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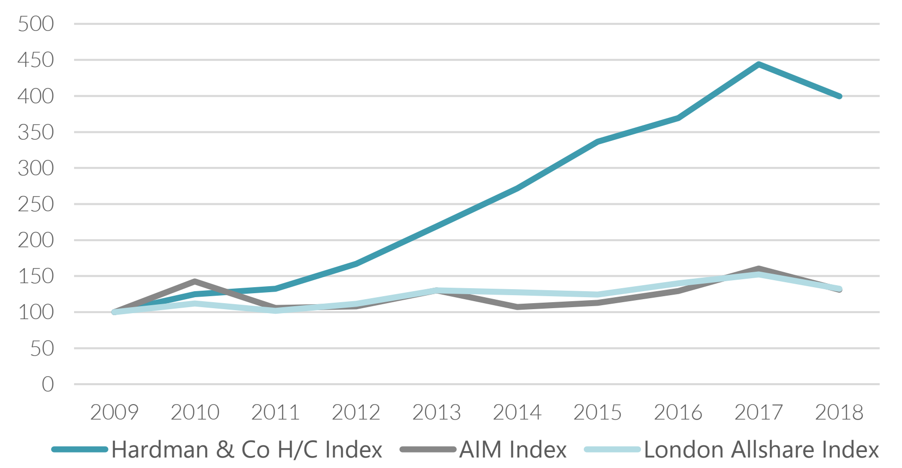
HARDMAN & CO HEALTHCARE INDEX

2018 – failed to meet expectations

The Hardman & Co Healthcare Index (HHI) has been running since 2009. Its main function is to highlight the attractions of life sciences investments over the long term. 2018 was a difficult year; however, the index still outperformed its comparative London indices, falling 10.0% to 393.2, compared with -13.0& and -18.2% for the Allshare index and the AIM index, respectively. Furthermore, several (17) companies in our index increased their capital base – 15 of our 50 constituents raised new funds, two issued shares as part consideration for acquisitions, and two had share buybacks – all factors that influence the performance of the index. Even allowing for both capital increases and share buybacks, the -12.5% fall in the index still represented a modest outperformance compared to the decline in the Allshare index. With active industry consolidation, shareholder returns remain attractive.

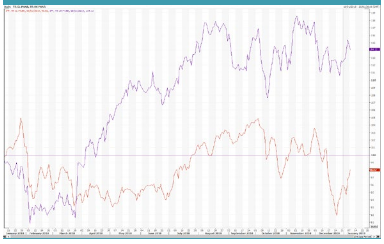
- Since inauguration, the CAGR for the HHI has been 16.6%, compared with 3.2% for the London Allshare Index and 3.1% for the AIM index, highlighting the attractiveness of the healthcare sector as a long-term investment, even though it is capital-intensive.
- Of the 50 companies included in the HHI, only 11 saw an increase in their share prices in 2018, whereas 39 fell, with no company simply marking time.
- The variance between the best- and worst-performing stocks was lower than usual, at 213% – **Bioquell (BQE)** rising 120% and **Immupharma (IMM)** falling 93% – the median share price change was -23%.
- Interestingly in relative terms, only 16 stocks outperformed the index during 2018, with the other 34 underperforming.
- Industry consolidation remains very much to the fore. Three companies included in our index were taken over in 2018, and the takeovers of two others (BTG and BQE) will complete early in 2019. Moreover, Bristol Myers Squibb has just agreed to pay $74bn for Celgene and Eli Lilly has proposed the acquisition of Loxo Oncology for $7.1bn

Performance of Hardman Healthcare Index – rebased



Source: Hardman & Co Life Sciences Research

Global pharma vs UK pharma



Source: Eikon Thomson Reuters

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Share price performance

Listing	Company	Ticker	Share price (p) 31 Dec 2017	Share price (p) 31 Dec 2018	Market cap (£m) 31 Dec 2018	Price change (%)
AIM	Abcam	ABC	1,055.0	1,090.0	2,239.0	3%
AIM	Advanced Medical Solutions	AMS	318.0	275.0	587.1	-14%
AIM	Advanced Oncotherapy*	AVO	57.5	39.5	67.0	-31%
AIM	Allergy Therapeutics*	AGY	28.5	13.6	86.5	-52%
AIM	Alliance Pharma*	APH	67.1	67.0	347.1	0%
Full	Assura	AGR	63.9	52.8	1,264.0	-17%
AIM	Avacta*	AVCT	64.0	30.5	35.2	-52%
Full	Bioquell	BQE	267.5	588.0	132.0	120%
Full	BTG	BTG	762.5	830.0	3,213.7	9%
AIM	Caretech	CTH	430.0	343.0	373.5	-20%
Full	Cathay International	CTI	7.6	7.5	32.9	-2%
Full	Circassia	CIRC	102.5	48.0	171.5	-53%
AIM	Collagen Solutions*	COS	2.8	2.9	9.2	4%
Full	Consort Medical	CSRT	1,168.0	935.0	461.6	-20%
AIM	Deltex Medical Group	DEMG	2.1	0.9	4.4	-58%
AIM	Diurnal*	DNL	146.5	22.0	13.6	-85%
AIM	Eco Animal	EAH	597.5	410.0	275.2	-31%
AIM	EKF Diagnostics	EKF	26.3	27.3	124.3	4%
AIM	Emis	EMIS	1,011.0	913.0	578.0	-10%
AIM	e-Therapeutics	ETX	9.3	6.4	17.1	-31%
AIM	Futura Medical	FUM	29.8	6.2	12.6	-79%
AIM	Genedrive*	GDR	33.5	21.0	7.1	-37%
Full	Genus	GNS	2,531.0	2,146.0	1,395.9	-15%
AIM	Immunodiagnostics	IDH	270.0	182.5	53.7	-32%
AIM	Immupharma	IMM	170.0	11.8	16.4	-93%
Full	IP Group	IPO	142.2	108.6	1,150.2	-24%
AIM	Ixico	IXI	36.5	23.5	11.0	-36%
AIM	Kromek Group	KMK	26.4	26.5	69.0	0%
AIM	Lidco Group	LID	7.4	4.4	10.6	-41%
Full	MD Medical Group	MDMG	10.2	4.5	265.2	-56%
Full	MedicX Fund	MXF	84.0	74.6	330.4	-11%
AIM	Motif Bio	MTFB	41.0	31.4	93.0	-24%
AIM	Omega Diagnostics	ODX	17.0	13.0	16.5	-24%
Full	Oxford BioMedica*	OXB	442.5	707.2	467.4	60%
AIM	Oxford Metrics	OMG	58.3	72.5	90.6	24%
Full	Primary Health Properties	PHP	117.0	111.0	853.6	-5%
AIM	Proteome Sciences	PRM	3.1	2.4	7.2	-22%
AIM	Realm Therapeutics	RLM	37.0	7.0	8.2	-81%
AIM	ReNeuron	RENE	188.0	49.0	15.5	-74%
AIM	Sareum	SAR	0.9	0.5	15.2	-38%
AIM	Scancell	SCLP	12.8	9.1	35.4	-28%
Full	Smith & Nephew	SN.	1,288.0	1,464.0	12,803.2	14%
Full	Spire	SPI	253.6	108.9	436.8	-57%
AIM	Surgical Innovations	SUN	3.6	2.8	21.9	-23%
AIM	Tissue Regenix*	TRX	9.3	6.5	76.2	-30%
AIM	Tristel	TSTL	250.0	247.5	108.2	-1%
Full	Vectura	VEC	117.7	70.0	465.8	-41%
AIM	Venture Life Group	VLG	43.0	44.0	36.8	2%
AIM	Verona Pharma	VRP	104.5	87.5	92.2	-16%
AIM	Yourgene Health*	YGEN	5.1	8.8	36.5	71%

**Client of Hardman & Co Life Sciences*
Source: Hardman & Co Life Sciences Research

Hardman & Co Healthcare Index

Review of 2018

HHI comprises 50 stocks…

The HHI was established in 2009. Its main function is to monitor the performance and to highlight the attractiveness of life sciences investments over the long term, and to try to identify those stocks that have disruptive technologies that consistently allow them to outperform the index and the markets. Many of the 50 constituents of the index are high risk, still being in the development stage, with micro-capitalisations and a long way from sales and profitability. Despite this, some companies can still make extremely attractive returns for investors, as evidenced by the top-performing stock in 2018, Bioquell (BQE), which saw its shares rise 120%.

…with disruptive technologies that allow them to outperform index and markets

HHI performed better during 2018 than London Allshare and AIM indices

During 2018, the HHI fell by 10.0%, which was a better performance than both the London Allshare index (-13.0%) and the AIM index (-18.2%). Even allowing for capital increases and share buybacks, the HHI, at -12.5%, still performed better than these London indices. Since inception, companies that comprise the HHI have shown a CAGR of 16.6%, highlighting the attractiveness of the sector.

Comparison of HHI with London markets

@ 31 Dec	2009 Index	2010 Δ	2011 Δ	2012 Δ	2013 Δ	2014 Δ	2015 Δ	2016 Δ	2017 Δ	2018 Δ	CAGR %
Hardman & Co Healthcare index	98.4	24.7%	6.2%	25.9%	31.2%	24.1%	23.9%	9.7%	20.3%	-10.0%	16.6%
AIM index	654.2	42.7%	-25.8%	2.0%	20.3%	-17.5%	5.2%	14.3%	24.3%	-18.2%	3.1%
London Allshare index	2772.0	12.1%	-9.0%	9.5%	16.7%	-2.1%	-2.5%	12.5%	9.0%	-13.0%	3.2%

Source: Hardman & Co Life Sciences Research

Comparison with the majors

Majors performed very strongly during 2018

In order to put the share price movement of our – generally – small market capitalisation index constituent companies into perspective, the following table shows the performance of the four major UK healthcare companies over the same period. Defensive qualities during uncertain economic times, coupled with some specific factors, meant that the majors performed very strongly during 2018, all of them seeing share price appreciation in the teens. Shire was the best performer, as a consequence of it being the target of a takeover by Takeda, which is about to complete.

Performance of healthcare majors

Company	Ticker	Share price (p) 31 Dec 2017	Share price (p) 31 Dec 2018	Change (%)	CAGR 2009-2018
AstraZeneca	AZN	5,121	5,873	15%	8.1%
GlaxoSmithKline	GSK	1,323	1,491	13%	1.4%
Shire	SHP	3,900	4,570	17%	15.9%
Smith & Nephew	SN.	1,288	1,464	14%	9.6%

Source: Hardman & Co Life Sciences Research

The market continues to take an optimistic view that AstraZeneca's (AZN) R&D pipeline will deliver, despite a number of Phase III trial setbacks during the year. GlaxoSmithKline (GSK) also improved its performance, with a late rally inspired by the decision to merge its consumer health business with that of Pfizer, as a prelude to spinning off the combined entity off as a separate company in about two years' time. In early December, the market capitalisation of AZN overtook that of GSK, something that we had never expected to see without major corporate activity, although the late rally by GSK meant that it finished the year as the bigger company (£80.2bn vs. £74.4bn). The defensive qualities and strong market positions of Smith & Nephew's (SN.) operations led to another good performance. For historical reasons, 25% of the market capitalisation of Smith & Nephew is included in our index.

Some changes required

Loss of four companies in index will require £3.7bn of market cap to be replaced

During 2018, Cambian Group was acquired by Caretech after two years of underperformance in the challenging nursing/specialist care home environment in the UK. As we enter 2019, a change in the constituents of the HHI will be required. Sinclair Pharma and Vernalis have both been acquired recently, and BTG and Bioquell are in the process of being acquired by Boston Scientific and Ecolab, respectively. The loss of these four companies will require £3.7bn of market capitalisation to be replaced. In order to achieve this, it might be necessary to add some UK-based pharma/healthcare/MedTech companies that have a US listing. More information will be provided when the adjustment is made.

Movers and shakers

16 companies outperformed and 34 underperformed

Of the 50 companies included in the HHI, only 11 saw an increase in their share price during 2018. Compared with the movement in the index, 16 companies outperformed and 34 underperformed. Furthermore, several companies in our index increased their capital base – 17 of our 50 constituents raised new funds, two of which issued shares as part consideration for acquisitions – and two had share buybacks, both of which influence the performance of the index. As mentioned earlier, allowing for both of these, the index fell by 12.5% in 2018.

Given our large portfolio of constituent companies, we usually focus on both the top five (outperformers) and the bottom five (underperformers), and try to offer a short explanation as to why the shares performed in the way that they did.

Best and worst performers in 2018

------------------ Top five ------------------			----------------- Bottom five -----------------		
Rank	Company	Δ	Rank	Company	Δ
1	Bioquell	120%	46	ReNeuron	-74%
2	Yourgene Health	71%	47	Futura Medical	-79%
3	Oxford BioMedica	60%	48	Realm Therapeutics	-81%
4	Oxford Metrics	24%	49	Diurnal	-85%
5	Smith & Nephew	14%	50	Immupharma	-93%

**Client of Hardman & Co Life Sciences*
Source: Hardman & Co Life Sciences Research

The 'top five'

Bioquell

Bioquell benefited from focusing its business…

…which then attracted the attention of Ecolab

Bioquell (BQE) is a global provider of specialist bio-decontamination products and services for the life sciences (pharmaceuticals and healthcare) markets. Over the last two years, management has been cleaning up its operations through a series of small disposals of non-core businesses – AirFlow (UK) and MDH Defence – leaving a focused provider of specialist hydrogen peroxide vapour bio-decontamination equipment, modular isolators and associated services. This has attracted the attention of Ecolab, a global leader in water, hygiene and energy technologies and services that protect people and vital resources, with annual sales of approximately $15bn. In November 2018, Ecolab made a recommended cash offer of 590p per share, valuing the entire capital of BQE at ca.£140.5m. We expect this deal to complete shortly. Consequently, BQE was the best-performing stock in the HHI, rising 120% in 2018.

Yourgene Health*

Now that the legal shackles have been removed, Yourgene can focus on accelerating operational growth

For the last two years, Yourgene (YGEN, formerly known as Premaitha) has been 'handcuffed' by an ongoing patent dispute with Illumina. Despite a strong case, when it came to court, the judgement went in favour of Illumina. Although YGEN has the right to appeal, given the costs, long time-frame, and detrimental impact on the business, management has decided that it is in the best interests of shareholders to settle out-of-court and to pay Illumina a royalty on tests performed in geographies where patents are held. YGEN raised £3.0m to fund the settlement with Illumina and to provide the working capital needed to move forward. Its strategy remains to expand its IONA (non-invasive pre-natal test) test into territories not covered by Illumina patents, and to expand the range of tests available. Even though the company is likely to require more capital in the future, it will be raised against an improved operating performance and in the absence of the shackles of patent litigation. Consequently, the shares performed well in 2018, rising 71%.

Oxford BioMedica*

More deals likely from OXB during 2019

For the second year running, Oxford BioMedica (OXB) has appeared in the top five performers. OXB is a specialist advanced therapy viral-vector biopharmaceutical company that offers vector manufacturing and development services to other companies, while retaining its own proprietary drug candidates for out-licensing or partnering. Significant investment has been made in state-of-the-art specialist manufacturing facilities, which has attracted a number of pharma companies, notably Novartis, highlighting OXB's position in the market and the opportunities within it. However, any further deals would likely stretch production capacity. Therefore, management has embarked upon securing, constructing and commissioning a second manufacturing site using a modular design to provide additional clean rooms and significantly increase future capacity. In addition, OXB announced the out-licensing of its Parkinson's gene-therapy candidate (formerly ProSavin, now AXO-Lenti-PD) to Axovant Sciences, Inc (AXON) for a potential total $842.5m/£624.1m (upfront $30m/£22m). This positive news flow was reflected in the share price uplift during 2018.

Oxford Metrics

Over half-way through a five-year investment in growth plan

Oxford Metrics (formerly known as OMG; ticker OMG) develops and markets analytics software that services government, life sciences, entertainment and engineering markets internationally. For example, its helps highways authorities to manage and maintain road networks, hospitals and clinicians to decide therapeutic strategies, and Hollywood studios to create stunning visual effects. The diversity of applications is growing all the time. The company is three years into a five-year core growth plan, with sales from recurring business tripled and profits back above levels in 2016 when the investment commenced. The group is cash-generative, recently announcing a 1.0p special dividend to add to the 25% increase in the ordinary dividend to 1.5p. The positive operating trends, cashflow and dividend increase resulted in a 24% rise in the shares during 2018.

Smith & Nephew

A very safe haven in uncertain times

Although the underlying operating performance of Smith & Nephew (SN.) is unspectacular – sales growth 2%-3%, flat trading margin – in these uncertain times and volatile markets the company does represent a safe haven. In addition, there is hope that the ongoing restructuring of the business will generate a little more growth in the future. Added to this, there is the perennial takeover speculation in a MedTech industry that is continually consolidating. Having said that, SN. has been speculated as a take-out candidate in each of my 30 years in the City – one year, it will be right! This safe play in uncertain times led to a 14% increase in the share price in 2018.

The 'bottom five'

Immupharma

Outlook for Lupuzor remains uncertain

What a difference a year makes. During 2017, Immupharma (IMM) was the top-performing stock in our universe, with the market anticipating results from a Phase III trial with its leading asset, Lupuzor, for the treatment of Lupus. Positive data were expected to pave the way to securing a commercialisation partner and a lucrative licensing deal. However, when the results were released in April 2018, the primary end-point was not achieved. Although the company has reported subsequently that there were some differences in results between the European and US arms of the study, the results severely impacted the commercial value of Lupus and the likelihood of finding a commercial partner, which was reflected in the share price, which fell 93% in 2018.

*Diurnal**

Likely to spend some time with the European and US regulators during 2019

Diurnal (DNL) is a commercial-stage specialty pharmaceutical company focused on diseases of the endocrine system. Its two lead products are targeting rare conditions where medical needs are currently unmet, with the aim of building a long-term 'Adrenal Franchise'. 2018 was expected to be a positive year for the company, with the first European launch of Alkindi for adrenal insufficiency including congenital adrenal hyperplasia (CAH) in children and adolescents up to 18 years, followed by data from the European Phase III trial with the adult version, Chronocort. While the launch of Alkindi has gone largely to plan, headline data from its European Phase III trial in CAH failed to meet its primary end-point – to show that Chronocort was superior to standard-of-care. Given the strong Phase II data, this outcome was unexpected. A direct consequence of this has been a delay to the start of the US trial to allow reconsideration about the best end-points for the trial, especially given that the drug was efficacious. The delays, coupled with likely need for further capital in the future, resulted in the share price falling 85% over the course of the year.

Realm Therapeutics

Company up 'for sale' after failure of clinical programme

Expectations were high for Realm (RLM) in 2018, to the extent that the company registered its intention to seek a NASDAQ listing with the SEC during the year, although this was a condition set out in a private placement in October 2017, which was to be used as a platform for further fund raises. However, this listing was followed by the failure of its lead product, PR022, to demonstrate efficacy in a Phase II trial in patients with atopic dermatitis. Consequently, management has put the company up 'for sale', although it would also consider undertaking a merger with another company looking for a listing, that is short of cash, but owns good scientific assets under clinical development. At 30 October 2018, RLM had cash of ca.£15m, compared with a market capitalisation of £8m. The shares fell 81% in 2018.

Futura Medical

Phase III data needed in order to obtain that elusive commercial deal for MED2002

Although news flow from Futura Medical (FUM) on product development was generally positive during 2018, investors have become increasingly frustrated by the lack of progress regarding commercial deals. This follows on from the decision by Church & Dwight to terminate the rights to CSD500 (erectogenic condom) during 2017. FUM has been concentrating resources on development of MED2002 for erectile dysfunction. Publication of pharmacokinetic data demonstrating safety at higher doses and data on dose-related absorption were expected to provide the platform for licensing deals. However, potential partners all want to see Phase III data before committing to a deal, even though they would have to pay more money. Therefore, management took the decision to embark on a Phase III trial with MED2002, which will run until the end of 2019. The delays caused a negative share price reaction, against which the company needed to raise more capital. Although this was successful, it was achieved at a price of 7p, resulting in a 79% fall in the shares in 2018.

ReNeuron

Drug development takes time and money

There is little doubt about the potential afforded by cell-based therapeutics. However, these therapies still have to go through all the same trials and regulatory procedures as a small molecule drug. In addition, the number of companies able to manufacture commercial-scale cell-based therapies are few and far between, which also adds to the development timelines. Although ReNeuron (RENE) appears to be making progress in line with its stated strategy, the shares have been in a long-term downward drift since peaking at 637p in the middle of 2015. The company has ca.£30m cash (30 September 2018) and an annual burn rate of ca.£15m p.a., so it is likely to be coming back to the market for more capital in the next 12 months. The shares fell 74% in 2018.

*Client of Hardman & Co Life Sciences

Upcoming sector newsflow

- **Advanced Oncotherapy*:** Accelerate proton beam to full power by completing the integration of all the modules and completing the LIGHT system to gain regulatory approval by the year-end.
- **Allergy Therapeutics*:** Read-out of results from the European Phase III PQ Birch trial is expected during 1Q'19. Positive outcomes would allow the company to file for marketing authorisation with the Paul Ehrlich Institute following the Therapieallergene-Verordnung (TAV).
- **Amryt:** Read-out for the Phase III trial (EASE) with AP-101 in epidermolysis bullosa (EB) has been pushed back to 2H'19, following a recommendation from the Independent Data Monitoring Committee. An additional 48 patients will be enrolled, taking the total up to 230. The recommendation suggests that the trial is performing well, but that additional data are needed in order to reach statistical significance.
- **AstraZeneca:** Phase III TULIP 1 data, investigating anifrolumab in lupus, was released on 31 August 2018, but did not meet its primary end-point. Data from TULIP 2 are due to be released around the end of 1Q'19.
- **Circassia:** The target action date for completing the review of Duaklir, for the treatment of chronic obstructive pulmonary disease (COPD), has been set for 31 March 2019. This date has also been set for the review of supplemental data on Tudorza demonstrating cardiovascular safety and the reduction of COPD exacerbations.
- **Evgen:** Read-out of both Phase II trials with SFX-01 in subarachnoid haemorrhage (stroke) and breast cancer. Both sets of data are due by the end of 1Q'19.
- **Motif Bio:** FDA approval of iclaprim, a targeted antibiotic with activity against MRSA, is expected in 1Q'19, following an accelerated evaluation procedure.
- **Orchard Therapeutics:** Recently listed on NASDAQ, Orchard is expected to announce Phase III trial results for OTL-101 (a lentiviral gene therapy for use in children affected by severe combined immunodeficiency (SCID), due to adenosine deaminase (ADA) defect (ADA-SCID), also known by the general public as 'bubble babies') in 2H'19, which would allow the company to hit its target to submit a BLA to the FDA in 2020.
- **Poseida Therapeutics:** Registered with SEC its intention to list on NASDAQ in 1Q'19, with the aim of raising $115m.
- **Redx Pharma*:** Re-start of Phase I proof-of-concept trial in patients with colorectal cancer with RXC004 during 1H'19. Designation of clinical candidates expected in two indications for its fibrotic assets, likely in 2H'19.
- **Shield Therapeutics*:** The PDUFA date for Feraccru®, the deadline for the FDA's authorisation decision, is set for July 2019. Approval would mean access to the large US market and building on European approval gained in March 2018.
- **Synairgen:** Results from the Phase II trial of SNG001, a broad-spectrum antiviral for COPD patients, are expected in 2H'19. SNG001 is an inhaled β-interferon that boosts the lungs' immune defences.
- **ValiRx*:** Read-out of Phase II trial with VAL201 in advanced prostate cancer around the middle of 2019.

*Client of Hardman & Co Life Sciences

About the authors

Dr Martin Hall

Martin's career in the City started as a healthcare analyst in 1987, working at Morgan Grenfell and then UBS. He joined HSBC in 1992, where he was Head of Global Pharmaceutical/Healthcare Equity Research. In 2005, he set up as an independent Life Sciences Analyst and Corporate Broker under the umbrella of Eden Financial Limited. Martin is acknowledged for his thought-provoking and opinionated research. He joined Hardman & Co in June 2013.

Martin qualified as a pharmacist (B.Pharm.Hons) at the School of Pharmacy, University of London, and has a PhD in Neuropharmacology, also from the University of London. After two years of post-doctoral research under a Royal Society Fellowship at the Collège de France, Paris, he became leader in Biochemical Pharmacology at the Parke-Davis Research Centre in Cambridge. Martin is a member of Royal Pharmaceutical Society of Great Britain.

Dr Dorothea Hill

Dorothea joined the Life Sciences team as an Equity Research Analyst in August 2016. She began her career researching vaccines as part of an international Gates Foundation/Wellcome Trust collaboration, following which she undertook a PhD in genetics and vaccines for meningococcal disease at the University of Oxford. She has broad experience in the field of vaccines research and development, having worked on the molecular biology of bacterial pathogens, antigen discovery, molecular diagnostics, and next-generation sequencing technologies. Dorothea has authored 13 papers, including first author publications in the Lancet Infectious Diseases and in Nature's Scientific Reports. She is passionate about drug development and the commercialisation of medical innovation.

Dr Grégoire Pavé

Greg is an analyst in the Life Sciences team at Hardman & Co, and has considerable experience in the field of drug discovery and development. In 2003, he enrolled in a team-leader post-doctoral position at Imperial College London, working on natural product synthesis. In 2005, he joined Cancer Research Technology, the development and commercial arm of Cancer Research UK, where he was involved in multiple oncology projects. Greg has broad experience in drug discovery and development projects, from target identification and validation through to clinical trials. He has also gained valuable experience in evaluating life science projects and their commercial opportunities. In addition, he has played a role of reviewer in peer-review journals from the American Chemical Society. He is also an author of 14 scientific papers and owner of four patents. Greg joined Hardman & Co in March 2016. He has a PhD in Medicinal Chemistry from the University of Orléans in France, and holds the IMC and PRINCE2 qualifications.

Notes

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The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf

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