Monitoring International Trends

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The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could potentially put financial or other pressures on the Australian sector.

A selection of recent matters of interest appears below. Highlights include:

- A trial\(^1\) has found that intravenous immunoglobulin could reduce brain atrophy and cognitive decline for a time in patients in the early, pre-dementia phase of Alzheimer’s disease (Section 1).
- CSL Behring hosted a symposium highlighting an option to slow the progression of emphysema in adults with documented severe alpha-1 antitrypsin deficiency (Section 1).
- Health Canada approved Baxalta’s OBIZUR for treating haemophilia A (Section 2).
- The US Food and Drug Administration (FDA) granted fast track designation to Dimension Therapeutics’ gene therapy product in development for the treatment of haemophilia B (Section 2).
- Biogen and Swedish Orphan Biovitrum received a positive recommendation from the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) for the marketing authorization of ELOCTA, a long-lasting recombinant factor VIII Fc fusion protein product for the treatment of haemophilia A (Section 2).
- LFB announced the first two marketing authorizations for its 10% liquid intravenous immunoglobulin in Europe (Section 2).
- The FDA approved its first reversal agent for a novel oral anticoagulant. Idarucizumab (Praxbind) works by binding to dabigatran (Pradaxa) in the blood when given via intravenous injection (Section 5).
- A Canadian study suggests that dabigatran is about as safe and effective as warfarin in elderly patients with atrial fibrillation (Section 5).
- The US National Institutes of Health (NIH) awarded a five-year, $US 1.9 million grant to a Case Western Reserve University researcher to transform clot-forming synthetic platelet technology into devices that can dissolve clots to prevent strokes and heart attacks (Section 6).

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1. Products

Here the NBA follows the progress in research and clinical trials that may within a reasonable timeframe make new products available, or may lead to new uses or changes in use for existing products.

Haemophilia treatments

a) Recent reports on the global haemophilia market\(^2\) forecast a 4 per cent compound annual growth rate in the haemophilia A market to 2019, and a six per cent compound annual growth rate in the haemophilia B market for the same period.

b) BioMarin Pharmaceutical of California announced that it had enrolled the first patient in a Phase I/II trial of BMN 270, its investigational gene therapy for the treatment of patients with haemophilia A. This gene therapy program for haemophilia A was originally licensed from University College London and St. Jude Children’s Research Hospital in February 2013, and has been further developed by BioMarin. "Hemophilia A results from mutations at the genetic level, making gene therapy a potentially powerful technique to treat patients with a single dose," said Hank Fuchs, Executive Vice President and Chief Medical Officer of BioMarin. "For the first clinical trial of BMN 270, we are looking to demonstrate that treatment with BMN 270 increases the expression of the factor VIII protein, necessary for blood clotting."

c) Alnylam has begun a Phase 1 open-label extension study with ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin (AT) for the treatment of haemophilia and rare bleeding disorders. The trial will evaluate the long-term safety and efficacy of ALN-AT3 and allow people with haemophilia previously

enrolled in the Phase 1 study the opportunity for continued dosing\(^3\). The company expects to report clinical data from the study at least annually, beginning in 2016. Akshay Vaishnaw, Executive Vice President of Research and Development and Chief Medical Officer at Alnylam said: “We believe the ALN-AT3 data presented to date have been very promising, demonstrating potent, dose-dependent, and durable knockdown of AT with the potential to re-balance hemostasis in people with severe haemophilia through normalization of thrombin generation. We look forward to providing continued clinical updates, including results for once-monthly subcutaneous dosing in haemophilia patients, later this year.”

### Other

d) A trial\(^4\) has found that intravenous immunoglobulin could reduce brain atrophy and cognitive decline for a time in patients in the early, pre-dementia phase of Alzheimer’s disease.

e) Protalex of New Jersey announced that the French National Agency for Medicines and Health Products had approved the company’s application to begin a Phase Ib clinical trial of PRTX-100 in adult patients with persistent/chronic immune thrombocytopenia (ITP) at several sites in France. Protalex also announced that the European Medicines Agency Committee for Orphan Medicinal Products (COMP) had issued a positive opinion recommending PRTX-100 for designation as an orphan medicinal product for the treatment of ITP. Protalex had previously announced initiation of a US Phase II/II clinical trial of PRTX-100 in adult ITP patients and receipt of Orphan Drug Designation for PRTX-100 to treat ITP from the FDA Office of Orphan Products Development. PRTX-100 is a new generation immunomodulatory therapy. It is a highly purified form of SpA, a protein found in the cell wall of *Staphylococcus aureus*.

f) Ablynx began a Phase III study to evaluate efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura (TTP)\(^5\). The company will enrol 92 patients across 17 countries in the double-blind placebo-controlled HERCULES study. The primary endpoint of the study is time to platelet count normalization, which avoids further microvascular thrombosis. Caplacizumab was awarded Orphan Drug Designation in both the US and EU in 2009. The drug inhibits the interaction between Von Willebrand factor (vWF) and platelets by targeting the A1 domain of vWF. Edwin Moses, CEO of Ablynx, said: "The ability of caplacizumab to rapidly inhibit the formation of small blood clots, resulting in the more rapid restoration of normal platelet counts and an important reduction in exacerbations, was well demonstrated in the Phase II TITAN study. Based on the clinical effect seen in this TITAN study, we are planning to submit caplacizumab for conditional approval to the European Medicines Agency in 2017."

g) Ergomed announced that the drug sevuparin which it is helping to develop for sickle-cell disease is moving into Phase II clinical trials. Patients will be treated for vaso-

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\(^3\) The AT3 Phase 1 OLE study is an open-label, multi-centre study designed to evaluate the long-term safety and tolerability of ALN-AT3 in haemophilia patients who were previously enrolled in the Phase 1 study. Eligible patients treated in the earlier Phase 1 study can now enrol in the OLE study, where they will receive ALN-AT3 for up to the earlier of two years or until the drug receives regulatory approval and becomes commercially available in their market. In addition to evaluating the long-term safety and efficacy of ALN-AT3 in haemophilia patients, the study will evaluate clinical activity of ALN-AT3, as measured by knockdown of serum AT, increases in thrombin generation, and reduction in the frequency of bleeding events.


\(^5\) Acquired TTP results in the formation of microvascular thrombosis and organ damage throughout the body, including in the brain and the heart. It affects about 11 per million people globally.
occlusive crisis, a common and painful complication. Ergomed’s partner, the Swedish firm Dilaforette, is recruiting 70 sufferers for a double-blind and placebo controlled trial. The primary aim is to see whether the drug reduces the time it takes to resolve the crisis. The secondary end-points are pharmacokinetics\(^6\) and safety.

h) BioMedomics of North Carolina has received a $US 222,950 grant from the National Institutes of Health to boost its development of a diagnostic test to aid in treating people with sickle cell disease. CEO Frank Wang said BioMedomics’ quantitative point-of-care system will test specifically for hemoglobin S (HbS) and hemoglobin F (HbF). Over 100,000 people in the US suffer from sickle cell disease. Up to half of them receive frequent blood transfusions to lower HbS, and about one-third of these patients are given chronic hydroxyurea therapy to raise their HbF levels. It is challenging for doctors to track and balance the appropriate levels of HbS and HbF, when current test procedures take several days before clinicians see results from remote testing labs.

i) Emmaus Life Sciences of California presented an abstract from its completed FDA Phase III sickle cell disease trial at the Ninth Annual Sickle Cell and Thalassaemia Advanced Conference in London. “There is great need for a widely available and well tolerated treatment for the sickle cell disease patients in Europe,” said Yutaka Niihara, Chairman of Emmaus. “As the only company to complete a Phase III trial in the US in nearly twenty years, we look forward to sharing the clinical trial results with the sickle cell disease community in Europe.” Emmaus’ therapy has Orphan Drug Designation in both the US and Europe and Fast Track Designation from the FDA.

j) During the European Respiratory Society International Congress\(^7\), CSL Behring hosted a symposium highlighting an option to slow the progression of emphysema in adults with documented severe alpha-1 antitrypsin deficiency (AATD). AATD is a hereditary condition marked by a lack of the alpha-1 antitrypsin protein, whose main function is to protect the lungs from inflammation.

k) A clinical trial at St. Mary’s Hospital in St. Louis will test whether the drug ATryn, or antithrombin recombinant, is effective at treating preeclampsia\(^8\) to increase the length of pregnancy and reduce perinatal mortality and disability. Dr Erol Amon, a professor of maternal-foetal medicine at Saint Louis University School of Medicine, said in a press release: “I am treating two patients—the mother and the child. If we were only concerned about the health of the mother, then we would deliver immediately. However, keeping the fetus in the womb increases the opportunity for lung maturity and improves outcomes for the child. We are concerned with both maternal and fetal health.” Amon said researchers have focused on recruiting women who are between their 23rd and 30th week of pregnancy. Previous trials in Japan and Italy have shown that ATryn can extend pregnancies by about a week. Dr Amon said there is concern about American women in comparison with other populations because of higher incidence and intensity of hypertensive disorders.

l) A group of bioengineers at Massachusetts Institute of Technology have developed a noninvasive, portable device that resembles a finger-worn, pulse oximeter to count white blood cells. They have three workable prototypes that are being tested with chemotherapy patients to track their immune system in real-time. The researchers hope to have an initial beta product that it can support via crowd funding in 2017, with a product on the market potentially in 2019. The focus is to create a device that can be used to continuously monitor immunosuppressed patients, such as those on

\(6\) how the drug is absorbed and treated by the body

\(7\) 26-30 September in Amsterdam

\(8\) Preeclampsia is characterized by high blood pressure, high levels of protein in urine and swelling in the hands and feet. It occurs in 5 to 8 per cent of pregnancies, generally developing anywhere between the 20th week of pregnancy and as late as 6 weeks after giving birth. There is no specific known cause of preeclampsia, however mothers who are obese, have diabetes or hypertensive disorders, or are teenagers are at higher risk of developing the condition.
chemotherapy, and to detect serious infections. The project, known as Leuko, is being financed by Madrid-MIT M+Visión, a consortium of Madrid and Boston research centres and hospitals, as well as the Center of Future Technologies in Cancer Care and the Coulter Foundation.

m) Eculizumab, which prevents complications of paroxysmal nocturnal hemoglobinuria\(^9\) (PNH), also can help reduce PNH symptoms during pregnancy, is associated with a higher rate of live births, and leaves little trace in breast milk, according to the report of a small study with industry connections\(^10\).

2. Regulatory

The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.

a) Health Canada has approved Baxalta’s OBIZUR [Antihaemophilic Factor (Recombinant) Porcine Sequence] for the treatment of bleeding episodes in patients with acquired haemophilia A caused by autoantibodies to coagulation Factor VIII. OBIZUR was cleared in the US for the same indication in October 2014.

b) The FDA granted fast track designation to Dimension Therapeutics’ DTX101, a gene therapy product in development for the treatment of patients with haemophilia B. DTX101 is designed to deliver blood clotting Factor IX gene expression, in contrast with the current standard of care which requires patients to undergo chronic replacement of Factor IX protein via intravenous infusion. This follows the earlier granting by the FDA of Orphan Drug Designation. A multicentre Phase I/II trial in adults with moderate to severe haemophilia B is expected to begin by the end of 2015.

c) Biogen and Swedish Orphan Biovitrum (Sobi) received a positive recommendation from the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) for the marketing authorization of ELOCTA, a recombinant factor VIII Fc fusion protein product for the treatment of haemophilia A that, if approved, would be the first haemophilia A treatment with prolonged circulation available in the European Union (EU)\(^11\).

d) The FDA approved Promacta (eltrombopag) to treat low blood platelet count in paediatric patients aged one year or more with chronic immune thrombocytopenic

\(9\) PNH is characterized by premature destruction of red blood cells.


\(11\) The positive opinion was based on results from the pivotal, Phase III A-LONG clinical study, which examined the efficacy, safety and pharmacokinetics of rFVIIIFc in previously treated males 12 years of age and older with severe haemophilia A, and from the Phase III Kids A-LONG clinical study, which evaluated the efficacy and safety of rFVIIIFc in previously treated male children with haemophilia A under 12 years of age. The Committee’s positive opinion is now referred to the European Commission (EC), which grants marketing authorization for medicines in the EU. “The CHMP’s recommendation to approve ELOCTA is an important milestone in potentially bringing this innovative therapeutic option to people with haemophilia A across Europe,” said Aoife Brennan, vice president of hematology, clinical development at Biogen, adding: “The potential of Elocta to provide protection against bleeding episodes with fewer prophylactic infusions will, if approved, represent the first treatment advance in nearly 20 years for Europe’s haemophilia community. Elocta is the European trade name for rFVIIIFc, which is also known as Eloctate (antihemophilic Factor [recombinant], Fc Fusion Protein) in the USA, Canada, Australia, New Zealand and Japan, where it is approved for the treatment of haemophilia A. Commonly reported adverse drug reactions (/>= 1% of subjects) in the clinical studies were arthralgia, malaise, myalgia, headache and rash. Development of Factor VIII neutralizing antibodies (inhibitors) may occur following administration of Elocta.
purpura (ITP). Promacta can be used when the children have not achieved an appropriate response using other ITP medicines or surgery to remove the spleen.

e) LFB announced the first two marketing authorizations for IQYMUNE, its 10% liquid intravenous immunoglobulin (IVIg), in Europe, namely in the United Kingdom and in Denmark.

f) Dyax Corporation announced that the European Medicines Agency Committee for Orphan Medicinal Products (COMP) has adopted a positive opinion recommending DX-2930 for designation as an orphan medicinal product for the treatment of hereditary angioedema (HAE). Dyax is developing DX-2930, an investigational fully human monoclonal antibody inhibitor of plasma kallikrein (pKal), as a subcutaneous injection for prevention of HAE attacks.

g) The FDA’s Gastroenterology and Urology Devices panel is to meet on 18 November to discuss Andover, Massachusetts-based TransMedics’ pre-market approval bid for its Organ Care System, which is designed to perfuse a donor heart with warm, oxygenated blood and monitor its status until transplantation.

3. Market structure and company news

The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.

a) CSL announced it will buy back $A 1 billion of its shares, its biggest buyback yet and its ninth buyback over the last 10 years. CSL chairman Professor John Shine told shareholders at the company’s annual general meeting that growth in CSL’s earnings per share in the 2015/16 financial year would exceed profit growth expectations as shareholders benefit from the ongoing effect of past and current buy backs. He said: “While the markets in which we operate remain highly competitive, our broad portfolio of innovative products, ongoing product development and growing demographic reach continue to ensure our business remains well positioned”.

b) CSL raised 400 million Swiss francs and $100 million via a private placement in the US. The funds will be used for the company’s capital management plan and for general corporate purposes. The private placement consists of several maturities with an average life of 9.4 years and a weighted average fixed interest rate of 1.43 per cent.

c) Kamada announced the third extension to supply Glassia to Baxalta, under its strategic agreement with Baxter International originally executed in August 2010. Through the extended agreement, Kamada secured approximately $US 50 million in additional minimum revenues of Glassia, its proprietary, ready-to-infuse liquid alpha-1 antitrypsin (AAT) treatment indicated as a chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital AAT deficiency (AATD). The agreement has been extended through 2018.

d) Genzyme has elected to opt into Alnylam’s investigational ALN-AT3 haemophilia program for development and future commercialization in territories outside North America and Western Europe. The companies formed a global alliance in January 2014. Genzyme’s current decision was based on the Phase 1 trial of ALN-AT3, from which positive interim data were presented at the International Society on Thrombosis and Haemostasis (ISTH) 2015 Congress in June 2015.

e) ADMA Biologics received a milestone payment from Biotest for filing a Biologics License Application with the FDA, in accordance with the license agreement signed on December 31, 2012. The product, RI-002, is a specialty plasma-derived, polyclonal, intravenous immune globulin derived from human plasma containing
naturally occurring polyclonal antibodies (e.g., Streptococcus pneumoniae, H. influenzae type B, cytomegalovirus, measles, tetanus, etc.) as well as standardized, high levels of antibodies to respiratory syncytial virus (RSV). ADMA is pursuing an indication for the use of this specialty intravenous immune globulin for treatment of patients diagnosed with primary immune deficiencies.

f) Octapharma is paying €80 million for an exclusive global licence to certain intellectual property behind Glycotope's recombinant technology, as well as a minority stake in the German company. Glycotope's CEO Steffen Goletz said in a statement: "Octapharma's ongoing commitment to haemophilia research, combined with its experience in developing and marketing haemophilia and other blood protein factor products, makes them an excellent partner for our human blood coagulation portfolio, GlycoExpress technology and long-lasting technologies."

g) Cerus Corporation announced that the Community Blood Center of the Carolinas (CBCC) had signed a three-year purchase agreement for the INTERCEPT Blood System for platelets and plasma.\(^{12}\)

h) Swedish engineering firm KeyPlants has been selected for the design and engineering of a plasma processing facility for Russia’s MasterPlasma. The $US 76 million facility is to be operational by the end of 2017 and will process up to 600,000 litres of plasma annually.

i) Fibrant announced that it has concluded an exclusive license agreement with the Netherlands Organization for Applied Scientific Research (TNO) to allow the company to further build its unique fibrinogen technology platform. The versatility of the platform enables the company to produce specific fibrinogen variants, either by sub-fractionation of human plasma fibrinogen, or by recombinant production in mammalian cells. Jaap Koopman, CEO, said: "The TNO license provides broad protection and significantly enhances our competitive position in the rapidly growing fibrinogen market. Fibrant was recently founded by a small group of experts in the fibrinogen field with a strong track record in industry and academia. For our own proprietary product pipeline as well as for third parties we aim to develop specific fibrinogen variants for tissue repair, remodeling and regeneration, and tools to further explore the role of fibrinogen in inflammation and immune response."

j) Opsonix announced the company's launch with a $US 8 million Series A financing to develop a pathogen-extracting therapy designed to remove infectious pathogens and toxins from circulating blood. The treatment potentially offers a new broad-spectrum approach to treat sepsis and other blood-borne infectious diseases. Opsonix will apply the proceeds from the financing to advance the development of its extracorporeal pathogen-extracting therapy. The Series A financing was led by Baxter Ventures and private investor Hansjörg Wyss. Opsonix's core technology employs proprietary pathogen-capture proteins to remove a broad range of bacteria, fungi, parasites, viruses, and toxins responsible for initiating the sepsis cascade, including antibiotic-resistant organisms. Opsonix's pathogen-extracting therapy has been designed to work in synergy with conventional antibiotic treatments. Opsonix enjoys an exclusive, global licence to intellectual property from Harvard University covering the use of engineered opsonin proteins in pathogen-extracting devices and companion diagnostics.

k) Ocata says it has published and patented methods for robust, scaleable production of platelets. Platelet production is highly amenable to any type of stem cell source because they do not need to divide; hence, there is no cancer risk. Ocata company presentations have been hinting at a partnership for the platelet program since last year.

\(^{12}\) CBCC provides over 12,000 platelet and 22,000 plasma units annually to 27 regional hospitals.
4. Country-specific events
The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia’s visitors and immigrants come.

a) The Irish Blood Transfusion Service (IBTS) owes the state €10.3 million in pension-related deductions from staff, according to the Comptroller and Auditor General. Seamus McCarthy said the provisions of the Financial Measures in the Public Interest (FEMPI) Act were not being complied with, as staff pension deductions were being deducted but not paid over. The deficit in the IBTS pension scheme has more than doubled in three years to €92 million last year, Mr McCarthy told the Dáil Public Accounts Committee.

b) The Baltimore Health Department has received more than $US 20 million in federal funding for a new HIV strategy targeting gay men and transgender people and pushing a drug that can prevent people from contracting the disease. With two grants from the Centers for Disease Control (CDC), city officials will partner directly with eleven community and provider groups. The strategy will focus on testing, treatment and helping people with social problems, such as poverty and drug abuse, that may affect whether they receive care. A significant part of the new strategy involves better marketing of PREP\(^{13}\), a drug given to people who engage in risky behaviour. The drug can reduce their chances of contracting the virus by up to 92 per cent. Approved by the FDA in 2012, the drug is not used as much as health officials believe it could be. Baltimore is only one of several cities receiving CDC funding. The grants follow an executive order President Barack Obama issued in July calling for such broader strategies to reach populations that have stumped efforts by public officials to eradicate HIV amid advancements such as rapid testing and anti-viral drugs that make the virus nearly undetectable in many people.

c) At the state-run Singapore General Hospital 678 patients and 273 medical workers were contacted to be screened for the Hepatitis C virus. The hospital earlier said 22 kidney patients had been infected with hepatitis C between April and June.

5. Safety and patient blood management
We follow current issues in patient safety and achieving favourable patient outcomes.

Appropriate transfusion

a) A study of 2,399 patients at Henry Ford Hospital, Detroit\(^{14}\), found that blood transfusion rates in hip and knee replacement surgery were dramatically lower in overweight or obese patients than patients of normal weight. Furthermore, no correlation was found between the heavier patients and post-surgical complications such as blood clots and heart attacks.

b) A team of researchers from the Trauma Program at Children’s Hospital Los Angeles reported that an admission haematocrit provides a reliable screening test for identifying paediatric patients who are at an increased risk of bleeding after injury\(^{15}\).

\(^{13}\) PREP, or pre-exposure prophylaxis, is a pill taken every day. It’s a mix of two medicines used to treat HIV that can keep the virus from permanently infecting someone when they are exposed to it. 

\(^{14}\) Presented at the International Society for Technology in Arthroplasty, 30 September to 1 October in Vienna

\(^{15}\) Their retrospective review of approximately 1,340 trauma patients, ages 0 to 17 years, will be published in the Journal of Trauma and Acute Care Surgery and is currently available on PubMed at [http://www.ncbi.nlm.nih.gov/pubmed/?term=26402528](http://www.ncbi.nlm.nih.gov/pubmed/?term=26402528)
Treating iron deficiency

c) Akebia Therapeutics has set the key elements of its Phase III program for vadadustat (AKB-6548) for the treatment of patients with anaemia related to non-dialysis-dependent chronic kidney disease (NDD-CKD). The Phase III program will be finalized after the company presents its completed Phase III results to the FDA and European Medicines Agency. The program, called PRO2TECT, includes two separate studies together enrolling over 3000 patients across 500 sites globally. The correction study will enrol anaemia patients not currently being treated with recombinant erythropoiesis-stimulating agents (rESAs) while the conversion study will enrol patients currently receiving rESA therapy who will be converted to either vadadustat or active control with the goal of maintaining baseline haemoglobin levels. Both trials will include a 1:1 randomization and an open-label, active-control, non-inferiority design. Efficacy endpoints will include haemoglobin response.

d) Xenetic Biosciences has started the third cohort of its mid-stage dose-escalation study with its lead drug candidate ErepoXen for the treatment of anaemia in pre-dialysis chronic kidney disease patients. There are nine clinical sites in Australia and six new clinical sites in South Africa. Subjects from the third cohort will receive injections of ErepoXen every two weeks until haemoglobin levels reach therapeutic levels. The patients will then receive injections of ErepoXen every 4 weeks during maintenance for a total trial time of 17 weeks. CEO Scott Maguire said: “We expect Cohort three to be the final leg of this Phase II trial”. This cohort is expected to be completed in the second quarter next year. The data from the second cohort showed that 91 per cent of the enrolled patients had an increase in haemoglobin levels over time, and that in 75 per cent of the enrolled patients, haemoglobin levels rose into the therapeutic range. The third cohort is designed to further increase the patient’s haemoglobin levels into mid-therapeutic range.

Other.

e) The FDA approved its first reversal agent for a novel oral anticoagulant (NOAC). Idarucizumab (Praxbind) works by binding to dabigatran (Pradaxa) in the blood when given via intravenous injection. It is indicated for emergency situations where there is a need to reverse Pradaxa’s blood-thinning effects, eg if emergency surgery is required. The FDA warned that reversing the effects of dabigatran increases patients’ risk of blood clots and stroke. The label on the reversing product recommends that patients restart their anticoagulant as it’s medically appropriate to do so.

f) In the UK, the National Institute for Health and Care Excellence (NICE) has issued final guidance recommending Daiichi Sankyo’s blood thinner Lixiana to prevent blood clots in certain adult patients. Patients with non-valvular atrial fibrillation (NVAF), who also have one or more further risk factors, should soon be able to routinely access the drug on the NHS in England and Wales to prevent stroke and systemic embolism. Clinical trials suggested that Lixana (edoxaban), a once-daily selective factor Xa-inhibitor, works as well as warfarin but with a better safety profile, significantly reducing the risk of major bleeds, and without the need for monitoring. NICE recently recommended Lixiana’s use for the treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults, in line with the drug’s other approved use in Europe.

g) A large retrospective analysis from Canada suggests that dabigatran is about as safe and effective as warfarin in elderly patients with atrial fibrillation (AF). The authors wrote in Thrombosis and Haemostasis: “Based on real-life experience, dabigatran can offer an alternative to warfarin in elderly patients, with fewer intracranial bleeding events. However caution is warranted for gastrointestinal bleeding”.

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16 Based in Lexington, Massachusetts
h) A consortium of physicians from Australia, New Zealand, and the United Kingdom has started a movement, EZDrugID, to set mandatory standards for medication packaging to make them more easily distinguishable to avoid accidents in the operating room, the intensive care unit, the emergency department, and the clinic.

i) Three anatomical sites are commonly used to insert central venous catheters—under the collarbone, in the neck and in the groin—but one site has been linked with lower rates of bloodstream infections in a study published in The New England Journal of Medicine. Researchers randomly assigned 3,027 intensive care unit patients to have catheters place in one of the three locations. Their primary outcome measure was a composite of catheter-related bloodstream infections and symptomatic deep-vein thrombosis. They found fewer infections or clots when the catheter was placed in the vein under the collarbone than in a jugular vein or in the large vein in the groin. However, placing a catheter in the vein under the collarbone has its own challenges, as 1.5 per cent of patients suffered a collapsed lung when the catheter missed the vein. Senior researcher on the study Leonard Mermel explained in an interview that using ultrasound to guide the placement of the catheter is one way to avoid complications like a collapsed lung.

j) A high risk for venous thromboembolism (VTE) following surgery for long-bone reconstruction was found in patients with metastatic cancer in a study by Sidney Kimmel Medical College at Thomas Jefferson University, published in Journal of Bone and Joint Surgery. The researchers retrospectively reviewed 336 cases in which patients underwent intramedullary nailing for metastatic bone lesions. Results demonstrated that VTEs developed in 24 patients (7.1 per cent) in the 90 days after surgery, but they also found a low incidence of postoperative wound complications (3.1 per cent). In addition, 66 per cent of the patients who had developed blood clots also had a primary cancer of the lung. Additional findings were that patients who did not receive radiotherapy after surgery had a slightly lower risk of developing blood clots. The researchers concluded that anticoagulation agents, as well as duration of therapy, should be individualized to each patient and their primary cancer. Anticoagulation therapy should also be managed with a team approach that includes the oncologic, medical, radiation, and surgical teams.

6. Research

A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

a) Scientists have found a new virus that can be transmitted by blood transfusions and other blood-based products. The team reported in the journal mBio\(^7\) that they’ve named it human hepegivirus-1 (HHpgV-1). Infectious disease expert Dr Ian Lipkin, who oversaw the study team at Columbia University in New York, said: "We have been able to find a new virus. It’s clearly transmitted as a result of human (blood) transfusion". He told NBC News: “It is the first transfusion-associated virus that’s been described in a long time. We don’t know if it is going to be a significant cause of human hepatitis”. Amit Kapoor, an assistant professor at Columbia University who led the study, said: "So far there is no need to be concerned. We really don’t know if there is ongoing transmission of this virus. It may be good for you."

b) New York Blood Center’s Laboratory of Complement Biology at its Lindsley F. Kimball Research Institute received a federal grant to identify the immune cells that block medications commonly used to treat patients with immune thrombocytopenia (ITP)—an autoimmune bleeding disease in which patients attack and destroy their own platelets.

c) New York Blood Center’s Erythropoiesis Laboratory at its Lindsley F. Kimball Research Institute received a federal grant to further the understanding of diseases such as sickle cell anaemia and beta-thalassemia in which anaemia is associated with too much iron in the body. Dr. Yelena Ginzburg, head of the Erythropoiesis Laboratory said: "We are now investigating the mechanisms underlying iron transport to support the premise of using transferrin to treat patients with beta-thalassemia and possibly other diseases associated with anaemia and iron overload, like sickle cell anemia and myelodysplastic syndrome."

d) The US National Institutes of Health (NIH) has awarded a five-year, $1.9 million grant to a Case Western Reserve University researcher\textsuperscript{18} to transform clot-forming synthetic platelet technology into devices that dissolve clots to prevent strokes and heart attacks.

e) A new study\textsuperscript{19} suggests that by disguising cancer drugs as a patient’s own platelets, their effectiveness could be improved significantly. “Because the platelets come from the patient’s own body, the drug carriers aren’t identified as foreign objects, so last longer in the bloodstream," says Zhen Gu, corresponding author of a paper on the work and an assistant professor in the joint biomedical engineering program at North Carolina State University and the University of North Carolina at Chapel Hill.

7. Infectious diseases

The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, and the tick-borne babesiosis and Lyme disease).

Mosquito-borne disease

a) Through a genetic association study in malaria, researchers believe they have identified a specific location on the genome where variations in DNA protect some African children from developing severe malaria, in some cases nearly halving a child’s chance\textsuperscript{20}.

\textsuperscript{18} Anirban Sen Gupta, associate professor of biomedical engineering at Case School of Engineering, and his collaborators Samir Mitragotri, PhD, at University of California Santa Barbara; and Wei Li, MD, PhD, at Cleveland Clinic; believe that platelet-inspired synthetic particles can be used to deliver anti-clotting medicines directly to clots that pose a serious health risk. "We originally designed synthetic platelets to potentially assist in stabilizing soldiers wounded on the battlefield or civilians injured in accidents and also treat patients who are at bleeding risks due to various disease scenarios," Sen Gupta said. "We soon realized that the technology can be refined to also do the opposite--deliver clot-busting drugs to dissolve clots in blood vessels before they trigger stroke and heart attack".


\textsuperscript{20} The research, published in Nature, was conducted by MalariaGEN, an international network of scientists and clinicians spread across Africa, Asia and other malaria-endemic regions of the world.
Influenza: strains, spread, prevention and treatment

b) BiondVax Pharmaceuticals of Israel received regulatory clearance from the Hungarian Regulatory Authority (National Institute of Pharmacology and Nutrition, OGYEI) and the Central Ethics Committee in Budapest to initiate a Phase IIb clinical trial of its influenza vaccine. This is a multicentre, randomized, double-blind, active-controlled trial to assess the immunogenicity and safety of the company’s universal influenza vaccine (Multimeric-001), followed by an administration of the H5N1 influenza vaccine. Results are expected in the second half of 2016. The trial will include 222 healthy adults aged 18-60 years. BiondVax has already completed two phase I/II and three phase II trials with 479 participants for its universal flu vaccine. The vaccine was found safe, effective, and able to trigger both cellular and humoral responses of the human immune system, against different strains of the influenza virus including existing and future strains. BiondVax says its technology uses a proprietary combination of conserved and common peptides from influenza virus proteins to activate both arms of the immune system for a cross-protecting and long-lasting effect.

c) Avian flu H5N1 continues to infect poultry in West Africa.

d) The US Department of Agriculture has contracted with two companies to manufacture avian flu vaccine for its National Veterinary Stockpile. It has granted Harris Vaccines a “conditional licence” for an avian influenza vaccine for chickens, but the company does not have approval to sell the vaccine.

e) A report, commissioned by the UK’s Department of Health and published by the Academy of Medical Sciences and the Wellcome Trust, has recommended further research into the use of neuraminidase inhibitors during an influenza pandemic, with emphasis on hospitalized patients and high-risk groups. The report focussed on Tamiflu (oseltamivir) from Roche and GlaxoSmithKline’s Relenza (zanamivir). The researchers are hoping to set up an EU-funded study of Tamiflu in twenty sites across Europe.

f) In the US, two innovative multi-million dollar programs to improve influenza vaccines are being sponsored by the Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response (ASPR). “Seasonal influenza contributes to tens of thousands of deaths every year in the United States and that number could reach hundreds of thousands during a pandemic or severe outbreak,” said Biomedical Advanced Research and Development Authority (BARDA) Director Robin Robinson. “Developing more effective and universal influenza vaccines is a vital element in our strategy to prepare the nation for a pandemic, as well as improving public health when seasonal influenza virus is circulating.” One project BARDA will support is the development of a room temperature stable, oral recombinant influenza vaccine under a two-year, $US 14 million contract with Vaxart of California21. The other project will create a data-driven strategy to inform the process for selecting more effective influenza virus vaccines to be added to the national pre-pandemic influenza vaccine stockpile. It may also support seasonal influenza vaccine strain selection. In another move, BARDA will spend $US 8 million overseas, with an option for a total value of $24.3 million over five years, for the University of Cambridge to develop methods of antigenic mapping, the forecasting of how the influenza viruses may change over time.

funded mostly by the Wellcome Trust. They analysed data from eight different African countries: Burkina Faso, Cameroon, Ghana, Kenya, Malawi, Mali, The Gambia and Tanzania.

21 The announcement said: “Through this partnership Vaxart will conduct clinical studies to test the safety, ability to produce an immune system response, and efficacy of their experimental oral influenza vaccine in human volunteers as compared to a licensed inactivated influenza vaccine. In earlier clinical studies, this experimental oral vaccine indicated that it may elicit immune responses associated with protection against multiple seasonal influenza viruses and viruses with pandemic potential.”
g) Development of an experimental influenza antiviral drug that may be more potent and could have a longer treatment window than existing drugs is also receiving support from BARDA, which will provide technical assistance and funding of over $US 100 million to Janssen Pharmaceuticals, one of the pharmaceutical companies of Johnson & Johnson, in Raritan, New Jersey, for advanced development of the drug, JNJ-872 (also known as VX787). While other FDA-approved influenza antiviral medications are usually more effective if given within 48 hours of symptom onset, studies of JNJ-872 to date suggest that the experimental drug may provide clinical benefits when administered much later than 48 hours after symptoms begin. BARDA Director Robin Robinson said: “Typically patients are not hospitalized within 48 hours of developing flu symptoms, so doctors and their patients need treatment options that are effective later in the course of illness. This is a critical health priority as tens of thousands of flu patients are hospitalized each year in the United States and that number can be even higher in a pandemic.” The BARDA-supported late stage clinical development of JNJ872 includes Phase III studies in high risk populations and hospitalized patients, as well as final development of a validated commercial-scale manufacturing process, leading to the company’s submission of a new drug application to the FDA for potential approval.

h) The US National Institutes of Health (NIH) has awarded $1.55 million to a Purdue University-led avian influenza vaccine project. This will continue vaccine research led by Suresh Mittal, a professor of comparative pathobiology in Purdue’s College of Veterinary Medicine, and includes collaborators at the Centers for Disease Control & Prevention (CDC).

MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

i) A recent study found nearly half of the camels in parts of Kenya have been infected at some time by the Middle East Respiratory Syndrome (MERS) virus.

j) The patient thought to be the last South Korean with MERS was re-diagnosed with the disease in mid-October.

k) As at 30 October, Saudi Arabia had acknowledged within its borders a total of 1273 laboratory confirmed cases of MERS-CoV infection, including 543 deaths.

l) Arab News reported in early October that thirty three per cent of a total of 1,252 Middle East Respiratory Syndrome (MERS) coronavirus cases reported over the previous four years in Saudi Arabia contracted the disease within hospitals. Twelve per cent of total cases involved health workers inside hospitals and clinics. Arab News reported. Thirteen per cent involved people who came in contact with sick people inside their homes.

Ebola virus disease

n) In Guinea, two new Ebola cases in mid-October ended a two-week period of no new reported cases.

o) A Scots nurse was isolated in Royal Free London’s high-containment unit. She was declared to have recovered from Ebola eight months ago, but viral RNA had reappeared and she was suffering a severe central nervous system disorder. The implications of the reappearance were under discussion. She received convalescent plasma during her earlier hospitalisation, and there was speculation as to whether

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22 Janssen, in consultation with BARDA, will explore the feasibility of continuous manufacturing for JNJ872. Traditional drug manufacturing requires interruptions at multiple stages of the manufacturing process. Continuous flow of materials throughout the manufacturing process is thought to offer cost efficiencies.

this may have influenced her immune response and ability to clear the virus. Then an infectious diseases specialist treating her declared that she was suffering not from Ebola but from meningitis, a complication arising from her earlier infection.

p) Ebola is now known to be able to exist in the semen of male survivors of the disease for at least nine months after their initial infection appears. The World Health Organisation’s advice is that all male survivors should be tested three months after the onset of symptoms and then monthly until they know they have no risk of passing on the virus.

q) Crucell Holland, a unit of Johnson & Johnson, was awarded $US 28.5million by the US Biomedical Advanced Research and Development Authority (BARDA) to speed up the development of its Ebola prime-boost vaccine regimen. This uses a combination of two components, based on Crucell Holland’s AdVac technology and Bavarian Nordic’s MVA-BN technology respectively. The agreement includes options for a further $US 40.5million funding, for optimizing manufacturing systems and capacity of the regimen. Phase I clinical trials of the regimen started in the UK and US in December 2014, followed by various sites in Africa.

r) NewLink Genetics Corporation of Iowa announced that BARDA has exercised a $US 18 million option on NewLink Genetics’ existing contract to support the scale-up of the manufacturing process relating to its investigational rVSV-ZEBOV GP (Ebola) vaccine candidate. BARDA awarded an initial $US 30 million contract award to NewLink in late 2014. Merck has the license for research, development, manufacturing and commercialization of the rVSV-ZEBOV GP (Ebola) vaccine24.

s) A novel Ebola virus disease treatment based on three monoclonal antibodies will be developed by agreement between the US Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response (ASPR) and Regeneron Pharmaceuticals of Tarrytown, New York. ASPR’s BARDA will provide up to a total of $US 38 million over the next 23 months to support development as well as manufacturing of the experimental monoclonal antibody therapeutic drug for use in studies. These monoclonal antibodies bind to a key Ebola viral protein and neutralize the virus, decreasing the amount of virus in the body that the patient’s immune system has to fight. Regeneron generated the fully human Ebola monoclonal antibodies using their proprietary VelociGene and VelocImmune technologies which manufactured the antibodies in a specialized proprietary line of mammalian cells. These technologies allowed for rapid discovery, development and production of monoclonal antibodies, which makes the system potentially well suited for generating therapeutic drugs during public health emergencies when turnaround time is critical. The work conducted through this program will support filing of an investigational new drug application with the FDA. BARDA also could provide an additional $US 11.3 million to manufacture alternative monoclonal antibodies.

Other diseases: occurrence, prevention and treatment

v) Researchers reported that avoiding or delaying the measles vaccine has left nearly 9 million children in the US vulnerable to the disease. Matthew M. Zahn, medical director for epidemiology for Orange County Public Health in California, who was not involved with this study, said: "With the number of outbreaks that we are seeing around the country, with the increase of events of the virus being imported into this country, it really gives the sense that there’s some work to do to make sure that our kids are safe. The whole world is connected on this issue".

24 The rVSV-ZEBOV GP (Ebola) vaccine candidate was originally developed by the Public Health Agency of Canada and was subsequently licensed to a subsidiary of NewLink Genetics. In late 2014, Merck licensed the vaccine from NewLink Genetics to apply Merck’s vaccine expertise to help accelerate the development of this vaccine candidate. Clinical studies of the vaccine candidate are continuing.
w) In the US, the Carlos Slim Foundation awarded $US 2.6 million to the National School of Tropical Medicine at Baylor College of Medicine for the Chagas Vaccine Initiative, to fight one of the major neglected tropical diseases in Latin America now spreading round the world through travel and migration.

x) The US Centers for Disease Control and Prevention (CDC) said five New York residents contracted Q fever after going to Germany for a controversial treatment involving injections with foetal cells from sheep. The treatment is not permitted in the US. Two told investigators that they were part of a group that, for the previous five years, had travelled to Germany twice a year for the injections which they hoped would improve their health and vitality. US health officials said there is no published clinical proof the treatments work.

y) The Bill & Melinda Gates Foundation has awarded nearly $US 6 million to a team of scientists at the Jupiter, Florida campus of The Scripps Research Institute to develop a revolutionary HIV/AIDS alternative vaccine. Professor Michael Farzan and his team have a drug candidate called eCD4-Ig, which was tested in animal models and offered them complete protection against the virus for up to one year.

25 Chagas disease is a vector-borne, caused by the single celled parasite called Trypanosoma cruzi, which is transmitted to humans by triatomine “kissing” bugs. It is estimated that one in four people infected with Trypanosoma cruzi will go on to develop heart complications.