Monitoring International Trends

posted August 2014

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

- The US Army is using freeze-dried plasma (French Lyophilized Plasma, or FLYP) through an international partnership. Soldiers in special operations can carry the product in their backpack. With the addition of water they have a product ready to transfuse in three minutes to make blood clot. (page 3)
- Johns Hopkins University undergraduates have developed an injectable foam system to stop profuse bleeding in wounded soldiers, usually from a wound where a limb or the head connects with the torso and tourniquets or gauze pads with a clotting agent are difficult to apply to deep wounds.(page 4)
- The European Commission published approval of Octapharma's human cell line recombinant FVIII Nuwiq (simoctocog alfa) across all age groups in haemophilia A, for the treatment and prophylaxis of bleeding. (page 6)
- Alnylam has received orphan drug designation in the European Union for ALN-AT3, an RNAi therapeutic in development for the treatment of haemophilia. (page 7)
- CSL said it would consider another $A 950 million share buyback after reporting a small rise in annual net profit on higher sales of immunoglobulin in the US and Europe. (page 7)
- Baxter announced the formal opening of its first advanced recombinant biologic facility in Singapore, and expansion plans for a new recombinant protein processing suite. (page 8)
- The House of Commons Science and Technology Committee has accepted that tens of thousands of people in the UK could be silent carriers of the prions that cause "mad cow disease". (page 10)
- Researchers have reported on a meta-analysis of clinical trials of human albumin for volume expansion and resuscitation in adults with sepsis. (page 12)
- A recently published study has examined shifts in resuscitation practices in military combat hospitals. It found that hospital deaths after damage control resuscitation (DCR) policies were implemented were more likely to be severely injured and have a severe brain injury, which was consistent with fewer deaths among "potentially salvageable" patients. (page 12)
- A retrospective analysis has shown that patients with severe combined immunodeficiency improved their prospects of survival when they underwent hematopoietic-cell transplantation when young, either before the onset of infection or after the infection resolved. (page 14)
- Researchers have managed to rewrite a mutant gene that causes beta thalassemia. (page 14)

- The World Health Organization (WHO) in August declared the continuing spread of Ebola in West Africa an international public health emergency. (page 19)

Contents

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.

Plasma and recombinant products

a) Pfizer announced that a Phase III study showed that once-weekly prophylaxis with nonacog alfa (BeneFIX) significantly reduced the annualized bleeding rate in haemophilia B patients, compared with on-demand treatment[1].
b) Octapharma USA announced the US Food and Drug Administration (FDA) approved Octagam10% [Immune Globulin Intravenous (Human) 10% (100 mg/mL) Liquid Preparation] for the treatment of adults with chronic immune thrombocytopenic purpura (ITP)[2].
c) Dermatologists at the Rudolfstiftung Hospital in Vienna have successfully used high doses of immunoglobulin G (IgG) via infusion to ameliorate the skin disease livedoid vasculitis[3].
d) The US Army is using freeze-dried plasma (French lyophilized plasma, or FLYP) through an international partnership[4]. Soldiers in special operations can carry the product in their backpack. With the addition of water they have a product ready to transfuse in three minutes to make blood clot. Lt. Col. Andrew Cap, the army's Chief of Coagulation and Blood Research, said because the French military manufacture only limited quantities of FLYP, the US Army Blood Program and Institute of Surgical Research are expanding the program. Plasma collected at US military blood donor centres will be shipped to France for freeze drying. The product is compatible with any blood type, and can withstand warm temperatures for long periods of time.

Devices

a) "Selfies" may be used as a simple and easily accessible tool to detect anaemia risk, thanks to the work of two Monash University medical students. Eyenaemia uses a photo of the eye on a smartphone to calculate risk.
b) Collaborative funding from the Bill and Melinda Gates Foundation and the Indian government is enabling two Bombay developers to engineer a microfluidic chip combined with a mobile phone based diagnosis platform that could be used in remote areas to detect sickle cell anaemia.
c) Researchers in Sweden have proposed a microfluidic device that would sort blood cells by elasticity, offering an alternative for detecting disease biomarkers[5].
d) Misonix announced that a team of spine surgeons from Rady Children's Hospital in San Diego, has published findings from a recent study on utilization of the company's ultrasonic BoneScalpel in spinal fusion surgery[6]. The authors concluded that use of the ultrasonic

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[1] Pfizer said no inhibitor development, thrombotic events or allergic reactions were observed. Adverse events reported during prophylaxis were arthralgia (20%), upper respiratory infection (20%), toothache (20%), pyrexia (16%), headache (16%), pharyngitis (12%), back pain (12%) and local swelling (12%).
[2] ITP is a platelet disorder. It is associated with a tendency to excessive bruising and bleeding. Adverse events observed during the clinical trial were: headache, fever, and increased heart rate.
[3] This is an uncommon disease. The patients initially experience lockage of small arteries and arterioles in the skin, particularly in the lower legs and feet, with the tissue dying from lack of oxygen.
[4] This was achieved through an Expanded Access Investigational New Drug protocol, supervised by the FDA and the military Institutional Review Board. The product is approved by the French regulatory authorities and used by France's military for their combat casualties. Lt. Col. Andrew Cap said "The French military has been making this product, basically since the 1940s with technology they got from us and have since modified and improved……The United States developed freeze-dried plasma for WWII and we used it all through WWII and the Korean War but at that time, we didn't understand a lot about blood-borne infections, and patients would get hepatitis from the plasma they were given. So we stopped making this product."
[5] Lailai Zhu, Cecilia Rorai, Dhrubaditya Mitra and Luca Brandt. "A microfluidic device to sort capsules by deformability: A numerical study|". *Soft Matter*, 2014. DOI: 10.1039/C4SM01097CFirst published online 20 Jun 2014.
[6]Carrie E. Bartley, Tracey P. Bastrom, Peter O. Newton," Blood Loss Reduction During Surgical Correction of Adolescent Idiopathic Scoliosis Utilizing an Ultrasonic Bone Scalpel",*Spine Deformity*, Volume 2, Issue 4, Pages 285-290 doi:10.1016/j.jspd.2014.03.008

BoneScalpel to perform the bone cuts, compared with standard cuts, limited overall blood loss by 30 to 40 per cent.

e) A microbe detection array technology developed by scientists at the Lawrence Livermore National Laboratory (LLNL), California, could assist public health authorities to conduct surveillance for emerging viral diseases. A team of scientists from eight countries studied this possible use of the Lawrence Livermore Microbial Detection Array (LLMDA) and published its findings[7]. Using the LLMDA, combined with a DNA amplification technique developed by Danish researchers, the team correctly identified 29 different emerging viruses in samples tested[8]. One advantage of this tool is that it can perform thousands of tests in parallel within 24 hours, while polymerase chain reaction (PCR)—though faster—can run only dozens of tests simultaneously. The current version of the array can identify 4,377 viruses, 5,457 bacteria, and over 775 protozoa, fungi and archaea[9] species.

f) Needle-phobia (trypanophobia)is a common fear, and drawing blood is a ubiquitous medical procedure, so the use of a microscopic laser beam in place of a needle would be popular with many patients. NoNeedles Venipuncture with Dr. Rodrigo Amezcua Correa, assistant professor of optics at the University of Central Florida are working under the Florida High Tech Corridor Council's Matching Grants Research Program to develop a process that uses laser pulses to draw blood without pain, which would be especially beneficial in paediatrics. The laser beam is fired through the skin in one quadrillionth of a second to create a microscopic channel into the vein. The vein is connected to a port to collect the blood sample, then the laser is fired again to seal the channel.[10]

Other

a) rEVO Biologics, a subsidiary of LFB Biotechnologies, announced the enrolment of the first patient in its Phase III clinical trial of ATryn [antithrombin (Recombinant)], for the treatment of preeclampsia during the 24th to 28th week of pregnancy. This PRESERVE-1 trial will assess whether ATryn prolongs pregnancy in mothers with early onset preeclampsia[11], thus reducing the rate of neonatal mortality and disability.

b) Rigel Pharmaceuticals announced a Phase III clinical program for its drug fostamatinib, in patients with chronic ITP. These clinical studies will evaluate potential to increase platelet counts.

c) Johns Hopkins University undergraduates have developed an injectable foam system to stop profuse bleeding in wounded soldiers, usually from a wound where a limb or the head connects with the torso. Tourniquets or gauze pads with a clotting agent are difficult to

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[7] Maiken W. Rosenstierne, Kevin S. McLoughlin, Majken Lindholm Olesen, Anna Papa, Shea N. Gardner, Olivier Engler, Sebastien Plumet, Ali Mirazimi, Manfred Weidmann, Matthias Niedrig, Anders Fomsgaard, Lena Erlandsson, "The Microbial Detection Array for Detection of Emerging Viruses in Clinical Samples-A Useful Panmicrobial Diagnostic Tool" , PloS One,Published: June 25, 2014, DOI: 10.1371/journal.pone.0100813

[8] Including dengue fever, West Nile virus, Crimean-Congo haemorrhagic fever, chikungunya, polyomaviruses, herpes simplex, hepatitis, and Coxsackie.

[9] Archaea are single-celled microorganisms

[10] http://www.floridahightech.com/publication/magazine/fht2014.pdf

[11] Preeclampsia affects the placenta. It may mean reduced blood flow (and hence reduced nutrients and oxygen) from mother to baby, with the baby then at risk for prematurity and abnormal foetal growth. Inflammation extends from the placenta through the mother's blood vessels and internal organs. High blood pressure, stroke, seizures and liver and kidney problems can occur, and mother and/or baby may die. If preeclampsia occurs it is usually after the twentieth week of gestation. The American Congress of Obstetricians and Gynecologists (ACOG) says the incidence of the disorder has increased in the US by approximately 25 percent from 1987 to 2004. Currently, delivery of the baby is the only known way to stop the progression of preeclampsia, which can lead to multiorgan failure, seizures, coma or death for the mother and baby.

apply to deep wounds at these junctions. The foam injection system fills the wound area[12] and blocks blood loss while the patient is transferred from the battlefield to a medical facility, ideally within 60 minutes.

d) ProMetic Life Sciences will launch its fibrinogen commercially during the fourth quarter of 2014 after its successful scale-up at its plasma purification facility, ProMetic BioProduction Inc. (PBP), located at Laval, Quebec. Proteins already scheduled for production at Laval are plasminogen, intravenous immunoglobulin (IVIg) and Alpha-1 Antitrypsin.

e) A study led by the University of Utah School of Medicine has found a way of blocking the pharmaceutical inhibiting of platelet production experienced by multiple myeloma patients treated with bortezomib. Researchers say giving Fasudil to multiple myeloma patients could prevent their platelet counts from dropping dangerously low (thrombocytopenia)[13].

f) Oxygen Biotherapeutics will pay $US 500,000 to Imperial College London to test the drug levosimendan in the UK. The drug is a possible treatment for patients suffering organ failure from septic shock. Oxygen will conduct its own Phase III trial in the US.

g) A study[14] by scientists at Washington University School of Medicine in St. Louis found that the drug APT102 in animals decreased damage to heart muscle from a heart attack and reduced the risk of bleeding during follow-up treatments. Senior author Dana Abendschein, an associate professor of medicine and of cell biology and physiology, said: "This also may be a better way to treat strokes caused by or associated with a blood clot." The research was funded by a National Institutes of Health (NIH) Small Business Innovation Research Grant and by APT Therapeutics which developed the drug.

h) A test developed by British scientists detects a heart attack in 30 minutes (compared with the usual 6 hours). It detects a small protein (H-FABP) which is released after a heart attack. Dr Rick Body, consultant in emergency medicine trialled the test at Manchester Royal Infirmary.

i) Xenetic Biosciences began announcing results from its ongoing data analysis of its Phase II ErepoXen clinical trial being conducted in Australia and New Zealand. This is a sequential multiple-dose study evaluating the safety and efficacy of subcutaneously administered ErepoXen[15]for the treatment of anaemia in chronic kidney disease (CKD) patients who are neither on dialysis nor receiving erythropoiesis stimulating agents. The company said of the first cohort of 12 patients (who completed treatment with ErepoXen at the lowest dose level) that ErepoXen was found to be safe and well tolerated with no drug-related serious adverse events. Even at the lowest dose levels being administered twenty five per cent of the cohort reached the target 10-12 g/dL haemoglobin levels.

2. Regulatory

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

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[12] The foam hardens and applies pressure to the walls of the cavity. The chemicals that produce the foam-a polyol and a diisocyanate-are in separate canisters stored within the injector device till needed. The injector is about the size of a whiteboard marker, and includes a mechanism for mixing the chemicals. Then a plunger is pushed to insert the foam into the wound. The canisters will keep the chemicals stable at temperatures up to 38 degrees Celsius for at least a year.

[13] Dallas S. Shi et al "Proteasome function is required for platelet production", *Journal of Clinical Investigation* online July 25, 2014: *J Clin Invest.* 2014. doi:10.1172/JCI75247

[14] Douglas Moeckel et al.,"Optimizing human apyrase to treat arterial thrombosis and limit reperfusion injury without increasing bleeding risk ", 6 August 2014, vol.6, issue 248. Sci. Transl. Med. DOI: 10.1126/scitranslmed.3009246

[15] (PSA-EPO, a polysialylated erythropoietin)

Plasma and recombinant products

a) The FDA approved NovoNordisk's NovoSeven (Coagulation Factor VIIa [Recombinant]) for .use in bleeding episodes and perioperative management in patients with Glanzmann's Thrombasthenia[16] with refractoriness to platelet transfusions. NovoSeven is also approved in the European Union for the treatment of bleeding episodes in patients with this condition.
b) The Blood Products Advisory Committee of the FDA voted 15-1 that Baxter's HyQvia [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase], a subcutaneous treatment for patients with primary immunodeficiency (PI), has a favourable risk/benefit profile. In 2013 HyQvia was approved in Europe for adults with primary immunodeficiency syndromes and myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. Baxter expects the FDA's response to the BPAC recommendation in the third quarter.
c) The European Commission published approval of Octapharma's human cell line recombinant FVIII Nuwiq (simoctocog alfa) across all age groups in haemophilia A, for the treatment and prophylaxis of bleeding. Nuwiq is produced in a human cell line cultured without additives of human or animal origin. It is devoid of antigenic non-human protein epitopes and has a high affinity for the von Willebrand coagulation factor, both of which are potentially important in reducing the formation of FVIII inhibitors. The development of Nuwiq aimed to address the challenges of inhibitor formation as well as the frequent infusions required for prophylaxis.
d) Emergent BioSolutions submitted a Biologics License Application to the FDA for Anthrax Immune Globulin Intravenous (Human) [AIGIV] as part of a development contract with the Biomedical Advanced Research and Development Authority (BARDA). Emergent acquired AIGIV, in the Cangene acquisition completed earlier this year. It is being developed as an intravenous therapy for inhalation anthrax. AIGIV is a sterile solution of purified human immunoglobulin G containing polyclonal antibodies that target the anthrax toxins of *Bacillus anthracis*, the bacteria that causes anthrax disease[17].
e) Baxter announced that the FDA had approved Flexbumin [Albumin (Human)], USP, 5% Solution. The product is indicated for hypovolemia, hypoalbuminemia due to general causes, burns and in patients undergoing cardiopulmonary bypass surgery. This approval expands Baxter's Flexbumin product portfolio to encompass both 5% in a 250 mL solution and 25% in 50 and 100 mL solutions.

Other

a) Cerus Corporation announced in mid-July that it had submitted the third and final module for its premarket approval (PMA) application to the FDA for review of the Intercept Blood System for platelets. Having concluded a $US 30 million capital credit facility with Oxford Finance, Cerues received $US 10 million in July, and has the option of drawing a further $US 10 million on FDA approval of the Intercept Blood System for either platelets or plasma.

[16] Glanzmann's Thrombasthenia is a rare genetic bleeding disorder. The condition, occurs because certain surface proteins on platelets are missing or do not work, preventing the blood from clotting. Patients may be given platelet transfusions when experiencing severe bleeding or when surgical procedures are required but some patients do not respond well or at all.

[17] AIGIV is prepared from the plasma of healthy, screened donors immunized with BioThrax (Anthrax Vaccine Adsorbed), an FDA-licensed vaccine for the prevention of anthrax disease. AIGIV was evaluated in studies conducted in animals of inhalation anthrax. It received Orphan Drug designation from the FDA in 2008. AIGIV is being developed as part of a $US 160 million contract with BARDA, within the office of the Assistant Secretary for Preparedness and Response in the US Department of Health and Human Services. Under this contract, awarded in 2005, 10,000 doses of AIGIV have been delivered to the US Strategic National Stockpile and Emergent will receive a $US 7 million milestone payment upon FDA approval of AIGIV.

b) A study by the Tufts Center for the Study of Drug Development found the pace of approvals for new orphan drugs[18] has increased in both the US and Europe[19]. However, patients can face challenges in accessing the drugs, because insurers may require patients to share high costs.
c) A coalition of European medicines advocates[20] has alleged the European Medicines Agency (EMA) has a conflict of interest when it provides paid confidential advice to pharma companies to guide their development plans for new drugs.
d) Regado Biosciences halted enrolment in its Phase III study of the anticoagulant Revolixys[21], revealing that "serious adverse events related to allergic reactions" had occurred. The halt in enrolment was so the company's data and safety monitoring board (DSMB) could consider the matter. However the FDA imposed an official clinical hold, formalizing the agency's involvement in future decisions.
e) Alnylam has received orphan drug designation in the European Union[22] for ALN-AT3, an RNAi therapeutic in development for the treatment of haemophilia. ALN-AT3 is a subcutaneously administered RNAi therapeutic targeting antithrombin (AT), for the treatment of haemophilia and other rare bleeding disorders.
f) Bristol-Myers Squibb and Pfizer announced that the European Commission had approved Eliquis (apixaban) for treating deep vein thrombosis (DVT) and pulmonary embolism (PE), and for preventing recurrent DVT and PE in adults. This applies to all EU member states as well as Iceland and Norway. Eliquis is also approved in the EU for preventing venous thromboembolism (VTE) in adults who have had elective total hip or knee replacement surgery, and for preventing stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors.

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 said it would consider another $A 950 million share buyback after reporting a small rise in annual net profit on higher sales of immunoglobulin in the US and Europe. The company said that net profit in the year to June 30 rose 7.8 per cent, a little above the company's own guidance for a 7 per cent rise. CSL said it expects net profit in the current financial year to rise by about 12 per cent in constant currency terms, and earnings before interest and tax to grow by about 15 per cent. CSL's shares were up 2.3 per cent recently, compared with a 0.4

[18] Drugs that treat rare conditions.These are defined in the US as those that affect fewer than 200,000 people nationally, whereas in the EU the definition is those affecting fewer than five people in 10,000.
[19] Between 2000 and 2013, 86 orphan drugs were approved in the US, while 65 had been approved during the previous 18 years. The figures in Europe for comparable periods were 96 and 44.
[20] Health Action International Europe, the International Society of Drug Bulletins, the Medicines in Europe Forum and the Association International de la Mutualité,
[21] Revolixys combines pegnivacogin and anivamersen and is designed to control bleeding during coronary interventions and open-heart surgeries.
[22] from the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP). Orphan drug designation by the European Commission provides regulatory and financial incentives for companies to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the European Union (EU), and where no satisfactory treatment is available. In addition to a 10-year period of marketing exclusivity in the EU after product approval, orphan drug designation provides incentives for companies seeking protocol assistance from the EMA during the product development phase, and direct access to centralized marketing authorization

per cent fall in the benchmark S&P/ASX 200 index. The company's sales rose 7.7 per cent. Sales of immunoglobulin products grew 12 per cent in constant currency terms, helped by strong demand for Hizentra, a subcutaneous immunoglobulin treatment[23], in the US and Europe. The company's top-selling product is its IVIg product, Privigen.

b) Baxter formally opened its advanced recombinant biologic facility in Singapore, and announced expansion plans for a new recombinant protein processing suite. The current suite supports the processing of Advate, currently the market leading full-length recombinant factor VIII worldwide for the treatment of patients with haemophilia A. The additional suite will initially process RIXUBIS [Coagulation Factor IX (Recombinant)], for the treatment of adults with haemophilia B. When it comes on stream, it will be the primary commercial processing facility in the world. This suite will also support production of the company's investigational extended half-life recombinant FVIII treatment BAX 855 if/when it is approved by regulators.

c) Baxter has acquired AesRx, a private US company concentrating on orphan drug targets, including Aes-103, an investigational prophylactic treatment for sickle cell disease (SCD)[24]. Studies suggest the oral compound Aes-103 may work by binding to haemoglobin and increasing oxygen affinity and stabilization, and reducing the sickling of red blood cells. This in turn may reduce vaso-occlusive crisis, pain, severe anaemia, and fatigue. Aes-103 has orphan drug designation in the US and appears eligible for orphan designation in Europe.

d) Baxter said its second-quarter earnings fell 12 per cent as higher costs and expenses offset a strong gain in revenue, which beat expectations. The rise in bioscience revenue was 6.9 per cent. Baxter overall reported a profit of $US 520 million, down from $US 590 million a year earlier. The quarter's results included net after-tax special items amounting to $US 172 million, arising from costs associated with product development milestone payments, integration of the company's earlier acquisition of Gambro AB, and Baxter's planned separation into two independent healthcare companies, among other factors. The company’s new earnings guidance for the full year is based on sales growth of 9 to 10 per cent. For this third quarter, the company expects revenue growth of 12 to 13 per cent.

e) Portola Pharmaceuticals has an agreement with Daiichi Sankyo for late-stage clinical testing of an antidote drug for people on anticoagulants[25]. This is Portola’s third deal with new-generation blood-thinning drugs in two years. Portola now has collaborations in Phase III trials with all the major manufacturers of the new oral anticoagulants, or Factor Xa inhibitors[26]. Portola's antidote, andexanet alfa, is designed to stop serious bleeding in people taking those blood-thinning drugs for other conditions eg. patients who are taking oral anticoagulant drugs for deep vein thrombosis or pulmonary embolism, or after hip or knee replacements, but who require emergency surgery or have severe bleeding.

f) Shares of Emergent BioSolutions declined marginally following the company's mixed performance in the second quarter of 2014. Second quarter 2014 earnings were below the year-ago figure by 17.2 per cent. The year-on-year decline was primarily due to higher costs incurred by the company in the reported quarter. Revenues climbed 33.8 per cent year over year to $US 110.3 million in the second quarter of 2014. A 19 per cent increase in product

[23] Subcutaneous immunoglobulin is delivered using a small needle inserted into the tissue just under the surface of the skin, rather than into a vein as with intravenous immunoglobulin, so subcutaneous immunoglobulin can be self-administered at home.

[24] Aes-103 is in a Phase II clinical trial in collaboration with the US National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) through its Therapeutics for Rare and Neglected Diseases (TRND) program. Aes-103 was initially patented by Virginia Commonwealth University.

[25] Portola and Daiichi Sankyo have already collaborated on a Phase II test.

[26] Previously the Bristol-Myers Squibb Co./Pfizer Inc. drug Eliquis and Bayer HealthCare/Janssen's Xarelto, now Daiichi Sankyo’s edoxaban. Portola is also planning a mid-stage study of its own Factor Xa inhibitor, betrixaban.

sales to $US 78.3 million boosted revenues in the reported quarter. BioThrax[27] sales grew 2.9 per cent to $US 67.5 million in the quarter due to the timing of deliveries to the Strategic National Stockpile. Emergent BioSolutions' acquisition of Cangene in February 2014 broadened the company's product portfolio and pipeline[28]. It also added a contract manufacturing services business under the Biosciences division. Contract manufacturing revenues were $US 9.2 million in the second quarter of 2014.

g) Seventh Sense Biosystems has developed a touch activated phlebotomy device which uses micro-needles to collect 20 to 100 microliters of blood. The company has announced $US 16 million in new financing from the Venture Capital unit of Siemens Financial Services, Novartis and Laboratory Corporation of America Holdings, along with existing investors Flagship Ventures and Polaris Partners.

h) Roche continued to move back into RNA research and development[29], signing a $US 450 million (€335 million) deal to buy Denmark's Santaris Pharma. The Santaris lab in Copenhagen, will be the centre of Roche RNA R&D efforts.

i) Pfizer agreed to acquire Baxter's portfolio of marketed vaccines for $US 635 million. The deal includes Pfizer's acquisition of the section of Baxter's facility in Orth, Austria, where these vaccines are manufactured.

j) Grifols' share price suffered its biggest single-day drop since the company's initial public offering in 2006, after second quarter results were less than analysts expected[30]. Market value fell 14 per cent to €10.9 billion ($US 14.6 billion).

k) Cerus Corporation announced its second quarter 2014 results. Product revenue for the quarter of 2014 was $US 8.6 million, a 15 per cent decrease from the second quarter of 2013. Product revenue for the first six months of 2014 was $US 16.5 million, a 17 per cent decrease from the first six months of 2013. Total operating expenses for the second quarter were $US 14.9 million, compared with $US 11.5 million for the second quarter of 2013. Total operating expenses for the first six months of 2014 were $US 27.8 million compared with $21.1 million for the first six months of 2013. Cerus reiterated its annual revenue guidance for 2014 as $US 38 to 40 million[31].

[27] BioThrax is the only vaccine approved by the FDA for the pre-exposure prophylaxis of anthrax disease. Emergent BioSolutions hopes to have BioThrax approved for the post-exposure prophylaxis of anthrax resulting from exposure (suspected or confirmed) to *bacillus anthracis* in combination with antibiotics for treating patients with suspected or confirmed exposure to anthrax spores.

[28] Prior to the Cangene acquisition, the biodefence segment at Emergent BioSolutions had only two marketed products-BioThrax and Reactive Skin Decontamination Lotion (RSDL). The Cangene acquisition took the number of revenue generating products in biodence to five. The new additions are botulism antitoxin heptavalent-equine), Vigiv (vaccinia immune globulin intravenous (human)) and Aigiv (anthrax immune globulin intravenous (human)).Aigiv, though not yet approved by any regulatory agency, is purchased by US Health & Human Services for delivery into the SNS to combat a crisis under an emergency use authorization. Aigiv is being developed under a contract (worth $US 160 million) with the Biomedical Advanced Research and Development Authority (BARDA) for treating inhalation anthrax.

[29] Roche already has a $US 392 million RNA agreement with Isis Pharmaceuticals of California.

[30] Second-quarter sales of 812.8 million euros fell short of the average analyst estimate of 826.9 million euros and net income of 103.9 million euros fell short of the average prediction of 123.4 million euros.

[31] Grifols has submitted to the FDA the final module of its premarket approval (PMA) application for INTERCEPT Platelets; and expects a decision in the first half of 2015. The company's application for approval of INTERCEPT Platelets has also been submitted in Canada. The Phase III European acute anaemia clinical trial is fully enrolled; and Cerus hopes to submit an application for CE mark approval of INTERCEPT Red Blood Cells in the first half of 2016.

4. Country-specific event

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.

United States

a) Johns Hopkins researchers showed[32] that children who have emergency surgery at weekends have a greater risk for complications than those who have weekday surgeries. They analysed data on 440,000 simple emergency surgeries that children across the US had over a 22-years – including appendix removal, treatment of broken bones, hernia repair, draining and cleaning of infected wounds, and draining excess fluid in the brain. Children who underwent surgery at the weekend were 40 per cent more likely to have complications, and 14 per cent more likely to be given a blood transfusion than those who had weekday surgeries. Children who had weekend surgeries were 63 per cent more likely to die than those who had weekday surgeries[33]. The study did not examine reasons for the disparity between weekend and weekday surgical experience, but authors said possible reasons could be differences in staffing levels, increased response times and less availability of some imaging and testing services.

b) In mid-July, a group of US scientists urged curbs on creating dangerous pathogens in laboratories. While they had particularly in mind "gain of function" studies of highly pathogenic strains of flu, the call came after recent incidents in government labs concerning, anthrax, smallpox and avian flu which served as a reminder of the "fallibility" of supposedly secure labs. At the same time, which could have been coincidence, the US National Science Advisory Board for Biosecurity had the service of eleven of its 23 members terminated.

c) On July 31, Louis M. Katz, chair, AABB Transfusion Transmitted Diseases Committee presented to the FDA's Blood Products Advisory Committee a .statement on *Reentry of Blood Donors Deferred on the Basis of Screening Test Results for Antibodies to Trypanosoma cruzi.* This was a joint statement on behalf of AABB, America's Blood Centers, and the American Red Cross.

United Kingdom

d) The House of Commons Science and Technology Committee has accepted that tens of thousands of people in the UK could be silent carriers of the prions that cause "mad cow disease". It says since blood transfusions are a potential source of transmission there should be more work to test and filter donated blood of prions.

e) Seven pharma companies[34] have joined with the Medical Research Council to establish a "virtual library" where compounds that have failed earlier trial will be open for other researchers to evaluate. Since they have already undergone safety trials, repurposing them could be a relatively fast process.

f) By 6 July every GP in the UK had been advised to watch for symptom of the ebola virus. There was concern about residents returning from family visits in West Africa, and also the influx of visitors for the Commonwealth Games.

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[32] In a study published in the July issue of the *Journal of Pediatric Surgery*

[33] There were 30 deaths over the 22 years attributable to what the researchers called "the weekend effect". "Numerically speaking, the number of deaths was quite small, but even a single preventable death is one too many. This demands that we examine any factors that may cause or contribute to such occurrences and find ways to prevent them," study senior investigator Dr Fizan Abdullah, a paediatric surgeon at the Johns Hopkins Children's Center in Baltimore, said in a Hopkins news release.

[34] AstraZeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, Takeda and UCB

g) Systematic analysis[35] of the transmission of hepatitis E virus (HEV) by blood components suggested that 1 in 3000 donors in England have HEV in their plasma. The researchers suggested that around 1200 HEV-containing blood components (eg, red cells, platelets, and fresh frozen plasma) are likely to be transfused in England annually.

Canada

f) Canadian Blood Services suffered a collection setback after a fire in its Bloodmobile, thought to have been caused by an electrical fault.

g) On July 22 the Ontario Government again introduced legislation to protect the existing model of voluntary donations for blood and plasma, prohibiting payments for blood and plasma, including reimbursement of expenses or other forms of compensation. The proposed Safeguarding Health Care Integrity Act, 2014, combined two bills that were previously introduced but that did not pass before the dissolution of the legislature in the spring[36].

Ireland

h) The Irish Blood Transfusion Service (IBTS), revealed in its 2013 annual report that its income from sales of products and services provided to hospitals last year was €65 million compared with €78 million in 2012. CEO Andy Kelly said "It is unclear what the exact reasons are but undoubtedly some of them are less wastage, improved surgical techniques, reviewing at hospital level of transfusion practice and less elective surgery taking place due to the cutbacks in health spending. This trend looks like it will continue over the next few years and this poses a major challenge to IBTS to reduce costs even further. While there may be some scope for further reduction in costs this will not be sufficient to meet the expected reduction in income." Chairperson Professor Anthony Staines commented "In 2012, the IBTS moved to single site testing as part of a larger programme of structural reform and cost saving. The next step in this programme is the move to single site processing of blood and blood products at the National Blood Centre in Dublin. This will take about 18 months to implement, and will be linked to many other changes, including a much larger stock holding and dispatch operation in Cork".

i) In 2013 IBTS approached lapsed donors through a mail survey. Thirty eight per cent of respondents said they had migrated to another country.

Australia

k) The Commonwealth Department of Health, in cooperation with state and territory Health Authorities, has developed a coordinated national response with five strategies to target HIV, hepatitis B, hepatitis C, sexually transmitted infections (STIs) and blood borne viruses and STIs in the Indigenous community.

5. Safety and patient blood management

We follow current issues in patient safety and achieving favourable patient outcomes.

Appropriate transfusion

a) Virginia Commonwealth University Medical Center, with other academic medical centres, is evaluating the use of fresh frozen plasma to facilitate clotting when paramedics reach a

[35] Patricia E Hewitt et al., "Hepatitis E virus in blood components: a prevalence and transmission study in southeast England", *The Lancet*, Early Online Publication, 28 July 2014 doi:10.1016/S0140-6736(14)61034-5

[36] the Enhancing Patient Care and Pharmacy Safety (Statute Law Amendment) Act, 2013, originally introduced on Oct. 10, 2013, and the Voluntary Blood Donations Act, originally introduced on March 20, 2014.

trauma patient rather than when the patient arrives at the hospital. The study is funded by the US Army Medical Research and Materiel Command, Combat Casualty Care Research Program[37]. The principal investigator at VCU is Bruce Spiess, professor in the Department of Anesthesiology and researcher with the VCU Reanimation Engineering Science Center.

b) The AABB (formerly the American Association of Blood Banks) released five key recommendations to assist clinicians in wise transfusion choices: don't transfuse more units of blood than absolutely necessary; don't transfuse red blood cells for iron deficiency without haemodynamic instability; don't routinely use blood products to reverse warfarin; don't perform serial blood counts on clinically stable patients; don't transfuse O negative blood except to O negative patients and in emergencies for women of child bearing potential with unknown blood group[38].
c) Researchers have reported on a meta-analysis of clinical trials of human albumin for volume expansion and resuscitation in adults with sepsis[39]. After analysis of data from 16 randomised trials including more than 4000 patients, they found no statistically significant survival benefit from using albumin overall or in any predefined subgroup. These new results call into question the Surviving Sepsis Campaign's recommendation to consider giving albumin to patients who "require substantial amounts of crystalloid."[40]
d) A recently published study has examined shifts in resuscitation practices in military combat hospitals[41]. It found that hospital deaths after damage control resuscitation (DCR) policies were implemented were more likely to be severely injured and have a severe brain injury, which was consistent with fewer deaths among "potentially salvageable" patients. The basic principles of DCR have been early, balanced administration of blood products, aggressive correction of coagulopathy (when blood will not clot) and the minimization of crystalloid fluids (intravenous fluids)[42].
e) Northwestern Medicine scientists have developed a model for predicting the probability of major blood transfusion in adults undergoing complex spine fusion surgery[43].
f) Researchers from the University of Texas Health and Memorial Hermann in Houston have compared the morbidity and mortality of trauma patients who received fluid during pre-hospital care with morbidity and mortality in patients who received packed red blood cells

[37] Studies on soldiers in Iraq and Afghanistan and on patients in US trauma centers suggest that the earlier, more vigorous replacement of clotting factors by giving plasma increases chances of survival from massive injuries.

[38] For editorial comment see *BMJ* 2014;349:g4701

[39] Patel A, Laffan MA, Waheed U, Brett SJ. "Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality". *BMJ2014;349:g4561.*For comment see *BMJ* 2014;349:g4611

[40] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. "Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock": 2012. *Crit Care Med*2013;41:580-637.

[41]Langan NR, Eckert M, Martin MJ, "Changing Patterns of In-Hospital Deaths Following Implementation of Damage Control Resuscitation Practices in US Forward Military Treatment Facilities",*JAMA Surgery*. Published online July 16, 2014. DOI: 10.1001/jamasurg.2014.940

[42] Researchers reviewed data from the Joint Theater Trauma Registry (2002-2011) for combat hospitals. They examined injury patterns, early care and resuscitation among personnel who died in the hospital before 2006 and from 2006 to 2011 after implementation of DCR policies. Of 57,179 soldiers admitted to a forward combat hospital, 4.5 per cent died in hospital. 74 per cent were severely injured and 80 per cent died within 24 hours of admission. DCR policies meant a decrease in average 24-hour crystalloid infusion volume and increased use of fresh frozen plasma. The average ratio of packed red blood cells to fresh frozen plasma changed from 2.6:1 (pre-DCR) 1.4:1 during the DCR period. There was a shift in injury patterns with more severe head trauma cases in the DCR group.

[43] Louanne M Carabini et al., "Development and Validation of a Generalizable Model for Predicting Major Transfusion During Spine Fusion Surgery", *Journal of Neurological Anesthesiology,* July 2014

and fresh frozen plasma (FFP)[44]. Their conclusions: "The largest takeaway from this study is that blood products may be more viable in the out-of-hospital resuscitation environment than we previously thought. …..waste is quite low, and there were no documented adverse reactions in the blood group…. Can we attribute the administration of blood as a definite reducer of mortality? Probably not…. data points are too small; however, this study is a stepping point toward more research…. Because the research of blood is currently limited to the battlefield, maybe it's time for us to start trialing blood in the civilian EMS setting."

Other

g) The *BMJ* precipitated a heated exchange concerning the safety of Boehringer Ingelheim's anticoagulant Pradaxa. With three articles and an editorial devoted to the drug in a single issue, the journal advocated regular blood tests for Pradaxa patients, and accused the company of burying data that would have backed that testing[45]. The journal criticised US and European regulators for undue haste, and for not following up adequately when reports of bleeding came in. The company denied that it had withheld analyses from regulators and that it had played down the risk of bleeding[46].

h) A new study found in-hospital mortality for patients with atrial fibrillation who experienced intracranial bleeding was similar whether they were treated with dabigatran or warfarin.[47]

Other.

a) Researchers confirmed that speed is critical when treating stroke patients with a powerful clot-busting drug, tissue plasminogen activator. tPA, also known as alteplase. The drug "is a very effective means of limiting the degree of disability in stroke patients," study co-author Dr. Jonathan Emberson, of the University of Oxford, said in a news release from *The Lancet*, which published the study on 5 August.

b) In catheter-directed thrombolysis (CDT), doctors use X-ray imaging to guide medication or a medical device to the site of a blockage in a blood vessel. The procedure may help patients live longer, but it can give rise to complications, such as pain, swelling, heaviness and ulceration. Researchers have found that patients using anticoagulants alone (compared with anticoagulants plus CDT) may have similar mortality rates but fewer safety concerns[48].

c) Researchers from the University of North Carolina School of Medicine have found that eliminating factor XIII shrinks clots by 50 percent. They suggest their discovery could lead to a safer alternative to blood thinners for patients at high risk of deep vein thrombosis[49]. The study was funded by NIH and the American Heart Association.

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[44] Holcomb JB, Donathan DP, Cotton BA, et al. "Prehospital transfusion of plasma and red blood cells in trauma patients". *Prehosp Emerg Care*. June 16, 2014. (published online ahead of print).

[45] *BMJ* 2014;349:g4670, doi:10.1136/bmj.g4670; also *BMJ* 2014;349:g4793

[46] "Our company has provided regulators with the complete data set and analyses of clinical evidence demonstrating Pradaxa's benefits and safety, and FDA and EMA have affirmed RE-LY's conclusions," the company said in a statement. "*BMJ* was provided this information by Boehringer Ingelheim, but chose not to include it."

[47] Alvaro Alonso et al.,"Intracranial Hemorrhage Mortality in Atrial Fibrillation Patients Treated With Dabigatran or Warfarin**",***Stroke.* 2014;45:2286-2291, published online before print July 3 2014, doi:10.1161/STROKEAHA.114.006016

[48] Riyaz Bashir et al., "Comparative Outcomes of Catheter-Directed Thrombolysis Plus Anticoagulation vs Anticoagulation Alone to Treat Lower-Extremity Proximal Deep Vein Thrombosis"**,** *JAMA Intern Med*. Published online July 21, 2014. doi:10.1001/jamainternmed.2014.3415

[49] Maria M Aleman et al., ""Factor XIII activity mediates red blood cell retention in venous thrombi" *J Clin Invest.* 2014;124(8):3590–3600. doi:10.1172/JCI75386.

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) A retrospective analysis[50] has shown that patients with severe combined immunodeficiency improved their prospects of survival when they underwent hematopoietic-cell transplantation when young, either before the onset of infection or after the infection resolved.
b) Researchers have managed to rewrite a mutant gene that causes beta thalassemia[51].
c) The July issue of *AABB*[52] *News* highlighted the advances that have been made in using living cells as the "ink" to create customized body parts-and eventually transplantable organs. Another article concerned blood substitutes, both haemoglobin-based oxygen carriers and blood manufactured from stem cells. A third article describes newly added haemovigilance activities in WHO's NOTIFY Library of adverse occurrences associated with medical products of human origin.
d) New research can enable doctors to detect the presence in the bloodstream of newborns of infection-causing bacteria, and to target them. They can identify the pathogens by decoding a signal generated from the baby's DNA[53].
e) Delaware State University and the Nemours Center for Cancer and Blood Disorders have received from NIH a $US 10.2 million grant for comprehensive genetic research on sickle cell disease.
f) Korean researchers have identified a specific gene associated with leukopenia (a decrease in white blood cells) in patients with autoimmune diseases receiving immunosuppressive treatment.
g) Scientists led by Professor David Beech, from Leeds University, have identified a gene (called Piezo10) which allows new blood vessel networks to grow in response to changes in blood flow. They say the gene can be manipulated to restrict blood supply to some cancers, and it could be used in treating atherosclerosis, where arteries narrow, leading to heart attacks and strokes.
h) A new study describes an innovative approach of cryopreserving red blood cells using vitrification in conjunction with bio-printing technologies[54].
i) Researchers from the Weizmann Institute and the Hebrew University have developed a new technique for epigenetic analysis[55] and are questioning the conventional understanding of the way blood stem cell fate decisions are controlled[56].

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[50] Sung-Yun Pai et al., "Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009", *New England Journal of Medicine*, 2014. http://www.nejm.org/doi/full/10.1056/NEJMoa1401177

[51] F. Xie et al., "Seamless gene correction of β-thalassemia mutations in patient-specific iPSCs using CRISPR/Cas9 and *piggyBac*," *Genome Research*, doi:10.1101/gr.173427.114, 2014. Paul Schmidt, from Children's Hospital Boston and Harvard Medical School, who did not participate in the study cautioned that there are a number of hurdles that "need to be overcome before it can be used in the clinic."

[52] formerly the American Association of Blood Banks

[53] Ghazal P, Smith CL, Dickinson P, et al. Identification of a human neonatal immune-metabolic network associated with bacterial infection. *Nature Communications*. 2014.

[54] Utkan Demirci et al., "Bio-Inspired Cryo-Ink Preserves Red Blood Cell Phenotype and Function During Nanoliter Vitrification", *Advanced Materials* 2014. The study involved researchers from from Stanford University School of Medicine Harvard Medical School Case Western Reserve University Worcester Polytechnic Institute and Akron Biotechnology.

[55] Epigenetic mechanisms are environmental influences other than genetics

j) Speckle contrast optical spectroscopy (SCOS) is a new non-invasive method for measuring the movement of red blood cells under the surface of the skin, which could be used to assess blood flow in deep tissues[57].

k) New York Blood Center's Laboratory of Complement Biology has received a $US 2.5 million, four-year grant from the NIH National Heart, Lung and Blood Institute to study hyperactive immune cells in patients with sickle cell disease. The grant includes a subcontract with the Children's Hospital of Philadelphia. Although sickle cell patients are transfused with extended antigen-matched donor red blood cells, up to two-thirds of patients develop antibodies against polymorphic antigens on donor cells, (alloimmunization) that can cause the rejection of the transfused cells and life- threatening complications. Identification of biomarkers of alloimmunization would help identify at-risk patients in advance. "We believe that these individuals have certain hyperactive immune cells," said Dr. Karina Yazdanbakhsh. "Our goal is to identify these cells and understand what makes them hyperactive. This knowledge will help us to pre-screen for SCD patients who are likely to reject transfusions. It will also create a strong foundation for development of treatments to cure their hyperactive immune system."

l) Researchers at Brigham and Women's Hospital (BWH) have developed a scalable, next-generation platelet bioreactor to generate fully functional human platelets in vitro[58]. "The ability to generate an alternative source of functional human platelets with virtually no disease transmission represents a paradigm shift in how we collect platelets" said Jonathan Thon, Division of Hematology, BWH Department of Medicine, lead study author. The researchers want to commence human clinical trials in 2017.

m) Henry Daniell, a professor in the Departments of Biochemistry and Pathology and Director of Translational Research at the University of Pennsylvania's School of Dental Medicine has worked with colleagues on a novel method preventing inhibitor formation to clotting factor VIII.[59] Their plant-based drug-delivery platform uses genetically engineered plants to produce biotherapeutic proteins. They fused genes that encode parts of FVIII with the gene for cholera toxin, as this protein can cross the intestinal wall and assist some immune responses. The scientists then introduced the fused genes into tobacco plant chloroplasts, grew the plants, ground them, and suspended the ground material in a solution. The solution containing the modified plant material was fed over two months to mice with haemophilia A. Another cohort of mice was fed a solution incorporating normal plant material. Both cohorts were then given FVIII infusions. The cohort fed normal plant solution developed higher levels of inhibitors. When the modified plant material was fed to mice that had already developed inhibitors, the mice's inhibitor formation slowed and then reversed, decreasing up to seven-fold over a few months compared with mice fed normal plant material. "The only current treatments for inhibitor formation cost $1 million and are risky for patients," Daniell said. "Our technique, which uses plant-based capsules, has the potential to be a cost-effective and safe alternative."

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[56] D. Lara-Astiaso, A. Weiner, E. Lorenzo-Vivas, I. Zaretsky, D. A. Jaitin, E. David, H. Keren-Shaul, A. Mildner, D. Winter, S. Jung, N. Friedman, I. Amit. "Chromatin state dynamics during blood formation**"**. *Science*, 2014; DOI: 10.1126/science.1256271

[57] Claudia p Valdes et al., "Speckle contrast optical spectroscopy, a non-invasive, diffuse optical method for measuring microvascular blood flow in tissue", *Biomed Opt Express*. Aug 1, 2014; 5(8): 2769–2784. Published online Jul 23, 2014. doi:10.1364/BOE.5.002769

[58]Thon,JN et al.,"Platelet bioreactor-on-a-chip" Blood. 2014 Jul 21. pii: blood-2014-05-574913. [Epub ahead of print]

[59] Henry Daniell et al., "Suppression of inhibitor formation against factor VIII in hemophilia A mice by oral delivery of antigens bioencapsulated in plant cells" in the journal *Blood,*online 2014. DOI:http://dx.doi.org/10.1182/blood-2013-10-528737

n) Scientists have found that blood cells engineered from blood vessel, or endothelial cells, could potentially provide not just a plentiful and safe source of new blood stem cells, but a means capable of treating a variety of diseases. Patients' own cells might be reprogrammed into blood cells free of the defects that led to disease[60].

o) A small study has found that bone marrow transplants can reverse severe sickle cell disease in adults, matching results with a similar technique used in children. The transplant worked in 26 of 30 adults, and 15 of them were able to stop taking anti-rejection drugs a year later. Average age of patients was 29[61].

p) Australian researchers[62] studying zebrafish have discovered how a critical type of stem cell found in blood and bone marrow, and essential to replenishing the body's supply of blood and immune cells, is formed. These hematopoietic stem cells (HSC) are already used in transplants for patients with blood cancers such as leukaemia and myeloma. HSCs are regarded as having potential to treat a wider variety of conditions because they appear to be able to form all kinds of vital cells including muscle, blood vessel and bone. The knowledge of how they are formed may facilitate growing them in a lab and perhaps eventually using them to treat spinal cord injuries, diabetes and degenerative disorders.

7. Legal actions and enquiries

The NBA is interested in the implications for Australia of any proceedings against companies, governments and professional practitioners in relation to blood and blood products; or of relevant public enquiries.

a) In the US a business court judge granted a motion that Grifols brought against a group of former employees, signalling that Grifols could have a case against them. Grifols accused three former executives of scheming to raid the company of talent, customers and trade secrets in order to set up a competing blood plasma business with Bio Products Laboratory USA. As part of the judge's order, the executives are expressly "restrained from soliciting or encouraging" Grifols employees to leave and "restrained from reviewing, using, copying or profiting from any confidential or proprietary information obtained" from Grifols. The executives were also ordered to preserve Grifols data, information and property and return account or contacts lists taken from Grifols, to include a list of Grifols customers that the executives might have done business with. Grifols had brought various other motions before the court, though they were denied, including allegations surrounding trade secrets.

b) Bayer and Johnson & Johnson face their first lawsuits about the safety of their blood thinner Xarelto. Plaintiffs claim severe internal bleeding hospitalized them. Earlier this year, Boehringer Ingelheim paid $US 650 million in settlements of internal bleeding cases concerning its blood thinner, Pradaxa.

8. 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

[60] Rafii Shahin et al., "Reprogramming human endothelial cells to haematopoietic cells requires vascular induction",*Nature*, July 17 2014 DOI 10.1038/nature13547

[61] John F Tisdale et al., "Bone Marrow Transplantation Shows Potential for Treating Adults with Severe Sickle Cell Disease", *JAMA, 1 July 2014*

[62] led by Professor Peter Currie, from the Australian Regenerative Medicine Institute at Monash University. The research was published in *Nature.*

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 diseases: malaria, dengue, and chikungunya

a) Malaria is becoming resistant to the potent drug artemisinin. Now a study has scoped out the resistance in South-East Asia and demonstrated that a blood test can identify people with resistant malaria. It also revealed that resistant *Plasmodium* is still susceptible to artemisinin if the treatment continues long enough[63].
b) Sanofi has delivered the first large-scale batches of an antimalarial drug made using semi-synthetic artemisinin. This will reduce reliance on volatile supplies of the Chinese medicinal plant, sweet wormwood.
c) Researchers from Johns Hopkins Bloomberg School of Public Health led a study[64] which found that injecting a vaccine-like compound into mice protected them from malaria. The injected virus had been genetically altered, and produced high levels of the anti-malaria antibody in the mice. The approach, known as vector immunoprophylaxis, or VIP, had already shown some promise in HIV studies.
d) GSK submitted its malaria vaccine to the European Medicines Agency for approval.
e) Papers published in the journals *Science* and *eLife* proposed fighting malaria by genetically engineering the mosquitoes themselves.
f) Researchers at Washington University School of Medicine in St. Louis reported in *Nature* that scientists may be able to entomb the malaria parasite in a prison it makes itself–as it invades a red blood cell, the parasite uses part of the host cell's membrane to build a protective compartment. A separate study by researchers at Australia's Burnet Institute and Deakin University, published in the same issue of *Nature*, also highlights the importance of an escape route to the parasite's survival.
g) Research confirms that malaria parasites can hide inside bone marrow and evade the body's defences[65].
h) Novartis reported that its KAE609 is the first antimalarial drug candidate with a novel mechanism of action to achieve positive clinical proof-of-concept in over 20 years[66].,
i) The US has been seeing some locally acquired cases of chikungunya after domestic mosquito vectors bit travellers returning from the Caribbean, which this season has been a hotspot for the disease.
j) The US National Institutes of Health (NIH) said its chikungunya vaccine elicited an impressive immune response in all 25 adult volunteers in a Phase I trial. They experienced no side effects of concern[67].
k) The Vaccine & Gene Therapy Institute of Florida (VGTI Florida) has developed a new platform vaccine technology. Ted Ross, VGTI Florida's Program Director of Vaccines & Viral Immunity, said: "We have developed a novel virus-like particle (VLP) vaccine that is a next-generation cell-culture technology unique from traditional vaccines which are predominantly produced in chicken eggs …Our VLP platform uses specific proprietary proteins from the chikungunya virus capable of eliciting a potent robust and enduring immune response enabling the immune system to prevent replication of virus and thus

[63] *The New England Journal of Medicine*, doi.org/t5z
[64] Reported online 11 August in *the Proceedings of the National Academy of Sciences (PNAS).*
[65] *See Science Translational Medicine.* The team was led by Prof Matthias Marti, of the Harvard School of Public Health.
[66] Clinical trial results were published in the *New England Journal of Medicine.*
[67] Lee-Jah Chang, Julie Ledgerwood et al., "Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial", *The Lancet*, Early Online Publication, 15 August 2014 doi:10.1016/S0140-6736(14)61185-5

prevent infection……We believe this approach can also be translated into the manufacture of many similar kinds of vaccines targeting virtually any viral threat including the Ebola virus". The Institute exhibited at the Military Health System Research Symposium (MHSRS) in Fort Lauderdale August 18th-20th.

l) Scientists at North Carolina State University are continuing to work with a Raleigh bio-tech company, Arbovax, to develop a vaccine for chikungunya, .

m) The chikungunya outbreak in the Caribbean has continued.

n) Mosquitoes infected with the bacteria *Wolbachia* are more likely to become infected with West Nile virus and more likely to transmit the virus to humans, according to a new study[68]. "Previous research has shown that *Wolbachia*—a genus of bacteria that live inside mosquitoes—render mosquitoes resistant to pathogen infection, thereby preventing the mosquitoes from infecting humans with the pathogens," said Jason Rasgon, an associate professor of entomology at Pennsylvania State University. "As a result, researchers are currently releasing *Wolbachia*-infected mosquitoes into the wild as part of a strategy to control dengue virus. They also are investigating *Wolbachia* as a possible control strategy for malaria." Rasgon said he and his colleagues[69]."… were surprised to find that *Wolbachia* infection did not block West Nile virus in this mosquito. Instead, these mosquitoes had significantly higher West Nile virus infection rates seven days after we fed them infected blood. In other words, *Wolbachia* infection allowed the mosquitoes to become infected with West Nile virus faster than our controls."

o) Singapore's Environment and Water Resources Minister Dr Vivian Balakrishnan told Parliament in response to a question that the dengue vaccine to be marketed by Sanofi in 2013 is "not good enough" for Singapore. Dr Balakrishnan said the vaccine was not effective enough against the two most common types of dengue locally, types 1 and 2. The vaccinated group's risk of developing dengue is reduced by 50% and 35% respectively for types 1 and 2, compared with an unvaccinated group. He said: "Until further clinical data is available for us to be sure that the benefits outweigh the risks, I don't think the Ministry of Health or Health Sciences Authority will rush into approving the vaccine".

p) Scientists from the Singapore General Hospital and the Duke-NUS Graduate Medical School found Celgosivir, a medicine derived from the seeds of Moreton Bay chestnut trees, to be safe for dengue patients. They have been trialling it as a potential treatment.

Influenza: strains, spread, prevention and treatment

a) The developer of the universal flu vaccine BiondVax announced that its studies validate the effectiveness of a vaccine against the H7 avian flu virus as well as the H5 strain.

b) The seriousness of viral disease often results from the strength of immune response. Turning down that response, rather than attacking the virus, might be a better way to reduce severity, says Juliet Morrison of the University of Washington, Seattle. She and her colleagues have begun doing that for H7N9 influenza. They have identified six potential therapeutics[70].

c) As many as 22 per cent of poultry samples tested positive for H7N9 avian flu in live-poultry markets in a Chinese city (Huzhou) after the markets reopened in the summer of 2013 following their closure over H7N9 cases[71].

d) A strain of highly pathogenic avian influenza, H5N6, has been found in Vietnamese poultry.

[68] The results appeared on 10 July in *PLOS Neglected Tropical Diseases*

[69] Including researchers from the University of Maryland, the New York State Department of Health and the State University of New York at Albany

[70] See the September 2014 issue of the *Journal of Virology*.

[71] The study was published 14 July in the *International Journal of Infectious Diseases*

Mers-CoV (Middle East respiratory syndrome, novel coronavirus)

a) A ban has been placed on sacrificing camels during this year's Haj in Mecca[72]. Camels can be sacrificed in other parts of the country, just not by the pilgrims during Haj. WHO has advised pilgrims to avoid close contact with camels, not to consume unpasteurized camel milk, and not to consume improperly cooked meat.
b) Kazakhstan citizens have been advised to postpone their trips, particularly Hajjs, to Saudi Arabia. The Indonesian government is raising awareness among would-be hajj pilgrims on how to protect themselves from MERS and Ebola virus disease during their pilgrimage in Saudi Arabia. Around 168,600 prospective Muslim pilgrims will travel to Saudi Arabia from Indonesia from 1 September onwards.

Ebola Virus Disease

a) Ebola continued to spread, reaching Nigeria and the Democratic Republic of Congo as well as continuing in Guinea, Liberia and Sierra Leone. By 11 August, the cumulative number of cases was estimated at 1975, with 1069 deaths. Between 10 and 11 August 128 new cases were reported, along with 56 deaths[73].
b) WHO in August declared the continuing spread of Ebola in West Africa an international public health emergency.
c) On 12 August WHO declared it ethical to use untested drugs and vaccines in the Ebola outbreak, although the small supply of one experimental drug appeared to have been exhausted after five doses, made available for two US aid workers, a Spanish priest and two Liberian doctors. The two US recipients improved while the Spanish priest died. The treatment was ZMapp, developed by Mapp Pharmaceuticals of California, and produced from tobacco plants by Kentucky Bioprocessing, a unit of tobacco company Reynolds American[74]. It has not been tested in humans, but an early version appeared effective in some monkeys infected with Ebola.
d) The Obama administration has formed an Ebola working group to consider policy for the potential use of experimental drugs to help people infected. The group is being chaired by Dr. Nicole Lurie, Assistant Secretary for Preparedness and Response at the Department of Health and Human Services.
e) Jeremy Farrar, a professor of tropical medicine and director of The Wellcome Trust, has said Ebola's spread in Guinea, Sierra Leone and Liberia is "out of control" and the normal drug development process with its careful sequential testing is too slow. He said that there are experimental drugs and vaccines which could be offered to very ill people who would otherwise have a high probability of death.[75]
f) NewLink Genetics of Iowa is preparing to test a possible Ebola vaccine in 100 healthy humans (volunteers)[76], but did not announce at that time whether it had submitted an application to the FDA. Scientists from Canada's public health agency developed the vaccine

[72] Usually about 1.3 million animals–camels, goats, sheep and cows–are sacrificed during the Haj in Mecca.
[73] An increased rate, as for example between 18 and 20 July there had been 45 new cases and 28 deaths reported.
[74] ZMapp uses antibodies to inactivate the Ebola virus and help the body kill infected cells.
[75] Amongst experimental compounds is an injectable drug for Ebola developed by Tekmira Pharmaceuticals in conjunction with the US Department of Defense. That drug entered a Phase 1 trial in healthy volunteers last January. Vaxart and Inovio have experimental vaccines in animal testing. When GlaxoSmith Kline acquired Swiss company Okairos in 2013, it brought with it an early- stage Ebola compound. Thomas Giebert , a University of Texas Medical Branch researcher, said in March he was developing a potential Ebola vaccine, which had shown good results in animal tests and could be offered to people at risk in the current outbreak.
[76] NewLink Genetics said the vaccine had been 100 per cent effective in preventing Ebola in non-human primates, and that it acted sufficiently fast to be effective when a lethal dose of the virus was administered. NewLink has a $US 1 million contract with the US Defense Threat Reduction Agency to help fund research leading up to the human testing.

and licensed it to NewLink[77]. An earlier version was administered in 2009 to a German lab worker who pricked her finger with a syringe that had contained Ebola.

g) GlaxoSMithKline's Ebola vaccine has appeared promising in non-human primates, and is expected to enter Phase I testing in humans when it has FDA approval. GSK's partner is the US National Institute for Allergy and Infectious Diseases (NIAID). This vaccine is based on a chimpanzee adenovirus with two Ebola genes inserted. These genes generate an immune response. Niaid is also sponsoring work on other experimental Ebola vaccines, including one from Crucell that may enter Phase I testing next year. This vaccine is designed to give additional protection against the Marburg virus.
h) BioCryst Pharmaceuticals of Durham, announced a $US 4.1 million award in federal research funds to develop a potential treatment for Ebola. The National Institute of Allergy and Infectious Diseases grant will be used to test BioCryst's BCX4430.
i) Tekmira Pharmaceuticals of Canada has been developing a drug that targets Ebola's genetic material. The FDA stopped a safety study with questions about a reaction in healthy volunteers. The FDA has now modified its restriction, clearing the way to possible experimental use of this RNA-interference drug in infected patients.
j) A team led by Gaya Amarasinghe from Washington University School of Medicine says it has found how the Ebola virus disables the body's ability to battle infections. The team found that Ebola carries a protein (VP24) that interferes with interferon, vital to the immune response.
k) NanoViricides is restarting its anti-Ebola drug development program.
l) For one US doctor in West Africa, treatment has been with an immune plasma infusion donated by a 14 year old survivor he had himself looked after,
m) Saudi Arabia's Ministry of Health has banned Muslim pilgrims from Sierra Leone, Guinea, and Liberia from performing Umrah and Haj in the current season.

Other diseases: occurrence, prevention and treatment

a) Cytomegalovirus (CMV) can lead to life-threatening infections in transplant recipients. Chimerix announced the presentation of three abstracts[78] on its investigational broad-spectrum antiviral, brincidofovir at the 2014 World Transplant Congress held July 26-31, 2014 in San Francisco. The data emphasises brincidofovir's antiviral activity and safety profile in transplant recipients who were treated with brincidofovir for viral infections, such as CMV. Merck has initiated a Phase III study of Letermovir, an investigational antiviral for the prevention of CMV in high-risk bone marrow transplant patients.
a) US health officials revealed that a four year old child, treated for HIV for eighteen months from immediately after her premature birth, and then going two years without antiretroviral medicines and without detectable HIV levels, was now showing detectable levels of the virus. It had been hoped that for this "Mississippi baby" such early treatment and extended remission may have meant a cure. However, new research in rhesus monkeys suggests that untouchable "viral reservoirs" form before HIV can even be detected in the blood. Antiretroviral drugs may keep HIV in check in the bloodstream but cessation of the drugs

[77] Canada says it will donate 800 to 1000 doses for use in healthcare workers in Africa. This is the vaccine that was used in 2009 for a German lab worker who pricked her glove with a syringe that had contained Ebola. It was never known whether she had become infected.

[78] Diana Florescu, "Brincidofovir (CMX001) for the Treatment of Serious00000000000 or Life-Threatening Double-stranded DNA Virus Infections in Patients Receiving Liver Transplant as Part of Multiorgan Transplantation" (Publication #A2979); Marion Morrison, "Switch from Existing Antivirals to Brincidofovir Leads to Improving Renal Function" (Publication #1472); and Kathleen Mullane, "Brincidofovir (CMX001) Experience in Renal Transplant Patients for Treatment of Refractory CMV Infection" (Publication #D2364)

causes the virus to re-emerge[79]. A recent study covering Europe, the US and Australia found that "with the advent of effective antiretroviral treatment, the life expectancy for people with HIV is now approaching that seen in the general population"[80].

b) A horse died from Hendra virus in Calliope (Central Queensland) on 17 July, the third case of Hendra virus in Queensland this year.
c) WHO announced a plan which would see tuberculosis (TB) eliminated from 33 countries where there are fewer than 100 cases per million people. The idea would be to aim for fewer than ten new cases annually per million people by 2035, with only one new case per million by 2050.
d) The Drugs for Neglected Diseases initiative (DNDi) announced at the International Congress of Parasitology the launch of a Phase II trial of fexinidazole for Chagas disease (American trypanosomiasis) patients. The drug is being tested in Africa for sleeping sickness and visceral leishmaniasis.
e) The concentration of prions in the urine of people with variant Creutzfeldt-Jakob disease, vCJD, is very small, and researchers have managed to amplify the protein so it can be detected[81]. Researcher Claudio Soto, a professor of neurology at the University of Texas Health Science Center at Houston Medical School said the risk of transmission through urine should be studied, because animal studies have shown that the disease can be transmitted by injecting an animal with the urine of an animal that has the disease. Another study in the same journal, suggests that a similar test could be used to diagnose the sporadic form of Creutzfeldt-Jakob disease. In this form, the disease is usually limited to the brain, so samples are collected from inside the nose, which contains neurons connected to the brain. This nasal test also amplifies prions in a similar way to the test used in Soto's study[82].,

[79] James B. Whitney, Alison L. Hill,′ Srisowmya Sanisetty,′ Pablo Penaloza-MacMaster,′ Jinyan Liu,Mayuri Shetty, Lily Parenteau,′ Crystal Cabral,′ Jennifer Shields, Stephen Blackmore,′Jeffrey Y. Smith, Amanda L. Brinkman,′ Lauren E. Peter,′ Sheeba I. Mathew, Kaitlin M. Smith,′ Erica N. Borducchi,′ Daniel I. S. Rosenbloom,′ Mark G. Lewis,′ Jillian Hattersley,Bei Li, Joseph Hesselgesser, Romas Geleziunas, Merlin L. Robb,′ Jerome H. Kim,Nelson L. Michael *et al.*, "Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys", *Nature*, published online 20 July 2014, doi:10.1038/nature13594

[80] Colette Smith et al., "Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration**",** *The Lancet*, Volume 384, Issue 9939, Pages 241 to 248, 19 July 2014 doi:10.1016/S0140-6736(14)60604-8

[81] The new test detects tiny amounts of prions by speeding up the process through which they replicate, until they can be detected. The researchers used ultrasound waves to accelerate replication. This test detected abnormal prions in the urine of 13 out of 14 people with Creutzfeldt-Jakob disease. What's more, the test was highly specific — it did not give a positive result for people with other forms of Creutzfeldt-Jakob disease, or with other neurological diseases. The study was published online on 6 August in the *New England Journal of Medicine*. Soto has a patent on the test that was used in his study, and has started a company to develop the test for commercial use.

[82] It uses shaking instead of ultrasound to speed up the prion replication. The test detected prions in nasal samples from 97 percent of participants with sporadic Creutzfeldt-Jakob disease. One of the researchers of the second study, from the National Institutes of Health, has a patent on the technology used in that study.