Platinum International Health Care Fund

Bianca Ogden Portfolio Manager

Disposition of Assets

REGION	DEC 2015	SEP 2015
Europe	36%	36%
North America	27%	25%
Japan	3%	3%
Asia	3%	3%
Australia	1%	1%
South America	1%	0%
Cash	29%	32%
Shorts	-1%	-1%

Source: Platinum. Refer to Note 3, page 4.

Performance

(compound pa, to 31 December 2015)

	QUARTER	1YR	3YRS	5YRS	SINCE INCEPTION
Platinum Int'l HC Fund	2%	23%	28%	22%	10%
MSCI AC World HC Index	3%	20%	35%	25%	10%

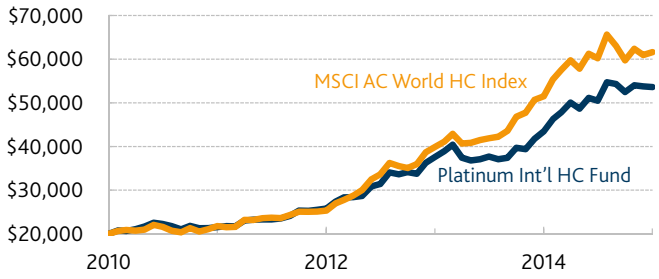
Source: Platinum and MSCI. Refer to Note 1, page 4.

This year US biotech performance has moderated and the mood is now more reflective as well as selective. Recent IPOs have found a less receptive audience with some companies having to postpone their raising altogether[1]. On the other hand, pharma and big biotech have continued with their purchases (e.g. AstraZeneca and Gilead Sciences both have recently been active outside the US) and asset swaps (as we have seen between Sanofi and Boehringer Ingelheim), keeping things interesting.

For the year and the quarter, our European holdings have added to performance while the high cash position held things back, reflecting our more cautious view. Sartorius advanced 47% for the quarter (up 214% for the year) while Genmab was up 50% for the quarter (155% for the year).

Value of $20,000 Invested Over Five Years

31 December 2010 to 31 December 2015



Source: Platinum and MSCI. Refer to Note 2, page 4.

1 In 2015 there were 38 biotech IPOs versus 64 in 2014, with a gradual shift to earlier stage biotech.

Genmab's CD38 antibody is now approved and it is clear that it will change the way multiple myeloma is being treated. Danish Lundbeck, a position we added to recently, continues to garner interest as it gradually leaves its patent cliff behind (up 32% for the quarter and 92% for the year). Sanofi (-7% for the quarter and +4% for the year) has been disappointing this quarter as it will require more spending over the next two years while diabetes becomes more competitive. Sanofi does need to strengthen its pipeline and we have already seen some deal activity, but we are expecting more.

Changes to the Portfolio

During the quarter we trimmed our position in **Novartis**. Although it gained approval for its chronic heart failure drug, we were rather disappointed by how Novartis spends its capital.

We added to **Qiagen** during the quarter. The company has done well in establishing its molecular diagnostic franchise, developing its next generation sequencing equipment and establishing itself as the leading bioinformatics software provider. In today's molecular biology world it is no longer about the equipment; it is about the software that adds functionally and clinically relevant knowledge to the vast amount of available data. Qiagen is closing this loop.

We also added to **Roche**. Biosimilars will come, no doubt, but this is a company with a solid science track record and a pipeline that has never been as big as today.

Commentary

Ever since scientists identified and learned to manipulate DNA the plan has been to translate genetic engineering into a therapeutic. The hope is that one day **a faulty gene can simply be replaced or modified**. While it is often clear which gene needs to be replaced or modified, the struggle has been to get it into the right cell, maintain its presence and control the expression of the corrected gene without disrupting the existing delicate regulatory network. Once that is achieved, the challenge remains to transmit the corrected gene to the cell's progeny, allowing a lasting therapeutic effect.

For the past two decades scientists have been busy improving each of the above steps. Assets moved into clinical trials producing mixed results, with some causing serious side effects such as leukemia. All along pharma has been cautious, at times dabbled in gene therapy, but in the end left disappointed.

As everything in science, caution reigns initially, but over time, as more data and more sophisticated approaches emerge, sentiment will change. We have seen it with antibody drugs. Here, Roche (and to some extent Johnson and Johnson) was an early adopter while its peers remained sceptical for a long time. Gene therapy is, however, more complex, as it is about permanently manipulating the inner workings of a cell at its core which requires a deep understanding of genomics using more sophisticated analytical tools. Scientists are now getting there and clinical trial results are now more reproducible, showing sustainable effects.

Delivery technology is key for gene therapy and in this respect **viruses are proving to be the ideal tool**. Their genomes can be manipulated to eliminate the elements that make them pathogenic and self-replicating. At the same time **new genes can be introduced** and quickly one has a nice gene delivery vector.

Different viral vectors have been tested over the years and for now lentiviral vectors (HIV is a lentivirus) and adeno-associated virus (AAV) are popular. These vectors are made in the laboratory and over the past 10 years have improved immensely.

Essentially, these viruses carry the structural viral proteins along with the gene (or genes) of interest, but lack the ability to replicate and be infectious. Thus all they do is deliver the gene construct together with regulatory elements to the host genome.

Lentiviral vectors are particularly interesting as they **integrate the "gene cassette" into the host genome, making the change permanent**. Over the years these vectors have improved at every level. The rate of transduction (meaning the rate at which the viral vector gets into the target cell) is now consistent while the issue of integrating near oncogenes and causing cancer has been dealt with. The regulatory elements controlling the expression of the new gene are also much better engineered these days to allow robust and stable production once the cassette has been delivered.

All of these changes have made a difference and today gene therapy using lentiviral vectors is in late stage clinical testing for some blood cancers. Here lentiviral vectors are engineered to encode proteins that will prime a T cell (part of the adaptive immune system) to attack a patient's cancer. It is an ex vivo procedure, meaning that T cells are obtained

from the patient (simply by blood draw and followed by purification steps) and then transduced with the viral vector in the laboratory (hence ex vivo). Once enough cells are available, they are re-infused into the patient. These T cells are now engineered to recognise the patient's cancer cells and destroy them. Things are never without side effects, but doctors are learning to deal with them.

We recently added **Oxford BioMedica** to the Fund's portfolio. This UK biotech was founded in 1995 by a husband and wife team who were experts in DNA recombinant technology. Today this company is the world's leading lentiviral vector specialist. Oxford BioMedica has been quietly working away in its labs, improving its vector technology, and has invested time and money into its commercial manufacturing capability. Several years ago Novartis came along, and today Oxford BioMedica is the manufacturer for all lentiviral vectors for Novartis T cell therapies (with approval potentially forthcoming in 2017). Making these lentiviral vectors is a crucial step and requires a lot of know-how that has been accumulated (and patented) over time. Other companies have started taking out licences for Oxford BioMedica's IP and, to us, more will follow as we are moving closer to the commercial reality of gene therapy.

Gene therapy has come a long way and the next instalment will be all about gene-editing technologies[2], a subject for future reports.

Outlook

Pricing flexibility in the US will decrease over time, making innovation ever more crucial to success. Competition is also fiercer than ever as companies these days work on the same drug targets, thus making drug monopolies short-lived. Science, the depth and commercial sense of clinical development programs, along with smart capital allocation, are the key aspects that we focus on. Tools and IT are another area we are exploring in more detail as a focus will be on how to stay ahead of the crowd in drug development labs.

2 Zinc-finger nucleases (ZFN), Transcription activator-like effector nucleases (TALEN) as well as the CRISPR/Cas9 system (CRISPR stands for "clustered regularly-interspaced short palindromic repeats" while Cas9 refers to a CRISPR-associated protein, a nuclease). These tools warrant their own quarterly report, but in a nutshell, these technologies allow genes to be edited directly by using a delivery vehicle like a viral vector.

Notes

1. The investment returns are calculated using the relevant Fund's unit price and represent the combined income and capital return for the specific period. They are net of fees and costs (excluding the buy-sell spread and any investment performance fee payable), are pre-tax, and assume the reinvestment of distributions. The investment returns shown are historical and no warranty can be given for future performance. You should be aware that historical performance is not a reliable indicator of future performance. Due to the volatility of underlying assets of the Funds and other risk factors associated with investing, investment returns can be negative (particularly in the short-term).

   The inception dates for each Fund are as follows:
   Platinum International Fund: 30 April 1995
   Platinum Unhedged Fund: 28 January 2005
   Platinum Asia Fund: 4 March 2003
   Platinum European Fund: 30 June 1998
   Platinum Japan Fund: 30 June 1998
   Platinum International Brands Fund: 18 May 2000
   Platinum International Health Care Fund: 10 November 2003
   Platinum International Technology Fund: 18 May 2000

   (NB: The gross MSCI Index was used prior to 31 December 1998 as the net MSCI Index did not exist.)

2. The investment returns depicted in this graph are cumulative on A$20,000 invested in the relevant Fund over five years from 31 December 2010 to 31 December 2015 relative to its benchmark index (in A$) as per below:

   Platinum International Fund - MSCI All Country World Net Index
   Platinum Unhedged Fund - MSCI All Country World Net Index
   Platinum Asia Fund - MSCI All Country Asia ex Japan Net Index
   Platinum European Fund - MSCI All Country Europe Net Index
   Platinum Japan Fund - MSCI Japan Net Index
   Platinum International Brands Fund - MSCI All Country World Net Index
   Platinum International Health Care Fund - MSCI All Country World Health Care Net Index
   Platinum International Technology Fund - MSCI All Country World Information Technology Net Index

   The investment returns are calculated using the relevant Fund's unit price. They are net of fees and costs (excluding the buy-sell spread and any investment performance fee payable), pre-tax and assume the reinvestment of distributions. It should be noted that Platinum does not invest by reference to the weightings of the benchmark index. Underlying assets are chosen through Platinum's individual stock selection process and as a result holdings will vary considerably to the make-up of the Index. The Index is provided as a reference only.

3. Invested position represents the exposure of physical holdings and long stock derivatives.

Disclaimer

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