

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:

- Baxter has completed enrolment in its Phase III clinical trial of BAX 855, an extended half-life, recombinant factor VIII (rFVIII). (Page 2)
- Biogen Idec and Swedish Orphan Biovitrum announced that the detailed phase III data for their long-lasting rFVIII Fc fusion protein compound ELOCTATE were published online. (Page 3)
- Novo Nordisk's NovoEight, also an rFVIII for the treatment of haemophilia A, which was approved by the FDA in October, received marketing authorisation from the European Commission in November. (Page 4)
- Cerus Corporation will file a regulatory submission for the INTERCEPT Blood System for platelets and plasma in Canada the first half of 2014. (Page 5)
- Novartis agreed to sell its blood transfusion diagnostics unit to Grifols. (Page 6)
- In November Grifols posted a 35 per cent rise in nine-month profit. (Page 6)
- Terumo BCT has a new US Department of Defense cost-share contract to advance the Mirasol System for the treatment of donated whole blood used in emergency transfusions in deployed military forces. (Page 6)
- Blood donated by an HIV-positive man slipped through safety checks by the Japan Red Cross Society and was transfused into two recipients. (Page 7)
- The Australian Bureau of Statistics has projected that with medium growth Australia's population will double by 2075. (Page 8)
- The Hemoglobin and Iron Recovery Study, or HEIRS, funded by the US National Heart, Lung, and Blood Institute, reported on the impact of iron supplementation given to blood donors. (Page 9)
- Scientists at King's College London have identified a biomarker for sepsis in blood. (Page 10)
- Researchers have characterized a fifth dengue serotype. (Page 12)
- A chikungunya vaccine is undergoing a phase I clinical study in Vienna. (Page 12)
- The H7N9 strain of avian flu is producing more cases, including the first two cases in Hong Kong. Vaccines are being developed. (Page 13)
- The Middle East respiratory syndrome coronavirus (MERS-CoV) is continuing to cause deaths. Vaccines are being developed. (Page 13)

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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.

Clotting factors

- a) Baxter announced it has completed enrolment in its Phase III clinical trial of BAX 855, an extended half-life, recombinant factor VIII (rFVIII). The trial is aimed at assessing the efficacy of the compound in reducing annualized bleed rates in both prophylaxis and on-demand treatment for haemophilia A patients. Other outcomes include a reduction in the number of infusions needed to treat bleeding episodes, increased time intervals between these episodes, pharmacokinetics and improved patient reported outcomes. So far, no inhibitors or safety issues have been reported. BAX 855 is based on the full-length ADVATE [Antihemophilic Factor (Recombinant) Plasma/Albumin-Free Method] molecule, which has been modified with PEGylation technology to extend its duration of activity after infusion. This PROLONG-ATE trial involves 146 adult patients with previously-treated severe haemophilia A. Baxter hopes to file for regulatory approval late in 2014. There will be a continuation study for all patients who complete the Phase II/III study. A trial of BAX 855 among paediatric patients is expected in 2014.
- b) Biogen Idec and Swedish Orphan Biovitrum announced that the detailed phase III data for their long-lasting rFVIII Fc fusion protein compound ELOCTATE were published online in *Blood*, the journal of the American Society of Hematology. They said their A-LONG study demonstrated that patients with severe haemophilia A may achieve effective prevention or reduction of bleeding episodes with one or two prophylactic infusions a week. The companies now expect that ELOCTATE will be launched commercially in the US in mid-2014. The US Food and Drug Administration (FDA) requested additional information pertaining to process validation of certain steps in the manufacturing process. This revised timeline for FDA approval may not affect European approval timelines.

Other

- c) CSL Behring launched DNA₁ Advanced Alpha-1 Screening, a new test that aims to improve diagnosis of Alpha-1 Antitrypsin Deficiency (Alpha-1). The test identifies clinically relevant genetic variants to facilitate accurate diagnosis.
- d) CSL announced that results of a Phase IIa trial of CSL112 showed favourable safety and tolerability in patients with stable atherothrombotic disease. The trial also demonstrated a rapid increase in key biomarkers of reverse cholesterol transport, the process which removes cholesterol from arteries and transports it to be cleared through the liver. Lead study author Pierluigi Tricoci, of Duke Clinical Research Institute, said: "We know there is a need for novel approaches to reduce the high risk of early recurrent ischemic events after acute coronary syndrome. CSL112 is a promising treatment targeting coronary atherosclerotic plaques causing these events and deserves further investigation." Analyses of study data presented at the American Heart Association 2013 scientific sessions examined safety and tolerability, pharmacokinetics and lipid biomarker profile, and potential antiplatelet effects of CSL112 on top of dual antiplatelet therapy. CSL112 is a formulation of apolipoprotein A-I (apoA-I), the active component of high-density lipoprotein (HDL). It is purified from human plasma and reconstituted to form HDL particles suitable for intravenous infusion.
- e) Viro Pharma announced study results that showed that routine prevention of hereditary angioedema (HAE) attacks with their Cinryze (C1 esterase inhibitor [human])¹ resulted in

¹ Cinryze is a purified, pasteurized and nanofiltered plasma-derived product for intravenous use.

improved health-related quality of life outcomes compared with acute therapy with C1 inhibitor².

- f) The 2013 American College of Allergy, Asthma & Immunology annual meeting was told more patients with HAE are being offered and are accepting self-administered therapy. Of the HAE treatment centres surveyed in Europe and North America, 70 per cent reported that at least 50 percent of patients were self-administering.
- g) At the annual meeting in Washington of the American Association for the Study of Liver Diseases, Alnylam presented new pre-clinical data for ALN-AAT, in a poster entitled *Developing an RNAi Therapeutic for Liver Disease Associated with Alpha-1-Antitrypsin Deficiency*.
- h) GlycoMimetics presented at the 2013 American Society of Hematology annual meeting, highlighting study data of its lead drug candidate, rivipansel sodium (GMI-1070)³. Rivipansel sodium is a potential treatment for vaso-occlusive crisis in sickle cell disease. GMI-1070 has previously received both orphan drug and fast track status from the FDA and orphan product status in the European Union. It is being developed in collaboration with Pfizer.
- i) Kamada reported preliminary data from its ongoing extension study of a Phase I/II clinical trial with its lead product Glassia to treat paediatric patients with recently diagnosed type 1 diabetes. Kamada plans to initiate a Phase II/III trial.
- j) The Medical College of Wisconsin has a four-year, \$US 3 million grant from the National Heart, Lung and Blood Institute of the US National Institutes of Health (NIH) to improve the diagnostic tools for von Willebrand Disease.
- k) Baxter launched Hemopatch Sealing Hemostat, a collagen-based haemostatic device, following CE mark approval in Europe. Hemopatch is a resorbable haemostatic device used for surgical procedures when control of bleeding by pressure, ligature or conventional procedures is either ineffective or impractical. It is said to provide fast haemostasis and strong tissue adherence, and does not require preparation time.

2. Regulatory

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

Plasma and recombinant products

- a) Novo Nordisk's NovoEight, a rFVIII for the treatment of haemophilia A, was approved by the FDA in October, and received marketing authorisation from the European Commission in November. Now it has passed the review by the Committee on Drugs of Japan's Pharmaceutical Affairs and Sanitation Council. The next step in the regulatory process will be approval from the Ministry of Health, Labour and Welfare. Price negotiations will then precede launch of the product in Japan. NovoEight was trialled in the guardianT clinical programme with more than 210 severe haemophilia A patients. The company said it

² Data were presented in the poster, "Quality of Life in Patients with Hereditary Angioedema Receiving Nanofiltered C1 Inhibitor for Prophylaxis: Results of a Randomized, Placebo-Controlled, Crossover Study", by William Lumry, et al. at the 2013 American College of Allergy, Asthma and Immunology (ACAAI) annual scientific meeting.

³ "GMI-1070: Reduction in Time to Resolution of Vaso-Occlusive Crisis and Decreased Opioid Use in a Prospective, Randomized, Multi-Center Double Blind, Adaptive Phase 2 Study in Sickle Cell Disease"; "Effects of GMI-1070, a Pan-Selectin Inhibitor, On Pain Intensity and Opioid Utilization in Sickle Cell Disease"; and "An Analysis of the Pediatric Sub-Group From the Phase 2 Study of GMI-1070--A Novel Agent For The Vaso-Occlusive Crisis of Sickle Cell Anemia".

demonstrated good efficacy in preventing and treating bleeds. It said there was no confirmed inhibitor development, and that patients in the surgery trial were treated effectively.

- b) Baxter submitted a marketing authorization application to the European Medicines Agency (EMA) for approval of Rixubis, recombinant factor IX (nonacog gamma) for the treatment and prophylaxis of bleeding in patients of all ages with haemophilia B. Rixubis was approved for adult patients and launched in the US and Puerto Rico earlier in 2013. In the US Rixubis is indicated for control and prevention of bleeding episodes in adults with haemophilia B, perioperative management in adults with haemophilia B and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with haemophilia B. Rixubis is not indicated for induction of immune tolerance in patients with haemophilia B.
- c) The EMA accepted for review a marketing authorization application from The Medicines Company for its investigational haemostatic agent Fibrocaps (human plasma-derived fibrinogen and thrombin). Fibrocaps was the subject of a 719-patient Phase III FINISH-3 clinical trial as an adjunct to haemostasis in surgical patients when control of mild or moderate bleeding by conventional surgical techniques is ineffective or impractical. The company expects to submit a biologics license application (BLA) to the FDA early in 2014. It will also submit to the FDA a 510(k) application for the complementary spray delivery device to assist surgeons in the accurate application of the dry powder Fibrocaps. The device already has a European CE mark.

Blood donation, processing, storage and use; blood substitutes

- d) Cerus Corporation has agreed with Health Canada that it will file a regulatory submission for the INTERCEPT Blood System for platelets and plasma in the first half of 2014. Both the platelet and plasma systems are currently under regulatory review in the US. They have received the CE mark, and both products have subsequently received national approvals in France, Germany and Switzerland.

Other

- e) Alnylam Pharmaceuticals filed a Clinical Trial Application with the UK Medicines and Healthcare Products Regulatory Agency to initiate a Phase I clinical trial with ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin and thereby treating haemophilia A and B, including patients with inhibitors. ALN-AT3 is expected to increase thrombin generation and reduce the annualized bleeding rate and severity of bleeding. It is expected to reduce the need for replacement clotting factors or a bypass agent, and to improve patients' quality of life. The company wants to start its Phase I trial early in 2014 and to have some interim data from patients by the end of 2014.
- f) The FDA issued a new warning on the use of the well-established anticoagulant Lovenox in patients fitted with a spinal catheter because of the risk of spinal column bleeding and potential paralysis. Healthcare workers were advised to consider timing when inserting or removing a spinal catheter in patients taking Lovenox, made by Sanofi, or its generic versions sold as enoxaparin. The FDA said placement or removal of the catheters should be delayed for at least 12 hours after a patient is dosed with enoxaparin, 24 hours if the patient is on a high dose. Enoxaparin should not be given for at least four hours after catheter removal.
- g) The FDA accepted for review a supplemental new drug application for Pfizer's Eliquis for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in adult patients who have undergone hip or knee replacement surgery. The date for a decision by the FDA is March 15, 2014.
- h) OrSense has received FDA clearance for its non-invasive haemoglobin monitor.
- i) Portola Pharmaceuticals has been granted breakthrough therapy designation by the FDA for andexanet alfa, its investigational Factor Xa inhibitor antidote. The designation is intended

to expedite the development and review of drugs for serious or life-threatening conditions. Portola is pursuing an accelerated approval pathway for andexanet alfa and will initiate registration-enabling studies in 2014.

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) DBV Technologies is collaborating with Institut national de la Santé et de la recherche médicale, Inserm and Inserm Transfert, to examine epicutaneous delivery of recombinant Factor VIII by way of the allergy treatment technology Viaskin in an animal model of haemophilia A. Their aim is to develop a non-invasive and cost-effective treatment for haemophilia A. Dr. Sébastien Lacroix-Desmazes of Inserm said, "Preventing the immune response to therapeutic proteins upon induction of tolerance is the approach of choice for patients with hemophilia A. To date, the only strategy to induce tolerance to FVIII in patients who have developed anti-FVIII antibodies consists in flooding the immune system with enormous amounts of FVIII every day, for periods that can extend up to several months or years. This obviously faces issues with patients' compliance and treatment costs. Being able to induce FVIII-specific tolerance in haemophilia A patients using low doses of antigen, such as is the case with the Viaskin delivery system, would drastically improve the life of alloimmunized haemophilia A patients and solve a crucial societal burden."
- b) Novartis announced a definitive agreement to sell its blood transfusion diagnostics unit to Grifols for \$US 1.675 billion. The transaction is expected to be completed in the first half of 2014. The blood transfusion diagnostics unit includes nucleic acid testing, blood testing products and immunoassay reagents to detect infectious disease. The unit's headquarters are in California. Net sales in 2012 were \$US 565 million. Grifols said that the deal is part of its growth strategy of complementing its range of plasma protein therapies with other diagnostic products and services. The assets acquired include patents, brands, licenses and royalties, the California production plant and commercial offices in the US, Switzerland and Hong Kong.
- c) Grifols spent 12 million euros buying a private placement of new shares from Belgian biotech firm Tigenix, which will use the funds for clinical trials and marketing of its main drug ChondroCelect, which repairs damaged cartilage in the knee.
- d) In November Grifols posted a 35 per cent rise in nine-month profit.
- e) Aethlon Medical is raising \$US2 million in an equity round. In June the FDA granted Aethlon an investigational device exemption for a feasibility study of its Hemopurifier device, designed to filter pathogens and cancer cells from human blood. The trial is in ten patients with end-stage renal cancer who carry the hepatitis C virus.
- f) Shire is buying ViroPharma for \$US 4.2 billion. ViroPharma makes Cinryze for the treatment of the immune disorder hereditary angioedema.
- g) Terumo BCT has acquired GADA Turkey which distributes blood bank components and equipment to Turkish healthcare facilities; it has been a distributor for Terumo since 2009.
- h) NovoNordisk's NovoSeven lost patent protection in the US and several other regions in 2010 and 2011, and the company is hoping its new haemophilia A treatment, NovoEight, will make up for it. NovoEight was approved by the FDA in October, but Novo will not launch NovoEight in the US until early 2015, in case it violates third-party patents. NovoEight received a positive recommendation from Europe's Committee for Medicinal Products for Human Use (CHMP), which could mean European approval and product launch early in 2014.

NovoNordisk's rFXIII was rejected by the FDA in August on grounds that there were problems with its manufacturing process.

- i) DSM Biologics and Sanquin are collaborating for commercial manufacture of a monoclonal antibody used for the recovery and purification of coagulation factor IX from human blood plasma. DSM has become a second supplier to Sanquin for this process intermediate.
- j) Cerus Corporation renewed its contract with the Transfusion Service of the Swiss Red Cross by entering into a five-year purchase agreement for the INTERCEPT Blood System for platelets. This follows an initial three-year purchase agreement signed in 2010. The new agreement also allows for automatic extensions in additional two-year increments.
- k) Terumo BCT has a new US Department of Defense cost-share contract worth up to \$US 29.9 million to advance the Mirasol System for the treatment of donated whole blood used in emergency transfusions in deployed military forces. The Mirasol system treats blood with a combination of riboflavin (vitamin B2), and ultraviolet light to render a range of disease-causing viruses, such as West Nile virus and HIV, bacteria and parasites less pathogenic. Terumo BCT is working with the US Army Medical Research and Materiel Command to develop an FDA-approved device. The new cost-share contract effort expands the Mirasol system development efforts initiated with the Department of Defense in 2007.
- l) MedMira has received an additional \$US 1.917 million from the US Army. MedMira is developing and commercializing two rapid tests for transfusion transmitted diseases under a United States Army Medical Research Acquisition Activity (USAMRAA) contract. The additional funding enables MedMira to extend testing for the Reveal Rapid Hepatitis B Surface Antigen Test and Multiplo Rapid HBc/HIV/HCV Antibody Test in parallel with current trials.

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 Infectious Diseases Society of America has recommended better diagnostics for infectious diseases, advocating collaboration between Congress, regulatory bodies, industry, professional societies and clinicians. IDSA's Public Policy report, "Better Tests, Better Care: Improved Diagnostics for Infectious Diseases", was published in *Clinical Infectious Diseases*.
- b) The American Red Cross has five blood testing labs- St. Louis; Philadelphia; Portland, Oregon, Charlotte, North Carolina, and Detroit. It plans to close the highest cost lab, Detroit, in February, amid a national trend of declining demand for blood. The US has seen a reduction of 7 per cent to 10 per cent in demand for blood over the past two to three years, compared with declines of 3 per cent to 4 per cent in demand for blood in Canada and 12 per cent to 15 per cent in the UK.
- c) A US study, reported to the American Academy of Pediatrics' national conference, suggested that teaching hospitals care for children with sepsis at a greater cost than non-teaching hospitals, but without improving mortality rates.
- d) In Ireland, a patient who had suffered major blood loss following an emergency caesarean-section at the National Maternity Hospital died after waiting 40 minutes for a transfusion. An emergency supply of blood was not kept in the operating theatre at the time.
- e) Domestic and international experts met in Shanghai for the launch of the first guidelines in China for haemovigilance. The guidelines were drafted by the Shanghai Blood Centre and the Chinese Society of Blood Transfusion.
- f) Japan's health minister said blood donated by an HIV-positive man slipped through safety checks by the Japan Red Cross Society and was transfused into two recipients at separate

medical institutions. According to the ministry, the man found to be HIV-positive during blood safety screening in November had also donated blood in February. While the blood he donated in November was not used in transfusions, HIV was detected in a stored sample of blood he had donated in February. The infected blood may have passed the virus-detection system because HIV levels are low during the early stage of infection. The donor admitted lying at the time of the February donation when answering a question concerning whether he had had risky sexual contact. The ministry now suspects the man donated blood to discover whether he was infected with HIV.

- g) In Scotland a £90,000 study, funded by the Scottish Infection Research Network, will assess the best way of cleaning surgical instruments to prevent vCJD infection risk. Professor Andrew Smith of the University of Glasgow who is leading the study, said: "With new data suggesting that one in 2,000 people potentially carrying vCJD prions, the risk of transmission of the disease via surgical instruments remains a public health concern."
- h) A University of New South Wales study found that patients admitted to NSW hospitals at weekends face a higher death rate.
- i) The Australian Bureau of Statistics has projected that with medium growth Australia's population will double by 2075, with Perth overtaking Brisbane by 2028 and the ACT overtaking Tasmania a decade later. The population of Western Australia is projected to double by 2040, and Tasmania's to fall from 2047. The number of people aged 85 years and over is projected to triple by 2040, with people aged 85 years or over making up four per cent of Australia's population, compared with two per cent in 2012⁴. Population projections are based on assumptions of future levels of fertility, life expectancy and migration, which are guided by recent population trends.
- j) Figures revealed in the Kirby Institute's Annual Surveillance Report, released at the Australasian HIV & AIDS Conference in Darwin in November, suggest that nearly half of the estimated 207,000 people living with chronic hepatitis B in Australia continue to remain undiagnosed, while 15 per cent of people living with chronic hepatitis C in Australia have not yet been diagnosed⁵.

⁴ Further information is available in [Population Projections, Australia, 2012 \(base\) to 2101](#) (cat. no. 3222.0), available on the ABS website.

⁵The report found that almost 400 deaths in 2012 were related to hepatitis B-related liver disease despite the rate of diagnosis of newly acquired hepatitis B infection declining among those aged 30 years or older as well as reducing substantially among people aged 15-29 since 2003. In 2012, NSW had the highest number of diagnoses of hepatitis B infection, with 34.7 percent of the national total. The report also found that an estimated 310,000 people living in Australia in 2012 had been exposed to hepatitis C, with it thought that 173,500 had chronic hepatitis C infection and early liver disease, 51,500 had chronic hepatitis C infection and moderate liver disease, and 6,500 were living with hepatitis C related cirrhosis. The other 80,000 people believed to have to have been exposed have cleared their infection. The Kirby Institute estimates that almost 80 per cent of all infections for hepatitis C occur among people who inject drugs, with only one per cent of those people currently receiving treatment. Unlike other types of hepatitis, there is currently no vaccine to prevent hepatitis C, and medication is the only way to manage the disease. It is believed that 10-15 percent of all people living with HIV in Australia may also have hepatitis C and that co-infection remains a serious issue.

5. Safety and patient blood management

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

Appropriate transfusion

- a) Hitinder S. Gurm, from the University of Michigan in Ann Arbor, and colleagues have analyzed outcomes in consecutive patients having emergent and non-emergent percutaneous coronary intervention (PCI) and concluded that vascular closure devices are associated with a significant reduction in vascular complications and need for transfusion in patients having transfemoral PCI⁶.
- b) A small study at the Johns Hopkins Children's Center suggested that some paediatric surgeries carry such low risk of serious blood loss that clinicians can safely omit blood typing and blood stocking before such procedures. Having reviewed the records of thousands of paediatric surgeries performed at The Johns Hopkins Hospital over thirteen months they listed in their report in *Pediatric Anesthesia* ten operations they described as carrying "zero" transfusion risk.
- c) A study reported to the annual meeting of the American Heart Association in Dallas suggested that trauma patients transfused with either plasma or red cells in a ground or air ambulance were somewhat less likely to die within six hours of hospital arrival, and probably more likely to survive to discharge.
- d) Dr Colleen G. Koch from the Cleveland Clinic in Ohio, and colleagues, reviewed the literature around storage-related complications in patients given blood transfusions⁷. They read studies in trauma and cardiac surgery that linked increased blood storage duration to post-injury multiple organ failure, infection, deep vein thrombosis, and hospital mortality. They found other studies reported no apparent relationship between storage duration and clinical outcomes. They concluded "Until results of ongoing randomized controlled trials in the area of storage duration are completed, we cannot recommend a change in the current FDA formal guidelines. However, we encourage surgeons to remain aware of the possible complications associated with red blood cell transfusion..... We recommend further work with inventory management to explore strategies that would optimize fresher blood for patients."
- e) A small retrospective study published by the American Academy of Pediatrics suggested that a high ratio of fresh-frozen plasma to packed red blood cells was associated with a significantly lower risk of fatal haemorrhage in massively transfused paediatric trauma patients⁸.

Treating iron deficiency

- f) In the Hemoglobin and Iron Recovery Study, or HEIRS, funded by the US National Heart, Lung, and Blood Institute, researchers conducted a randomized trial to evaluate the impact of iron supplementation given to blood donors on haemoglobin recovery post-donation⁹. Donors were randomized to receive daily iron supplementation at a dose of 38 mg or no iron for 24 weeks following blood donation. Dr. Joseph Kiss, who led the trial, said: "The main finding was that hemoglobin recovery was slower than most would think. So we found that the normal blood donor group or iron replete, took an average of 78 days to recover back to within 80 percent of their baseline haemoglobin level. If they were iron

⁶ *Annals of Internal Medicine*, November 19, 2013.

⁷ *The Annals of Thoracic Surgery*, November 2013

⁸ Hwu RS et al., "High blood product ratio may increase survival in pediatric trauma" *AAP 2013*; Abstract 2129.

⁹ Kiss J, Cable R, Brambilla D, Glynn S, Mast A, Spencer B, Stone M, Tobler L. "Hemoglobin Recovery After Blood Donation and the Effects of Iron Supplementation: The Hemoglobin and Iron Recovery Study (HEIRS)". Abstract Presentations from the AABB Annual Meeting, Denver, CO. October 12-15, 2013. *Transfusion* 2013;53 Supplement

deficient, it took them 158 days to recover. If they were randomized to iron, the group that was iron deficient recovered in 32 days and the group that was not iron deficient recovered in 31 days..... the implication is that increasing the deferral periodwill help some donors, but is probably not going to help the majority of donors because recovery of ferritin levels still takes a fair bit of time¹⁰ and if you have someone actively donating they may remain iron deficient over time... The study further suggested that to be fully effective, iron supplementation would need to be provided for 90 days, which is longer than most current iron replenishment programs recommend..... I think blood centers will have to decide overall where to place the emphasis – meaning who should receive iron, how much, and for how long. The results of HEIRS suggest that many donors would benefit from a small dose for 90 days, but taking iron in and of itself is logistically challenging, and there are some who will have side effects.”

- g) A systematic review of randomized clinical trials found that giving preoperative erythropoietin-stimulating agents in patients undergoing elective hip and knee arthroplasty improved postoperative haemoglobin levels and decreased the need for allogeneic blood transfusion¹¹.

Other

- h) A new meta-analysis¹² suggests that treatment with dabigatran etexilate (Pradaxa, Boehringer Ingelheim) raises the risk of gastrointestinal bleeding compared with treatment with warfarin. These results conflict with results of a recent analysis of dabigatran and warfarin use in the FDA Mini-Sentinel database.
- i) Research presented at the meeting of the American Heart Association in Dallas in November suggested Daiichi Sankyo’s edoxaban was as good as warfarin at preventing embolisms and strokes in patients with abnormal heart rhythms. In the study there were fewer incidents of serious bleeding¹³.
- j) Initial results from a Phase II study of Portola Pharmaceuticals’ andexanet alfa, an investigational Factor Xa inhibitor antidote, in healthy volunteers who were administered Bayer’s oral anticoagulant Xarelto (rivaroxaban) were presented in a poster session at the 55th American Society of Hematology annual meeting in New Orleans on December 9. The results suggested that andexanet alfa is able to dose-dependently reverse the anticoagulant effects of Xarelto. No serious adverse events were reported.
- k) Dr Partha Sardar of New York Medical College presented to the American Heart Association 2013 scientific sessions a meta-analysis addressing bleeding risks with the novel oral anticoagulants and concluded that there is very little difference between the new drugs but that bleeding risks associated with the new agents vary substantially based on their indication for use.
- l) NIH through its National Heart, Lung, and Blood Institute funded a study which showed that combining genetic data with clinical information to determine the initial dosage of warfarin was no more effective in achieving stable anticoagulation than using only clinical information¹⁴.
- m) NIH has made a \$US 23.8 million grant for a study of the causes of severe bleeding. It will be led by the University of Vermont’s Professor Emeritus Kenneth Mann. Other participants are

¹⁰ It took the iron replete donors more than 168 days for ferritin recovery.

¹¹ Alsaleh K, “Preoperative erythropoietin may reduce allogeneic blood transfusion in hip, knee arthroplasty”, *J Arthroplasty*. 2013; doi:10.1016/j.arth.2013.01.024.

¹² The report was published online November 18, 2013 in *JAMA: Internal Medicine*.

¹³ Edoxaban data were released by the *New England Journal of Medicine*, November 20, 2013

¹⁴ The results of this Clarification of Optimal Anticoagulation through Genetics (COAG) trial were presented at the American Heart Association scientific sessions in Dallas and published in the *New England Journal of Medicine*

the University of Pittsburgh, the University of Colorado and Virginia Commonwealth University.

- n) Researchers at Thomas Jefferson University have found that the formation of blood clots follows a different molecular route in African Americans compared with European Americans, providing a new understanding of the effects of race on heart disease¹⁵ and its outcomes.

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 at King's College London have identified a biomarker for sepsis in the blood, and say it could be possible to diagnose the condition within two hours by screening for this biomarker at a patient's bedside. Sepsis is estimated to cost the NHS over £2 billion each year, and kills around 37,000 people annually in the UK. Published in the journal *Plos One*, the work was performed in collaboration with Cepheid, a molecular diagnostics company and developer of the GeneXpert, which is capable of performing rapid molecular detection. The team identified that a certain group of microRNAs were more active in the sepsis patients than in others, highlighting a potential biomarker for the condition. Plans for a randomised clinical trial are in place.
- b) Researchers from bioMérieux report the development of a new method to reduce the time it takes to diagnose blood infections and remove the need for complicated manual processing and expensive equipment¹⁶. They combine a selective lysis stage to destroy blood cells in the sample, a centrifugation stage to collect bacteria or fungi in the sample, and a fluorescence stage that analyzes the fingerprints of any pathogens present in the sample. The method correctly identifies the species of bacteria or fungi in 96.5% of positive blood culture samples.
- c) Jamey Marth, director of the University of California Santa Barbara's Center for Nanomedicine and professor of the Sanford-Burnham Medical Research Institute, reported in the *Proceedings of the National Academy of Sciences* on a new method to increase survival in sepsis. He concluded: "... we can now imagine a simple effective treatment consisting of a non-refrigerated enzyme mixed with saline, placed in a syringe and injected intravenously. This has the potential to translate into saved lives among those in the developed and undeveloped world."
- d) Humacyte announced on November 20 the presentation of interim, first-in-human data from an ongoing, multi-center study in Poland, evaluating the company's investigational bioengineered blood vessel in haemodialysis patients with end-stage renal disease. The data were presented by Dr Jeffrey H. Lawson, Professor of Surgery and Pathology at Duke University Medical Center, at the American Heart Association scientific sessions 2013 in Dallas.
- e) Researchers at the University of Michigan are exploring how platelet rich plasma (PRP) specifically affects tennis elbow (or lateral epicondylitis).

¹⁵ L.C. Edelstein, et al., "Racial differences in human platelet PAR4 reactivity reflect expression of PCTP and miR-376c," *Nature Medicine*, DOI: 10.1038/nm.3385, 2013.

¹⁶ "Rapid Intrinsic Fluorescence Method for Direct Identification of Pathogens in Blood Cultures" in *mBio*.

- f) Heart valves calcify over time, and Rice University scientists believe the problem may be due to the infiltration of von Willebrand factor¹⁷.
- g) Michael Toledano, of the Mayo Clinic in Rochester, Minnesota, says a few weeks of intravenous immunoglobulin (IVIg) or methylprednisolone is useful in determining whether epilepsy not responding to conventional drugs is autoimmune in origin. He told the American Neurological Association annual meeting that such a trial could not alone establish diagnosis¹⁸.
- h) A new study shows that patients suffering traumatic brain injury may not benefit from transfusions of platelets to reverse their antiplatelet therapy. Joshua Bauer, of the University of Pittsburgh confirmed: "Reversal of antiplatelet therapy was not associated with decreased progression of intracranial injury," at the Congress of Neurological Surgeons 2013 annual meeting¹⁹.
- i) Scientists in Germany discovered a gene which makes blood platelets stickier, and increases the risk for heart attacks by 15 per cent.
- j) Professor Richard Pleass who was recently awarded the 2013 Universal Biotech Innovation Prize for developing a biomimetic to replace IVIg, says there is "an urgent clinical need to develop synthetic replacements for IVIg for use in autoimmune diseases". He says his team hopes that winning the prize will help "to leverage more significant translational funding to move (their product) HexaGard from proof-of-concept into the drug development pathway".
- k) Researchers at the University of Illinois at Chicago have identified a molecular switch that causes small clots that stop bleeding to enlarge during wound healing. In lab mice, the researchers were able to block this switch and prevent small clots from enlarging, although they retained their capacity to stop bleeding. They hope this will facilitate the development of anti-clotting drugs that don't increase the risk of bleeding²⁰.
- l) A study²¹ of 109 patients treated for beta-thalassemia more than twenty years ago with hematopoietic stem cell transplants has found their long-term health-related quality of life was comparable with that of the rest of the population. Patients who were older at transplant or who developed graft-versus-host disease had poorer overall health outcomes.

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).

¹⁷ Liezl Balaoing et al., in the American Heart Association journal *Arteriosclerosis, Thrombosis and Vascular Biology*

¹⁸ Toledano M, et al "Pilot study of immunotherapy as a diagnostic test in evaluating patients with presumed autoimmune epilepsy" ANA 2013; Abstract

¹⁹ Abstracts 164 and 195. Presented October 22, 2013.

²⁰ Findings were published online in *Nature*, lead author Xiaoping Du, professor of pharmacology in the UIC College of Medicine.

²¹ The investigation was conducted by Giorgio La Nasa, of the Bone Marrow Transplant Center at R. Binaghi Hospital in Italy, and colleagues.

Mosquito- borne diseases: dengue, chikungunya and malaria

- a) A confirmed case of dengue in New York is said to be the first instance of local acquisition of the infection. "Given the recent introduction of *Aedes albopictus* into New York State and the high level of travel in New York to areas of the world endemic for dengue, it is not surprising that a locally acquired case of dengue has been found in the state," said State Health Commissioner, Nirav R. Shah.
- b) Western Australia had its first case of locally-contracted dengue for seventy years.
- c) The EMA has awarded orphan drug designation²² to DengueCide, NanoViricides' drug candidate for the treatment of dengue and dengue haemorrhagic fever.
- d) Nikos Vasilakis, a virologist at University of Texas Medical Branch in Galveston, told the Third International Conference on Dengue and Dengue Haemorrhagic Fever in Bangkok: "We discovered and characterized a new dengue serotype". Researchers screening dengue viral samples collected during an outbreak in Malaysia's Sarawak state in 2007 suspected they were different from the four known serotypes. Sequencing proved them to be phylogenetically distinct from the other four types. Experiments found that monkey antibodies produced against the new type differed significantly from those resulting from the previously known dengue viruses. The existence of a new type which may spread can be expected to complicate vaccine development further.
- e) A vaccine against chikungunya has been developed by Vienna-based Themis Bioscience, and is undergoing a phase I clinical study at Vienna General Hospital. The vaccine is based on a standard anti-measles vaccine. The company's own Themaxyn platform also forms the starting point for a vaccine against dengue.
- f) A chikungunya outbreak in Papua New Guinea is one factor causing scientists to worry that chikungunya coming into Australia with returning travellers could soon be locally transmitted by mosquitos already present here.

Influenza: strains, spread, prevention and treatment

- g) The H7N9 strain of avian flu which emerged in China in the previous northern hemisphere winter saw 137 confirmed cases and 45 deaths through to late October, but the new northern hemisphere flu season is producing more cases, including the first two cases in Hong Kong.
- h) Results from an early stage trial of a Novavax virus-like particle (VLP) vaccine against the H7N9 strain of avian flu were published online in the *New England Journal of Medicine*. Scientists said the vast majority of subjects produced protective antibodies very quickly. The VLP nature of the vaccine facilitates large scale rapid production
- i) Novartis announced that early tests on its H7N9 vaccine showed that 85 per cent of subjects had a protective immune response after two doses.
- j) Chinese researchers announced they have developed a vaccine against the H7N9 virus. The vaccine was jointly developed by the First Affiliated Hospital under the School of Medicine of the Zhejiang University, Hong Kong University, the Chinese Centre for Disease Control and Prevention, the National Institute for Food and Drug Control, and the Chinese Academy of Medical Sciences.
- k) A study has found that closure of live poultry markets is the best way to slow the spread of H7N9²³.

²² One of the benefits of orphan drug designation is ten years of exclusivity in marketing.

²³ Hongjie Yu, Joseph T Wu, Benjamin J Cowling et al., "Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study", *The Lancet*, Early Online Publication, doi:10.1016/S0140-6736(13)61904-2. See also Wu Y, Gao G F. "Lessons learnt from the human infections of avian-origin influenza A H7N9 virus: Live free markets and human health", *Sci China Life Sci*, 2013, 56: 493-494, doi:10.1007/s11427-013-4496-y.

- l) The FDA approved a GlaxoSmithKline vaccine for use in an H5N1 epidemic. It will be added to the national stockpile for distribution by public health officials if required. It contains an adjuvant to boost the body's immune response to the vaccine.
- m) A woman in Taiwan tested positive for the avian flu strain H6N1 which had not been considered able to infect people²⁴.

MERS-CoV

- n) By early December the global total of laboratory confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) was 163 (and a dozen probable cases) with 70 deaths. Cases traced back to infections in a handful of countries on the Arabian Peninsula: Jordan, Saudi Arabia, Qatar, the United Arab Emirates and Oman. Camels in both Qatar and Saudi Arabia have tested positive to the virus.
- o) On 18 November Spain announced its second case in a woman who participated in the recent Hajj in Saudi Arabia, had travelled to Saudi Arabia with Spain's first MERS case, and had shared sleeping quarters with her.
- p) Scientists developed a strain MERS-CoV that could be used as the basis of a safe and effective live-attenuated vaccine against MERS²⁵. "Our achievement was a combination of synthetic biology and genetic engineering," said co-author Luis Enjuanes of The Autonomous University of Madrid. "The injected vaccine will only replicate in a reduced number of cells and produce enough antigen to immunize the host," he says, and it cannot infect other people, even those in close contact with a vaccinated person.
- q) Inovio reported positive results in preclinical tests for its MERS vaccine, whose production is based on its DNA (SynCon) vaccine technology.
- r) The World Health Organisation (WHO) on 19 November placed all health care providers on red alert on possible outbreak of Severe Acute Respiratory Infections (SARI). It said recent travellers returning from the Middle East who develop SARI should be tested for Middle East respiratory syndrome coronavirus (MERS-CoV).
- s) Scientists from Imperial College London, the University of Edinburgh and the Institut Pasteur in Paris, in a new analysis of MERS case data, suggest that for each case that is known, five to 10 may have been missed. The scientists further suggest that transmission of the MERS virus is occurring at a rate close to the threshold where it would be considered able to pass from person to person in a sustained manner. They said that on the evidence currently available they cannot rule out the possibility that person-to-person spread is the chief mode of transmission of the virus at this point. The other option is that viral transmission is through a combination of animal-to-person and then person-to-person transfer. They concluded "a slow growing epidemic is underway, but current epidemiological data do not allow us to determine whether transmission is self-sustaining in man"²⁶.

Other diseases: occurrence, prevention and treatment

- t) The EMA's CHMP recommended the authorization of Deltyba (delamanid) and Para-aminosalicylic acid Lucane (a new formulation of para-aminosalicylic acid), as options for use in combination with other drugs to treat multidrug-resistant tuberculosis.
- u) Mass polio vaccination campaigns have been occurring across the Middle East, targeting 22 million children in seven countries. This follows the confirmation of wild poliovirus cases in several locations. Two European infectious disease experts have warned that wild polio virus might endanger Europe, through the flow of refugees from Syria and through visitors returning from the Hajj in Saudi Arabia²⁷.

²⁴ See Lancet Respiratory Medicine

²⁵ mBio

²⁶ Lancet Infectious Diseases, 20 November 2013.

²⁷ Artin Eichner and Stefan Brockmann in Lancet Infectious Diseases, 8 November 2013 (online).

- v) Two US universities have experienced outbreaks of meningococcal disease.
- w) A number of Victorians were diagnosed with measles after returning from Bali, and passed on the disease to others. In South Australia six children and a 36 year old woman returned from Bali with measles. A Queensland prison had an outbreak of measles after a prisoner introduced it into the facility. The infected prisoners were in their late 20s and 30s, of an age group that avoided contracting the disease as children but were too old to have been vaccinated under a mass drive in the 1990s.
- x) By 30 October, around 150,000 horses in Australia had received the Hendra virus vaccine.
- y) In November, two hundred people in Brisbane were confirmed to have salmonella, and one died, following Melbourne Cup luncheons catered for by a single company.