Monitoring International Trends

**posted July 2013**

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 24th Annual Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Amsterdam June 29-July 4 heard updates from several companies about development of clotting factors with longer half- lives (page 2).
* The US Food and Drug Administration (FDA) has approved Baxter's Rixubis for haemophilia B patients over the age of 16 (page 4).
* Work continues on creating artificial platelets (page 4).
* The European Haematology Association theme of the year to June 2014 is dedicated to "Age and Aging in blood disorders". This includes both the aging of patients and the aging of cells (page 8).
* Researchers have found that restoring blood levels of nitric oxide in animals prior to transfusion improved their tissue blood flow, oxygen delivery, and kidney function (page 9).
* This year has seen major dengue and chikungunya activity in countries in our region (page 11).
* The World Health Organization (WHO) has been monitoring the possible pandemic potential of avian flu H7N9 which arose in China (page 11) and MERS- CoV, the Middle East Respiratory Syndrome Coronavirus (page 12).

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# Products

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

### Haemophilia treatments – highlights from the XXIV Congress of the International Society on Thrombosis and Haemostasis (ISTH), June 29-July 4, 2013, in Amsterdam.

* 1. rEVO Biologics[[1]](#footnote-1) completed the treatment and follow up phase of a key dose ranging study of LR769, a recombinant form of human Factor VIIa (rhFVIIa), in patients with congenital haemophilia A or B with inhibitors to factor VIII or IX. Results from the study were presented at the congress. LR769 was developed in collaboration with LFB Biotechnologies and manufactured using proprietary rPRO transgenic technology. The pharmacokinetic and pharmacodynamic data will provide the basis for further clinical efficacy studies of LR769. rEVO expects to initiate a Phase III registrational study later this year.
	2. Biogen Idec and Swedish Orphan Biovitrium (Sobi) made available data from research programs in haemophilia. They presented new analyses of the phase III A-Long study of Eloctate, their long-lasting rFVIIIFc fusion protein; and of the B-Long study of Aprolix, their long-lasting rFIXFc fusion protein.
	3. Eloctate was reported to control 87 per cent of bleeds with a single treatment, and 97 per cent with two or one treatments[[2]](#footnote-2); to have exhibited prolonged thrombin generation activity against a comparator[[3]](#footnote-3); to have allowed longer intervals between prophylactic treatments than the current standard of care[[4]](#footnote-4); and to have shown high efficacy levels during surgery[[5]](#footnote-5). Eloctate is under FDA review in the US and a marketing application has been submitted in Australia. Aprolix was similarly reported to show efficacy and safety[[6]](#footnote-6).
	4. Biogen Idec also presented data on its long-lasting FVIIa candidiate[[7]](#footnote-7).
	5. CSL Behring presented data from three ongoing trials: of its longer-acting rVIIa-FP and rIX-FP candidates based on recombinant albumin, and of its rVIII-SingleChain compound, which the company says improves the stability and half-life of FVIII.
	6. CSL Behring’s rFVIIa-FP (recombinant fusion protein linking coagulation factor VIIa with albumin) is designed to treat haemophilia A and haemophilia B patients with inhibitors. The extended half-life means fewer doses. Preclinical studies showed rVIIa-FP to have favourable pharmacokinetic properties compared with the comparator. Significant increases in half-life were observed with CSL Behring’s rVIIa-FP in all animal species in the trial.
	7. CSL Behring reported that data showed the clinical efficacy of rIX-FP (its recombinant fusion protein linking factor IX with albumin) with less frequent prophylactic doses than the current standard of care. The drug was also satisfactory in trials of on-demand use, with 95.3 per cent of bleeding events treated with a single infusion, and the rest requiring no more than two infusions.
	8. Pharmacokinetic results for CSL Behring’s rVIII-SingleChain (investigational recombinant coagulation single-chain factor VIII) showed increased half-life compared with octocog alfa. It established a safety and efficacy profile to support proceeding to late-stage clinical development.
	9. Baxter International presented two complementary studies of the ADVATE profile: an analysis of post-marketing data from 1,200 haemophilia A patients and 15 countries and safety findings from a 10-year database of 12 clinical trials. The company said the meta-analysis of post-authorization safety studies underlined the product safety and effectiveness and the low rate of inhibitor development; while the integrated safety analysis confirmed safety and tolerability in children and adults with moderately severe or severe haemophilia and did not bring to light any new safety signals.
	10. Alnylam Pharmaceutical presented new pre-clinical data from its RNAi therapeutic program for the treatment of haemophilia and rare bleeding disorders. The company said the data demonstrated that ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin, can normalize thrombin generation and improve haemostasis in haemophilia mice; as well as correct thrombin generation in a non-human primate haemophilia "inhibitor" model. Alnylam said it will submit an investigational new drug (IND) application for ALN-AT3 in mid-2013, and begin a Phase I clinical trial in late 2013. It expects to report initial clinical data in haemophilia patients in 2014.
	11. After the congress, Bayer HealthCare announced on July 8th 2013 that enrolment had begun in an international Phase III trial to evaluate its recombinant human factor VIII, BAY 94-9027, for treating haemophilia A. This PROTECT[[8]](#footnote-8) VIII Kids trial will investigate whether the drug can be used prophylactically to extend protection from bleeding events for up to seven days, while also being suitable for acute bleeds. Enrolment of adult patients with haemophilia A into the PROTECT VIII trial is already complete. BAY 94-9027’s claim to extend the half-life of rFVIII activity is via a site specific attachment of a polyethylene glycol (PEG) polymer to the light chain of the rFVIII molecule, without compromising its biologic activity.

### Sickle cell treatments

* 1. HemaQuest Pharmaceuticals completed enrolment in a randomized, double-blind, placebo-controlled Phase IIb study of HQK-1001 in patients with sickle cell disease. The drug is a small chain fatty acid derivative administered orally twice daily; its purpose is the induction of foetal haemoglobin and consequent reduced frequency of pain crises, lower frequency and intensity of daily pain, less analgesic use, and enhanced quality of life. HemaQuest expects an interim analysis of the trial later this year, and final results in mid-2014. HQK-1001 has Orphan Drug Designation in the United States and Europe for both sickle cell disease and beta thalassemia.
	2. Researchers from the La Jolla Institute for Allergy and Immunology, the Dana-Farber/Children's Hospital Cancer Center in Boston and the BloodCenter of Wisconsin in Milwaukee are beginning a Phase II clinical trial of a potential treatment to reduce the severity of symptoms in sickle cell anaemia. The trial, funded by the US National Institutes of Health (NIH), will test the drug Lexiscan (regadenoson - Astellas Pharma), already in use in diagnosing heart disease. It is thought the drug’s anti-inflammatory effects could substantially reduce the pain and disturbed blood flow in sickle cell anaemia[[9]](#footnote-9). A Phase I safety study was completed earlier this year.

### Artificial platelets

* 1. Biomedical engineers at Georgia Tech have created artificial platelets to enhance the natural clotting process. In animal trials, clotting time was reduced by 30 per cent. The clots offer potential for the battlefield, where an injured soldier could inject the freeze-dried material on the field, using a small device. However, there are a number of safety issues which remain to be considered such as how long the artificial platelets will circulate round the body, potentially leading to heart attacks and strokes.

### Anti-coagulants

* 1. Dr. Giancarlo Agnelli told the International Society on Thrombosis and Hemostasis (ISTH) meeting that apixaban (Eliquis, sold by Pfizer and Bristol-Myers Squibb) was as effective as warfarin in treating venous thromboembolism and caused less bleeding[[10]](#footnote-10).

### Devices and services

* 1. A new type of intravenous (IV) connector with zero displacement reduced the incidence of central-line associated bloodstream infections by 36 per cent in a quality improvement study[[11]](#footnote-11). The connector is impregnated with chlorhexidine and silver.
	2. Two Michigan entrepreneurs have developed CureLauncher, a service that matches patients with clinical-research trials offering cutting-edge treatments.

# 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

* 1. In February, Cangene acquired all rights to the development of the investigational haemophilia B drug IB1001 from Ipsen and Inspiration Biopharmaceutical. Cangene has withdrawn the Marketing Authorization Application in Europe and will refile with additional clinical data as requested by the European Medicines Agency (EMA). At the date of acquisition the drug was also being reviewed in the US. Cangene is continuing to address the FDA’s Complete Response Letter with a defined path to approval in relation to the Biologics License Application.
	2. In the US, the FDA has granted approval for Baxter's Rixubis for the treatment and prevention of bleeding episodes in haemophilia B in patients over the age of 16. It is a purified protein made with recombinant DNA technology. For prophylaxis it is administered intravenously twice a week. The drug's efficacy was assessed in 73 male patients aged from 12 to 65. Reported side effects included distorted taste, pain in an extremity, atypical blood results and - uncommonly- severe (possibly life- threatening) allergic reactions.
	3. In June 2013 the FDA said recent data had strengthened the association between the use of intravenous, subcutaneous and intramuscular human immune globulin products and the risk of thrombosis and that additional caution regarding the use of these products is warranted. It therefore required manufacturers to add information to the previous boxed warning in the labels of all intravenous human immune globulin products, and to add a boxed warning to the labels of all subcutaneous and intramuscular human immune globulin products. These warnings highlight the risk of thrombosis and provide information on risk mitigation. The data which prompted this action came from a health claims database and from continued post marketing adverse event reports.
	4. Kamada announced that it was granted an additional Australian Patent No. 2007213344 (co-owned with PARI PHARMA), entitled "Pulmonary delivery of Alpha-1 proteinase inhibitor."

### Blood donation, processing, storage and use; blood substitutes

* 1. The FDA has approved radio frequency identification technology to identify, reconcile and track blood products.
	2. The FDA has approved product from a system developed by Hemerus Medical and US Army Medical Materiel Development Activity. The SOLX® System is designed to better preserve the quality of collected red blood cells while extending the product’s shelf life. While the FDA’s approval is for storage of six weeks-the current standard-the developers claimed the cells could be stored for two weeks longer.
	3. In the US, the FDA now requires hydroxyethyl starch solutions used to treat hypovolemia to carry a boxed warning about increased risk of kidney injury and death. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee had earlier recommended that EU members suspend marketing authorizations for the products until the holder of the authorization could "provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks".

### Devices

* 1. The FDA has asked device manufacturers and healthcare facilities to make more effort to reduce the chance of cyber attack within medical devices. In its safety communication the FDA says it is conscious of vulnerabilities such as malicious software installed in networked medical devices, hospital computers, smartphones, and tablets.
	2. Johnson & Johnson subsidiary Codman Neuro has had its self-expanding clot removal device approved in Europe.

### Other

* 1. Abyrx has received FDA clearance for its absorbable haemostatic bone putty (AHBP). The putty is ready-to-use without requiring mixing or warming. It is composed of water soluble and synthetic dispersible components that are absorbed within days following surgery.
	2. The European Commission has granted orphan drug designation to Maribavir, [ViroPharma’s](http://www.bizjournals.com/profiles/company/us/pa/exton/viropharma_inc/3234097) experimental treatment of cytomegaloviral disease in patients with impaired immune systems.
	3. India’s Axio-Biosolutions has had its Axistat haemostatic dressing approved in Europe. This is non- absorbable and sticks to the wound, but wipes off when wetted with water or saline.

# 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.*

* 1. Recombinant clotting factors in development are expected to be the first therapies produced in **CSL Behring**’s new Biotechnology Facility in Broadmeadows. The new facility is currently producing test batches of recombinant proteins and will begin manufacture of clinical trial material early in 2014.
	2. **Grifols** announced the three publications concerning von Willebrand factor which won its Martin Villar Research Awards[[12]](#footnote-12).
	3. [**Novo Nordisk**](http://www.reuters.com/finance/stocks/overview?symbol=NVO&lc=int_mb_1001)was reported to be facing a tax claim for around $US 975 million from Danish authorities, relating to the valuation of two drug patents that were removed to Switzerland.
	4. **Cerus Corporation** has begun enrolling patients in two European Phase III clinical trials for the INTERCEPT System for red blood cells. One trial is for patients with acute anaemia, and the other for patients with chronic anaemia.
	5. **Cangene Corporation** reported its results for the third quarter of 2013, which ended on April 30, 2013. Total revenue for the quarter was $C40.2 million, compared with $C27.5 million in the same period last year.
	6. **Akebia Therapeutics** has raised $US41 million to challenge Amgen and Johnson & Johnson in the anaemia-drug market. Synthetic versions of the human hormone erythropoietin stimulate red blood cell production, but Amgen's Epogen and J&J's Procrit carry safety warnings, including one that patients could develop cardiovascular problems.
	7. **Amgen** has increased the price of Epogen, its anaemia drug for dialysis patients, by 5 per cent, the first price change for the drug since 2011. This followed the withdrawal of Affymax’s Omontys anaemia drug from the market after three patient deaths linked to a series of hypersensitivity reactions. Omontys required once-a-month dosing compared to three-times-a-week for Epogen.
	8. The Board of **NuSep** advised the market on 11 June that its Singapore subsidiary **PrIME Biologics** had been granted a human plasma importation licence by the Singapore regulatory authority. Plasma imported from countries such as India will be processed in the PrIME Biologics Singapore facility for re-export as finished therapeutic plasma products. Processing will not begin until the company has received the certificate of Good Manufacturing Practice approval from Singapore’s Health Sciences Authority.
	9. **Ativa** Medical is to issue debt in the amount of $US7 million to develop the "world's first micro-lab," a device that uses a single drop of blood on a test card. That is inserted in an analyzer which displays results in 3 to 5 minutes and can transfer them to other information systems.
	10. **The Medicines Co**. plans to buy **ProFibrix** subject to late-stage study results for a topical powder that the company is developing to stop bleeding during or after surgery. Netherlands company ProFibrix is developing Fibrocaps, which mixes the blood clotting proteins fibrinogen and thrombin to form the powder. The Medicines Co. makes the anti-clotting drug Angiomax, among other products. It has discontinued development of MDCO-2010, a drug designed to reduce bleeding during surgery, because of safety concerns.

# 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.*

* 1. In the US, the Agency for Healthcare Research and Quality (AHRQ) has sought public comment on its current plan for a consumer reporting system for patient safety events. AHRQ wants to reduce the number of adverse events not reported, by encouraging patients and families to report.
	2. A new study in the US suggests that a decrease in the number of black children suffering from ischemic strokes is the result of an increase in the use of blood transfusions for patients with sickle cell disease.
	3. France was this year’s host for World Blood Donor Day (June 14); Sri Lanka will be host next year. The World Health Organisation (WHO) says they are two of 60 countries collecting 100 per cent of their whole blood supply from voluntary unpaid donors. WHO says that in low-income countries, a large proportion of blood transfusions are to treat severe anaemia in children under five, and to manage maternal and neonatal health. In high-income countries transfusions have their main uses in cardiovascular and transplant surgery, major trauma and cancer treatment.
	4. The Kingdom of Saudi Arabia is establishing a manufacturing facility for plasma products.
	5. The Board of the Irish Blood Transfusion Service was advised its business continuity plan needed amendment to reflect need to import blood in the wake of a major disaster, including an act of international terrorism. European transfusion services are extending co-operation, facilitated by the introduction of common European standards of quality and safety for the collection, testing and processing of blood components.
	6. In Sri Lanka, the amended National Blood Transfusion Act will be presented in Parliament soon. Once the Act is passed, private hospitals can charge patients a nominal amount for blood but they have to bill for it specifically, and patients will have the right to query the amount. Currently the Health Ministry cannot intervene when private hospitals overcharge charge patients for blood. The Health Ministry charges private hospitals only Rs. 1,200 for each blood transfusion kit cost although the cost to the ministry is Rs. 1,500.
	7. Oman targeted 95 per cent voluntary unpaid blood supply by 2015 in response to the WHO call on World Blood Donor Day for 100 per cent tor all countries.
	8. In the UK, the government has published a set of proposals to end “health tourism" and collect charges owed from foreign use of the National Health Service.

# Safety and patient blood management

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

### Appropriate transfusion

* 1. A number of Canadian newspapers have carried two articles on appropriate and accurate transfusion. The first, *Researchers fear the "gift of life" may sometimes endanger it,* reviews the evidence around variability in transfusion practice in patients with the same risk profile; the fact that patients not transfused may have better outcomes; and the causes of transfusion-related death. The article acknowledges increasing concern over unnecessary transfusions, and outlines strategies hospitals are adopting to reduce blood use[[13]](#footnote-13).
	2. The second article, *Health experts confront the hidden hazards of blood transfusions*, highlights the research on transfusion errors conducted at Toronto's Sunnybrook Health Sciences Centre over six years. 15,134 errors were reported. Of the 23 which harmed patients, most involved unnecessary transfusions. Dr Jeannie Callum, director of transfusion medicine at Sunnybrook, said “One of the leading causes of major morbidity from a blood transfusion is just getting blood that wasn’t intended for you”. At Sunnybrook, surgical patients wear barcoded wristbands. Handheld devices scan these and print labels at the bedside when blood is drawn for matching. Before blood is transfused, the bag and patient wristband are read, and an alarm goes off if there is no match[[14]](#footnote-14).
	3. In the US a downward trend in blood usage began in 2009, with increasing evidence of the dangers of unnecessary blood transfusions. Transfusions of blood components provided by the American Red Cross, responsible for about half the nation's supply, fell by 3 per cent in 2009, 2010 and 2011 and by 5 per cent in 2012. There is diversity of experience across the country[[15]](#footnote-15). There is also variability in transfusion outcomes for patients in particular settings. In one comment the authors write “This variability could be the result of insufficient understanding of published guidelines; different recommendations of medical societies, including the specification of a haemoglobin concentration threshold to use as a transfusion trigger; the value of haemoglobin as a surrogate indicator for transfusion benefit, even though only changes in concentration and not absolute red cell mass of haemoglobin can be identified; and disagreement about the validity of the level 1 evidence for clinical practice guidelines”[[16]](#footnote-16)
	4. **Researchers from the Mayo Clinic College of Medicine, Rochester,** in reporting on a recent study, wrote that “Patients with chronic kidney disease undergoing major orthopedic surgery are at greater risk of requiring perioperative blood transfusions”. …..This risk is independent of intraoperative estimated blood loss, preoperative anemia and higher rates of cardiovascular disease.”[[17]](#footnote-17)

### Treating iron deficiency

* 1. A randomised trial at four high- altitude centres suggested that injections of an erythropoiesis-stimulating agent (ESA), particularly darbepoetin alfa, may reduce the need for red blood cell transfusions in preterm infants[[18]](#footnote-18).
	2. Research from Harvard University suggests that daily iron supplements in pregnancy reduces anaemia risk and chances of a baby with low birth- weight[[19]](#footnote-19). Researchers at the University of Melbourne found that expectant mothers who take a bi-weekly dose of iron experience the same benefits as those who take an iron supplement twice a week[[20]](#footnote-20).
	3. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended precautions for treating iron deficiency anaemia with intravenous (IV) iron supplements, because of the danger of allergic reactions. One recommendation is that clinicians administer IV iron supplements only in facilities equipped for resuscitation if the patient experiences anaphylaxis. This precaution matches that on the FDA-approved labels of iron dextran injection, iron sucrose injection, and sodium ferric gluconate complex in sucrose injection. CHMP recommends that clinicians discontinue giving small test doses as they are not "a reliable way to predict how the patient will respond when the full dose is given". Every dose should be approached with caution. However, a black box warning on the FDA-approved label for iron dextran injection calls for a test dose. CHMP also recommends not administering IV iron supplements to pregnant women "unless clearly necessary," and then only in the second or third trimester. The FDA also recommends caution but does not limit IV treatment to the second or third trimester.
	4. A study of data for 117,000 dialysis patients suggested that large (bolus) doses of IV iron were associated with a higher risk of infection compared with smaller and less frequent maintenance dosing[[21]](#footnote-21).

### Other

* 1. The European Hematology Association (EHA) held its 18th Congress in Stockholm, June 13-16, 2013. The EHA-theme of the year, from June 2013 to June 2014, is dedicated to "Age and Aging in blood disorders". This includes both the aging of patients with blood disorders and the aging of cells. The congress program combined all patient and policy related sessions into one comprehensive full-day advocacy program on June 15, covering: patients' involvement as partners in clinical research; explaining unavailability of treatment; delivering healthcare in times of economic crises; and personalized medicine.
	2. Christopher K. Kepler, from the Thomas Jefferson University in Philadelphia, and colleagues reported in the May issue of *The Spine Journal* that minimally invasive surgery for spinal lumbar interbody fusion is associated with reduced blood loss and shorter hospital stays when compared with open surgery. However if a concomitant decompression is necessary these advantages do not obtain.
	3. Patients whose platelet count falls after transcatheter aortic valve replacement (TAVR) have a heightened of adverse events, but the exact mechanisms for the condition and its effects are unknown[[22]](#footnote-22).
	4. At the 18th Congress of the European Haematology Association, the Thalassaemia International Federation presented guidelines addressing the Management of Non-Transfusion Dependent Thalassemias.
	5. Researchers at Vanderbilt University Medical Center say cardiac patients carrying the Leiden variant of a factor V gene lose less blood perioperatively than those without the variant; however they are more prone to thrombosis. Pre-surgical screening is suggested for consideration.

# 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.*

* 1. Jonathan Stamler and colleagues from Case Western Reserve School of Medicine and from Duke University Medical Center have developed an approach to restore nitric oxide (NO) to donated blood[[23]](#footnote-23). They found that restoring blood levels of NO in animals prior to transfusion improved their tissue blood flow, oxygen delivery, and kidney function. Stamler has now secured a grant from the National Heart Lung and Blood Institute to begin a clinical trial to evaluate the oxygen delivery function of banked blood.
	2. Doctors at San Raffaele hospital in Milan have recreated part of the function of the pancreas in the bone marrow of four patients. The team recovered endocrine cells from the pancreas surgically removed, "rebuilding" it in the bone marrow at the level of the pelvis. The endocrine tissue worked, in an observation period of nearly three years, according to the head of the Pancreatic Islet Transplantation Program and Beta Cell Biology Unit at the Diabetes Research Institute of San Raffaele.
	3. Platelets, in addition to slowing blood loss, appear to contribute to protection against bacterial infection. Researchers found that in the livers of mice, platelets and specialized white blood cells co- operate to engulf blood-borne bacteria[[24]](#footnote-24).
	4. **Whitehead Institute researchers have identified a protein that is the target of glucocorticoids, used to increase red blood cell production in patients with certain types of anaemia, including those resulting from trauma, sepsis, malaria, kidney dialysis, and chemotherapy. Further research could lead to ways of increasing this protein's production so patients do not have to experience the severe side effects of glucocorticoids**[[25]](#footnote-25)**.**
	5. Researchers who considered thousands of cases involving hospitalized patients found that women were at much lower risk for bloodstream infection and surgical-site infection than men[[26]](#footnote-26).
	6. A nonreactive bioengineered blood vessel has been implanted in the arm of a 62-year-old Virginia man. The two- hour surgery was performed by Dr. [Jeffrey H. Lawson](http://www.dukehealth.org/physicians/jeffrey_h_lawson), Duke University School of Medicine vascular surgeon. It was the first in a Phase I clinical trial to test the safety of lab-grown vein implants in 20 kidney dialysis patients.
	7. Harvard researchers report that two HIV-positive patients who received bone marrow transplants for cancer stopped anti-retroviral therapy and so far display no detectable sign of the HIV virus; they say it is too early to claim a cure.
	8. Research suggests that if liver cells are derived from human induced pluripotent stem cells and cultured with progenitor cells they will organize themselves into functional, three-dimensional liver buds. Their metabolisms exhibits some aspects found in human livers. If the liver buds are transplanted into mice, they connect to the circulatory system[[27]](#footnote-27).
	9. Researchers from Ryerson University, Toronto found that, using laser light, they can quickly detect pathogens in red blood cells. The cells emit high frequency sound waves in response to the light. The waves indicate cell health, as varying diseases change the shape and size of red blood cells[[28]](#footnote-28). Dr. Michael Kolios and his colleagues differentiated healthy red blood cells from diseased red blood cells using a photoacoustic microscope. Malaria, which is characterized by the swelling of red blood cells, could be rapidly distinguished from sickle cell anaemia, in which the red blood cells distort into a serrated crescent shape. Sample size was 21 cells. The team is developing a microfluidic device to measure thousands of cells quickly with minimal operator involvement. The technology is being tested for white blood cells.
	10. A team at the Max Planck Institute for Heart and Lung Research says it has found the mechanism that cancer cells use to make blood platelets “open a door” in the blood vessel wall so they can invade new organs[[29]](#footnote-29).
	11. Researchers have found how to identify prion diseases and other diseases involving defective proteins, with the use of a fluorescent molecule that changes colour according to the disease identified[[30]](#footnote-30).
	12. Engineers from Queen Mary, University of London have developed a computer simulation of how red blood cells might travel around the body. Professor John Williams says this could help doctors “visualise the cells’ movement, interaction, deformation and adhesion in three dimensions” and thus understand which areas of the body are short of oxygen as a result of particular conditions or procedures.
	13. Researchers from the Boston University School of Medicine, Boston University School of Public Health and Boston Medical Center have identified an approach to creating human red blood cells and platelets in vitro. They differentiated induced pluripotent stem (iPS) cells into the two cell types[[31]](#footnote-31).
	14. Scientists from Australia’s CSIRO have developed a method of testing whether iPS cells are safe.
	15. Scientists at the Icahn School of Medicine at Mount Sinai transferred four genes into mouse fibroblast cells and produced cells that resemble hematopoetic stem cells[[32]](#footnote-32).
	16. Biocompatible polymer-based sponges developed by engineers at the University of California, San Diego, are designed to circulate in the blood stream and suck up toxins from bacteria and venom before they damage healthy tissue. The next step will be clinical trials[[33]](#footnote-33).

# 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.*

* 1. A Baxter shareholder initiated action against 11 Board members, claiming they didn't do enough to investigate fraud accusations connected to a $US588 million infusion pump recall, and also that the company manipulated the blood plasma market by taking over competitors. Investor Ellen Fischer filed the suit in the Delaware Chancery Court.

# Infectious diseases

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

### Mosquito- borne diseases: dengue, chikungunya and malaria

* 1. The number of people contracting dengue in Singapore this year had passed the five figure mark by 17 June with 10,258 cases diagnosed. There was hope then that the rate of new infection had plateaued.
	2. Thailand’s health ministry predicted the country would see at least 100,000 dengue cases and more than 100 deaths this year, a three-fold increase from 2012.
	3. In early June, health authorities said unseasonal wet weather may be prolonging the dengue outbreak in Cairns. By 26 June there had been 170 cases in the Cairns region.
	4. NanoViricides filed an Orphan Drug Application to the FDA for DengueCide, a drug candidate for the treatment of [dengue](http://www.empr.com/dengue-fever-patient-information-fact-sheet/article/228513/) and dengue haemorrhagic fever.
	5. By 26 June, 11 people in Queensland had been diagnosed with Chikungunya, ten of them contracting it in Papua New Guinea and the eleventh in Indonesia. Because Queensland has mosquitoes that can transmit the disease, Tropical Public Health Services Director Dr Richard Gair said “Every import is a potential outbreak”.
	6. An Australian team says its experimental malaria vaccine protected mice against several strains of the disease. The vaccine caused existing white blood cells, or T-cells, to attack the malaria parasite inhabiting red blood cells[[34]](#footnote-34).

### Influenza: strains, spread, prevention and treatment

* 1. The World Health Organisation (WHO) has redefined what constitutes a flu pandemic to emphasise the risk it poses instead of its geographic spread. The definition is now “a period of global spread of human influenza caused by a new subtype”. The new system uses four phases -- interpandemic, alert, pandemic and transition -- to describe the spread. WHO currently considers the world is at the "alert" level when it comes to both the H5N1 and H7N1 bird flus.
	2. At 7 July, WHO had been informed of a total of 133 laboratory-confirmed cases of H7N9, including 43 deaths. Chinese researchers have warned that the virus could re-emerge later this year[[35]](#footnote-35). Some live poultry markets closed when the disease emerged have now re-opened.
	3. Chinese health officials have found co-infection of H7N9 and H3N2, and recognise co-infection as a possible source of reassortment of the virus.
	4. A study published in the journal *Radiology* shows how the H7N9 virus differs from pneumonia in the way it rapidly and progressively changes in the lungs and pulmonary connective tissues.
	5. Swiss firm Viroblock has developed a face mask incorporating technology which it claims will trap and kill over 99 per cent of H1N1 and H5N1 flu vruses and a similar percentage of aerobic human corona viruses.
	6. Vaxart took twenty days to develop a recombinant oral H7N9 vaccine which was successful in preclinical testing. Taiwan vaccine provider Adimmune’s H7N9 vaccine developed from a WHO- approved virus strain passed its Phase III clinical trial.
	7. By 2 June Australia had already seen the second-highest number of flu cases for this time of year recorded in a decade, reported Ian Barr, the deputy director of the Australian World Health Organisation Collaborating Centre for Reference and Research on Influenza. The national register of laboratory-confirmed flu cases had identified 3379 infections, compared with just over 3000 at the same time last year. Infections are being driven by the H1N1 swine flu virus.
	8. For the 2013-2014 influenza season in the US vaccines will contain two A and two B strains. The FDA has now approved Sanofi’s 4-in-1 influenza vaccine Fluzone Quadrivalent, which is approved for children 6 months and older, for adolescents and for adults. It joins two other quadrivalent vaccines already approved, GlaxoSmithKline's Fluarix Quadrivalent and AstraZeneca's [MedImmune](http://www.fiercepharma.com/tags/medimmune) vaccine. The latter two can be given to children only if they are aged at least 2 and 3 years respectively.
	9. A randomized, controlled trial examined whether double doses of oseltamivir would control viral replication faster than the standard dose in hospitalized patients, and/or improve clinical outcomes. The trial found no differences in virological or clinical outcomes[[36]](#footnote-36).
	10. Medicago has received approval from Health Canada to begin a Phase II dose-sparing clinical trial of its virus-like particle (VLP) candidate vaccine for H5N1 bird flu. Medicago is now to be acquired by Mitsubishi Tanabe Pharma, an affiliate of Philip Morris International.
	11. Studies published in the journal *Nature Genetics* in June described genetic factors affecting how ducks respond to bird flu. Ducks can catch more different strains than other animals. They survive bird flu not because they have more immune genes, but because they have specialised genes that resist the virus.
	12. WHO sent a mission to Israel following detection of wild poliovirus in sewage. It recommended surveillance in countries with contacts in Israel. A supplementary immunization campaign with oral polio vaccine will be undertaken locally.

### MERS-CoV

* 1. The Obama administration in early June designated Middle East respiratory syndrome coronavirus (MERS-CoV) a potential threat to public health and national security. This permitted fast-track approval of treatments and tests. In March, Congress had passed the Pandemic and All-Hazards Preparedness Reauthorization Act, strengthening the policies on emergency health threat designations.
	2. At the end of June, Saudi Arabia's Health Ministry announced seven further laboratory-confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and a death in a previously confirmed case. Virologists expressed concern about the possibility of transmission and geographic spread of the virus as a result of religious pilgrimages. Pilgrims were being encouraged to wear masks for the October Haj.
	3. WHO on 6 July announced it would convene an International Health Regulations (IHR) Emergency Committee on MERS-CoV as there is a lack of knowledge about the disease. At that time there had been 77 confirmed cases and 43 deaths
	4. On 12 July, the Saudi Ministry of Health announced that, in a measure to prevent the spread of MERS-CoV, the elderly and those suffering from chronic diseases would not be granted Haj visas this year, nor would they receive visas for the subsequent Umrah season.
	5. On 13 July, WHO announced that a laboratory confirmed case in the United Arab Emirates brought the global total to 82 cases.
	6. A report in the *New England Journal of Medicine* says Middle East respiratory syndrome coronavirus is readily transmitted in health care settings, and represents a serious risk to hospitals[[37]](#footnote-37).
	7. By the end of June Greffex announced it had developed a vaccine against MERS-CoV. The company’s proprietary GREVAX platform was developed with support from the US National Institutes of Health (NIH) and the US National Institute of Standards and Technology. GREVAX vaccines can be administered by injection or nasal mist.
	8. Purdue University researchers who previously created a drug to block the SARAS virus have been working with MERS-CoV.

### Other diseases: occurrence, prevention and treatment

* 1. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended approval of a new smallpox vaccine. *Imvanex* (Bavarian Nordic) is for active immunization against smallpox in adults - for primary vaccination (for individuals previously not vaccinated against smallpox) or booster vaccination. It can also be used in immunocompromised people. Unlike traditional smallpox vaccines, Imvanex is nonreplicating, which means it does not proliferate in the body, the committee notes."It is a live attenuated virus which works by inducing the immune system to produce antibodies against the smallpox virus. It will be available as a suspension for subcutaneous injection," the committee said.
	2. Legionnaire’s disease was discovered in the hot water system at Wesley Hospital, Brisbane. One patient died, another contracted the disease. Testing of hot water systems at other Queensland hospitals led to sanitization work at a number of them.
	3. In mid-June, NSW Health warned of an outbreak of mumps across the state.
	4. Hendra virus has killed unvaccinated horses on the mid north coast of New South Wales and west of Brisbane. There is no vaccine for humans. The disease is spread by flying foxes.
	5. Vical of San Diego and Astellas Pharma of Tokyo have initiated a multi-national Phase III trial of a vaccine to control cytomegalovirus. ASP0113, or TransVax, will be tested in about 500 hematopoietic cell transplant recipients.
	6. Chagas disease, endemic in Latin America, is now present in a number of countries. A recent case report from Canada, referring to the fact that Canadian Blood Services and HemaQuebec have both initiated blood donor testing for the Chagas antibody, describes an unusual “case of vertical transmission from a mother, most likely infected through blood transfusion, and detected as part of a concurrent seroprevalence study in blood donors”[[38]](#footnote-38).
	7. **Extensively drug-resistant tuberculosis in Papua New Guinea is a concern in Far North Queensland, with free movement between settlements in the Torres Strait.**
	8. An international team has identified a new anti-tuberculosis compound which it says is active not only against ordinary TB bacteria but also against non-replicating TB bacteria and even extensively drug-resistant TB strains[[39]](#footnote-39). The team was led by scientists from The Scripps Research Institute (TSRI), the Howard Hughes Medical Institute and Albert Einstein College of Medicine of Yeshiva University.
1. rEVO Biologics is an LFB Company. Its proprietary rPRO Technology platform is a scalable, transgenic, and cost-effective method of protein production. Its lead product is ATryn, is the only plasma-free antithrombin concentrate. ATryn was approved by the FDA in 2009. [↑](#footnote-ref-1)
2. *Treatment of Bleeding Episodes in Subjects with Haemophilia A With Long-Lasting Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Phase 3 A-Long Study* [↑](#footnote-ref-2)
3. *Evaluation of The Thrombin Generation Potential of a Recombinant Factor VIII Fc Fusion Protein in a Phase III Multi-National Clinical Trial* and *Evaluation of Whole Blood Clotting Activity of Recombinant Factor VIII Fc Fusion Protein by ROTEM Analysis in a Multi-Center Phase 3 Clinical Trial* [↑](#footnote-ref-3)
4. #  *Population Pharmacokinetic Analysis of Long-Lasting Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Patients with Severe Haemophilia A* and *A Platelet-Targeted Factor VIIa – XTEN Fusion Protein with Increased Circulating Half-Life and Improved Clotting Activity*

 [↑](#footnote-ref-4)
5. *Long-Lasting Recombinant Factor VIII Fc Fusion (rFVIIIFc) for Perioperative Management of Subjects with Haemophilia A in the Phase 3 A-LONG Study* [↑](#footnote-ref-5)
6. *Long-Lasting Recombinant Factor FIX Fc Fusion (rFIXFc) for Perioperative Management of Subjects with Haemophilia B in the Phase 3 B-LONG Study; Clinical Implications of Population Pharmacokinetics of rFIXFc in Routine Prophylaxis, Control of Bleeding;* and *Perioperative Management for Haemophilia B Patients; and Treatment of Bleeding Episodes in Subjects with Haemophilia B with the Long-Lasting Recombinant Factor IX Fc Fusion Protein (rFIXFc) in the Phase 3 B-LONG Study*  [↑](#footnote-ref-6)
7. #  *A Platelet-Targeted Factor VIIa – XTEN Fusion Protein with Increased Circulating Half-Life and Improved Clotting Activity*

 [↑](#footnote-ref-7)
8. #  PROTECT = PROphylaxis in haemophilia A patienTs via directly pEgylated long-aCTing rFVIII.

 [↑](#footnote-ref-8)
9. The Phase I results were published in the print edition of the journal *Blood* on April 25th, 2013. [↑](#footnote-ref-9)
10. Results of the study were published in the *New England Journal of Medicine.* [↑](#footnote-ref-10)
11. Reported at the Association for Professionals in Infection Control and Epidemiology (APIC) 2013 Annual Meeting: Abstract 9-434. Presented June 9, 2013. [↑](#footnote-ref-11)
12. "Factor VIII inhibitors: von Willebrand factor makes a difference in vitro and in vivo" by Shi Q, Kuether EL, Schroeder JA, Perry CL, Fahs SA, Cox Gill J, Montgomery RR; "A murine model to characterize the antithrombotic effect of molecules targeting human von Willebrand factor" by Navarrete AM, Casari C, Legendre P, Marx I, Hu JR, Lenting PJ, Christophe OD, Denis CV; and "Characterisation of von Willebrand factor A1 domain mutants I1416N and I1416T: correlation of clinical phenotype with flow-based platelet adhesion" by McKinnon TA, Nowak AA, Cutler J, Riddell AF, Laffan MA, Millar CM. [↑](#footnote-ref-12)
13. <http://o.canada.com/2013/07/12/blood-transfusions/> [↑](#footnote-ref-13)
14. <http://o.canada.com/2013/07/12/blood-hazards/> [↑](#footnote-ref-14)
15. Lawrence Goodnough, writing in the May 25 issue of *The Lancet* [↑](#footnote-ref-15)
16. [Lawrence T Goodnough](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Lawrence%20T+Goodnough), [Jerrold H Levy](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Jerrold%20H+Levy), [Michael F Murphy](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Michael%20F+Murphy), “Concepts of blood transfusion in adults**”,** The Lancet, [Volume 381, Issue 9880](http://www.thelancet.com/journals/lancet/issue/vol381no9880/PIIS0140-6736%2813%29X6026-X), Pages 1845 - 1854, 25 May 2013 doi:10.1016/S0140-6736(13)60650-9.  [↑](#footnote-ref-16)
17. [Ian D. Augustin](http://www.arthroplastyjournal.org/article/S0883-5403%2813%2900166-6/abstract) et al, “ Association Between Chronic Kidney Disease and Blood Transfusions for Knee and Hip Arthroplasty Surgery”, ***The Journal of Arthroplasty*,** [Volume 28, Issue 6](http://www.arthroplastyjournal.org/issues?issue_key=S0883-5403(13)X0005-1) , Pages 928-931, June 2013. [↑](#footnote-ref-17)
18. The study was published online June 17 in *Pediatrics*. [↑](#footnote-ref-18)
19. # Haider, Olofin, Wang, Spiegelman, Ezzati, and Fawzi, “Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis”, *:BMJ2013;346:f3443, published 21st June 2013*

 [↑](#footnote-ref-19)
20. See *PLOS Medicine.* [↑](#footnote-ref-20)
21. *Journal of the American Society of Nephrology*, news release, June 20, 2013 [↑](#footnote-ref-21)
22. Gallet R, Seeman A, Yamamoto M, et al. “Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences”. *Am J Cardiol*. 2013;111:1619-1624. [↑](#footnote-ref-22)
23. See the June 24 issue of *Proceedings of the National Academy of Sciences*(US) [↑](#footnote-ref-23)
24. The research was published June 16 in Nature Immunology [↑](#footnote-ref-24)
25. See “ZFP36L2 is required for self-renewal of early burst-forming unit erythroid progenitors”, *Nature*, online on June 9, 2013. [DOI: 10.1038/nature12215](http://dx.doi.org/10.1038/nature12215) [↑](#footnote-ref-25)
26. Lead author was Bevin Cohen, program director at the Center for Interdisciplinary Research to Prevent Infections at Columbia University School of Nursing. The study was published online in the *Journal of General Internal Medicine.* [↑](#footnote-ref-26)
27. **T. Takebe et al., “Vascularized and functional human liver from an iPSC-derived organ bud transplant,”** [*Nature*](http://dx.doi.org/10.1038/nature12271)**, doi:10.1038/nature12271, 2013.** [↑](#footnote-ref-27)
28. See the July 2 issue of *Biophysical Journal*, published by Cell Press. [↑](#footnote-ref-28)
29. Published in *Cancer Cell.* Senior author Stefan Offermanns, Director of the Department of Pharmacology at the Institute. [↑](#footnote-ref-29)
30. Christina J Sigurdson, K Peter R Nilsson, Simone Hornemann, Guiseppe Manco, Magdalini Polymenidou, Petra Schwartz, Mario Leclerc, Per Hammarström, Kurt Wüthrich, and Adriano Aguzzi. “Prion strain discrimination using luminescent conjugated polymers.” *Nature Methods* - 4, 1023-30 (2007). Published online: 18 November 2007; | doi:10.1038/nmeth1131 [www.nature.com/nmeth/journal/v4/n12/abs/nmeth1131.html](https://owa.nba.gov.au/owa/redir.aspx?C=8kBJ6R268Uu1h6p0B3MbI4RqUkt7TtAIe-jbCLVzCqbCCsf2MQx8jCELIkFjy-ktzzMFMLrZGBo.&URL=http%3a%2f%2fwww.nature.com%2fnmeth%2fjournal%2fv4%2fn12%2fabs%2fnmeth1131.html) [↑](#footnote-ref-30)
31. The study was published online in the journal *Blood*. [↑](#footnote-ref-31)
32. "Induction of a Hemogenic Program in Mouse Fibroblasts," was published online in *CELL STEM CELL* on June 13. [↑](#footnote-ref-32)
33. The findings were published in *Nature Nanotechnology,* April 14 2013. [↑](#footnote-ref-33)
34. *Journal of Clinical Investigation* [↑](#footnote-ref-34)
35. [Hongjie Yu](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Hongjie+Yu) et al,”Human infection with avian influenza A H7N9 virus: an assessment of clinical severity”, The Lancet, Early Online Publication, 24 June 2013 doi:10.1016/S0140-6736(13)61207-6 [↑](#footnote-ref-35)
36. [Farrar J, et al "Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomized controlled trial" BMJ 2013; DOI:10.1136/bmj.f3039.](http://www.bmj.com/content/346/bmj.f3039)

[Barr I, Hurt A "Double dose oseltamivir for severe influenza -- does it help?" BMJ 2013; DOI:10.1136/bmj.f3449.](http://www.bmj.com/content/346/bmj.f3449)

The study was funded by the US National Institute of Allergy and Infectious Diseases, the Wellcome Trust of Great Britain, and the Singapore National Medical Research Council. [↑](#footnote-ref-36)
37. Abdullah Assiri, M.D., Allison McGeer, M.D., Trish M. Perl, M.D., Connie S. Price, M.D., Abdullah A. Al Rabeeah, M.D., Derek A.T. Cummings, Ph.D., Zaki N. Alabdullatif, M.D., Maher Assad, M.D., Abdulmohsen Almulhim, M.D., Hatem Makhdoom, Ph.D., Hossam Madani, Ph.D., Rafat Alhakeem, M.D., Jaffar A. Al-Tawfiq, M.D., Matthew Cotten, Ph.D., Simon J. Watson, Ph.D., Paul Kellam, Ph.D., Alimuddin I. Zumla, M.D., and Ziad A. Memish, M.D, “Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus”. June 19, 2013DOI: 10.1056/NEJMoa1306742 [↑](#footnote-ref-37)
38. [MA Fearon,](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=MA%20Fearon&jnlKy=3&journal=3) [V Scalia,](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=%20V%20Scalia&jnlKy=3&journal=3) [M Huang,](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=%20M%20Huang&jnlKy=3&journal=3) [I Dines,](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=%20I%20Dines&jnlKy=3&journal=3) [M Ndao,](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=%20M%20Ndao&jnlKy=3&journal=3) [P Lagacé-Wiens](http://www.pulsus.com/servlet/com.pulsus.servlets.PulsusServlet?pageId=search&userAction=authSearch&searchStep=AdvSearch&searchtype=word&jnlKey=3&auth=%20P%20Lagacé-Wiens&jnlKy=3&journal=3), “A case of vertical transmission of Chagas disease contracted via blood transfusion in Canada”, *Canadian Journal of Infectious Diseases and Microbiology,* Spring 2013, Volume 24 Issue 1: 32- 34. [↑](#footnote-ref-38)
39. Their paper appeared online in June ahead of print in the *Proceedings of the National Academy of Sciences*. Senior authors of the study were Peter G. Schulz and William R.Jacobs,Jr. [↑](#footnote-ref-39)