0.1
Change in net debt	**11.03**	**-31.10**	**-1.15**	**-0.2**	**2.7**	**4.3**
Hardman FCF/sh. (p)	-0.3	-0.5	-0.2	0.1	0.1	0.2

Source: Hardman & Co Life Sciences Research

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