Monitoring International Trends

**posted January 2017**

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:

* + From early 2017Biotest AG will be adding to its haemophilia portfolio a recombinant factor VIII product which will be produced using a human cell line. (Section 1)
  + Microcapsules have been developed for use in haemophilia A patients to deliver factor VIII directly to the site of a developing clot to stop bleeding. (Section 1)
  + In hereditary angioedema treatments (Section 1):
    1. Shire expects phase III study results for its investigational drug SHP643 in the second quarter of 2017.
    2. In case SHP643 disappoints in the Phase III trial, Shire is developing a subcutaneous formulation of its currently approved Cinryze, with Phase III results expected by the end of 2017.
    3. CSL will launch in 2017 its new product, Haegarda, a subcutaneous version of its currently approved Berinert.
  + Kiadis Pharma is beginning a phase I/II clinical trial with its product ATIR201 for thalassemia. (Section 1)
  + In a phase II study Acceleron Pharma’s luspatercept (ACE-536) increased haemoglobin levels, decreased liver iron concentration and improved quality of life in patients with non-transfusion-dependent beta thalassemia. (Section 1)
  + A pilot study to assess the safety and efficacy of intravenous immunoglobulin (specifically CSL Behring’s Privigen) in people with scleroderma has been recruiting participants. (Section 1)
  + The US Food and Drug Administration (FDA) approved Adynovate, an extended circulating half-life recombinant Factor VIII treatment for haemophilia A, in paediatric patients under 12 years of age and for use in surgical settings for both adult and paediatric patients. (Section 2)
  + CSL received marketing authorisation from the European Commission for Afstyla, its new treatment for haemophilia A. This was designed for greater molecular stability and longer duration of action, and can be used for all age groups. (Section 2)
  + The FDA accepted for consideration HEMA Biologic’s biologic license application for its coagulation factor VIIa, recombinant (eptacog beta activated) as a potential new treatment for haemophilia A and B patients with inhibitors. (Section 2)
  + The FDA cleared Sangamo BioSciences’ investigational new drug application for its SB-525 gene therapy program for the treatment of haemophilia A. This enables clinical development to assess the safety, tolerability and potential efficacy of the drug in adults. (Section 2)
  + Portola’s new drug application for its oral, once-daily Factor Xa inhibitor anticoagulant, betrixaban, will receive priority review by the FDA. Portola hopes to have betrixaban approved for extended-duration prophylaxis of venous thromboembolism(VTE) in acute medically ill patients with risk factors for VTE. (Section 2)
  + Portola’s marketing authorization application for betrixaban for extended-duration prophylaxis of VTE in adults with acute medical illness and risk factors for VTE was also accepted for review by the European Medicines Agency (EMA). (Section 2)
  + Yisheng Biopharma has received orphan drug designation from the FDA for its rabies vaccine, which is currently under Phase II clinical development. (Section 2)
  + The FDA granted orphan drug designation to Alexion Pharmaceuticals’ ALXN1210, a longer-acting anti-C5 antibody which is being evaluated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). (Section 2)
  + ProMetic Life Sciences has commenced the rolling submission of its biologics license application to the FDA for plasminogen for treatment of patients with plasminogen congenital deficiency. (Section 2)
  + Biogen’s global haemophilia business, spun out into a new company, Bioverativ, began trading common shares mid-January. (Section 3)
  + Biogen entered into an exclusive, global license agreement with Amunix to use its XTEN half-life extension technology in developing a recombinant Factor IX candidate. (Section 3)
  + Catalyst Biosciences entered into a definitive agreement with Wyeth, a wholly-owned subsidiary of Pfizer. Wyeth has granted Catalyst an exclusive licence to Wyeth’s proprietary rights that apply to Factor VIIa variants, CB 813a and CB 813d, to research, develop, manufacture and commercialize the products. (Section 3)
  + Geoffrey McDonough, CEO of Swedish Orphan Biovitrum (Sobi), will leave the company on 1 July 2017. Executive handover took place at Grifols on 1 January 2017. (Section 3)
  + CSL and [Momenta Pharmaceuticals](http://www.biospace.com/company_profile.aspx?CompanyId=652720) have signed a research collaboration and global licensing deal to develop and commercialize Fc multimer proteins. (Section 3)
  + RaNA Therapeutics acquired an mRNA therapy platform from Shire. (Section 3)
  + The Medibank Better Health Index has suggested that in the nine years to 2016, the number of Australians who suffer iron deficiency and anaemia rose to over 1.1 million. (Section 4)
  + At a California clinic, people concerned about aging are paying $US 8,000 for a one-off infusion of two litres of plasma from teenagers or young adults. (Section 4)
  + In the UK, a nurse who used the wrong type of blood during a transfusion and caused a patient to die was found guilty of gross negligence. (Section 4)
  + Some researchers report that transfusing red cells in their sixth week of storage (compared with their fifth) may adversely affect patient morbidity and mortality. (Section 5)
  + A study has found that iron sucrose and sodium ferric gluconate complex, the two most commonly used intravenous iron formulations in haemodialysis patients, display similar long-term safety. (Section 5)
  + Researchers at the University of North Carolina at Chapel Hill found that iron deficiency anaemia protects children against the blood-stage of *Plasmodium falciparum* malaria. (Section 5)
  + Newborns with congenital cytomegalovirus have an increased risk of developing acute lymphocytic leukaemia. (Section 6)
  + A team at [Johns Hopkins](http://www.upi.com/topic/Johns_Hopkins/) Bloomberg School of Public Health genetically modified *Aedes aegypti* mosquitoes to boost their ability to fight dengue infection. (Section 6)
  + Researchers from the University of Texas say they have developed an effective vaccine against chikungunya. (Section 7)
  + European research groups are pooling their expertise to speed up development of an effective and affordable vaccine against the Zika virus. (Section 7)
  + Outbreaks caused by different highly pathogenic avian influenza H5 subtypes have been reported in wild and domestic/ industrial birds in Europe, Asia, the Middle East, Africa and elsewhere. (Section 7)
  + On 25 December, 2016, the Chinese Centre for Disease Control and Prevention warned that avian influenza A(H7N9) warranted greater attention in the current northern hemisphere winter, because the disease in humans was developing earlier than in previous years, and cases were increasing more quickly in some districts. It is known to be spread to humans by poultry, particularly in live poultry markets, and there has always been a concern that human-to human transmission, currently a rarity, could become widespread. (Section 7)
  + By 24 January the World Health Organization (WHO) had called on all countries to monitor carefully outbreaks of avian influenza in birds and poultry and to report promptly any human cases that could signal the start of a flu pandemic. “The rapidly expanding geographical distribution of these outbreaks and the number of virus strains currently co-circulating have put WHO on high alert,” Dr Margaret Chan had told the UN agency’s executive board in Geneva, adding: “We cannot afford to miss the early signals.” (Section 7)
  + A New York veterinarian became infected with bird flu A(H7N2) transmitted from cats housed at Animal Care Centres shelters. (Section 7)**.**
  + Saidu Arabia continues to report new cases of MERS-CoV infection. By18 January 2017, Saudi Arabia had reported 1537 laboratory-confirmed cases, including 640 deaths. (Section 7)
  + An Ebola vaccine, which WHO has been developing for 15 years and which is manufactured by Merck, has been shown to be 100 per cent effective in preliminary trials, but WHO has warned that it cannot be used as a long-term preventive vaccine. (Section 7)
  + In the US, the Infectious Disease Research Institute (IDRI) announced that a fusion antigen it developed and patented is being used as part of a Chagas disease diagnostic test created by InBios and approved by the FDA. (Section 7)
  + In the US, the Centers for Disease Control and Prevention (CDC) signed a contract worth $US 911 million to stockpile Emergent BioSolutions’ anthrax vaccine, BioThrax, while the Biomedical Advanced Research and Development Authority (BARDA) is buying $US 100 million worth of the product, to be delivered to the stockpile within two years. (Section 7)
  + In South Australia, the number of reported cases of Q fever in 2016 (27) was three times the number reported five years ago. (Section 7)
  + Residents of Central Australia were warned in mid-January about the potentially deadly mud disease melioidosis following heavy wet season rains in desert regions across the Northern Territory. (Section 7)

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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.*

## Products for treating haemophilia

* 1. From early 2017 Biotest AG will be adding to its haemophilia portfolio a recombinant factor VIII product which will be produced using a human cell line. The new product is indicated for the treatment and prevention of bleeding episodes in children and adults with haemophilia A. In studies in previously treated patients, this fourth-generation recombinant clotting factor has proved to be safe, effective, and well tolerated. In specific markets (Germany, Austria, and Switzerland) Biotest will market the new factor VIII product under a cooperation agreement with Octapharma. Because the factor VIII preparation is produced from a human cell line it recreates a wild-type preparation. Unlike conventional recombinant factor VIII preparations, which are produced using hamster cells, the wild-type factor VIII shows natural human structures. Dr Thomas Becker, Senior Director Haematology of Biotest AG says that a recombinant factor VIII preparation from a human cell line has many of the advantages of a natural plasma clotting factor.
  2. At the 58th American Society of Hematology (ASH) Annual Meeting and Exposition in San Diego in December, scientists reported on advanced biomedical engineering methods they are developing to improve the delivery of treatments *within* patients. New methods can carry therapies directly to the sites where they are needed most. One such development is microcapsules for haemophilia A patients with inhibitors. Factor VIII can be delivered directly to the site of a developing clot to stop bleeding[[1]](#footnote-1). In vitro experiments show the new microcapsules act as a shield that allows the FVIII to avoid the immune system’s radar. The microcapsules hitchhike on platelets. Caroline E. Hansen[[2]](#footnote-2) said: “This is a completely new way to target delivery of a biologic drug, capitalizing on the natural functions of cells that are already in your body. We’re utilizing platelets’ natural behaviour to accomplish targeting and delivery. Because platelets are so heavily relied upon in the clot formation process, they could actually carry these microcapsules to the forming clot or the site of injury.” When the platelets join a clot they contract and the microcapsules burst open, releasing their payload of FVIII. The FVIII stimulates the formation of fibrin at the site, producing a mesh network that holds the blood clot together. Laboratory experiments found that the microcapsules resulted in 2.7 times as much fibrin formation as did a systemic FVIII infusion when immune antibodies were present. The team plans to test the microcapsules in mouse modules.

## The pipeline for hereditary angioedema

* 1. Hereditary Angioedema (HAE)[[3]](#footnote-3) has been a growth area for Shire, accounting for around $US 1.2 billion in sales in 2016 (~10% of sales). HAE treatment options focus on rapid relief during attacks and on long-term prophylaxis for patients who experience a high frequency of attacks or who undergo dental or surgical procedures, which may trigger an attack. Shire currently dominates the HAE market with the leading treatment for both acute treatment (Firazyr)[[4]](#footnote-4) and long-term prophylaxis (Cinryze)[[5]](#footnote-5).
  2. In November 2015 Shire acquired Dyax, making an upfront cash payment of $US 5.9 billion. A further $US 646 billion was linked to the pipeline development of Dyax's lead asset, DX-2930, now known as SHP643. The phase 1b trial results in 2015 (that triggered the purchase) showed (in 37 patients):
     1. an HAE attack rate of zero in the 300mg group and 0.045 attacks per week in the 400 mg group, compared with 0.37 attacks per week in the placebo group.
     2. no safety signal in treatment-emergent adverse events, clinical laboratory results, vital signs, or electrocardiograms.
     3. subcutaneous injection was well tolerated.
     4. The added advantage of potential fortnightly or monthly dosing (versus twice weekly infusion for Cinryze).
  3. Phase III study results are expected in the second quarter of 2017. If they match the strong results showed in earlier trials, this could protect Shire’s leading position in HAE from potential competition coming in 2017/2018 from new agents (see below) and from potential generic competition for Firazyr from 2019, given that SHP643 has regulatory exclusivity beyond 2030.
  4. There are competitors who are developing new treatments for HAE. Biocryst has been trialling an oral drug, Avoralstat, and a second compound, BCX7353. Neither has yet emerged as serious competition to Shire. CSL, on the other hand, will launch in 2017 a subcutaneous version of Berinert. CSL's Haegarda showed a 95 per cent reduction in HAE attacks (P<0.001) at the highest dose (60 IU/kg twice per week) while Cinryze (1000 IU) showed a c50% response rate. However, the Haegarda injection is considered painful and injection site reactions with the CSL sub cutaneous formulation were relatively high (almost one-third of patients).
  5. Shire is also developing a subcutaneous formulation of Cinryze, with Phase III results expected by the end of 2017, in case SHP643 disappoints in the Phase III trial.

## Products for thalassemia patients

* 1. Amsterdam company Kiadis Pharma, which is developing T-cell immunotherapy treatments for blood cancers and inherited blood disorders, has obtained regulatory approval from the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA), as well as approval from the Ethics Committees of the Royal Manchester Children’s Hospital and the Birmingham Children’s Hospital, to start a Phase I/II clinical trial with its product ATIR201 for thalassemia[[6]](#footnote-6). This new trial will study the safety and feasibility of using ATIR201 in paediatric and adult patients suffering from beta-thalassemia major, the most severe form of the disease. The company hopes to expand the trial into Germany. Up to ten patients will be enrolled and Kiadis expects to announce the first safety and efficacy results in the second half of 2017.
  2. The American Society for Hematology (ASH) annual meeting in December was told that Acceleron Pharma’s luspatercept (ACE-536) increased haemoglobin levels, decreased liver iron concentration and improved quality of life in patients with non-transfusion-dependent beta thalassemia. Results of an ongoing phase II study were also reported to show that luspatercept decreased the red blood cell transfusion requirement in patients with transfusion-dependent beta thalassemia[[7]](#footnote-7). Antonio C. Piga, of the University of Turin, said: “There are over 200 mutations in beta-thalassemia, but the common point is ineffective erythropoiesis. Anaemia or haemolysis and iron overload are consequences of this complication, but we have treatment of these with red blood cell transfusion and iron chelation by which we can counterbalance some of these effects. But, we don’t have anything specific, so in theory a drug that can address ineffective erythropoiesis could eventually modify a lot of the severity of beta-thalassemia”. Luspatercept is a modified activin receptor type IIB fusion protein that promotes late-stage erythroid differentiation. It reportedly demonstrated the ability to correct the effects of ineffective erythropoiesis in a phase I study in healthy volunteers.
  3. Cerus’ SPARC trial (A Randomized Controlled Study to Evaluate Efficacy and Safety of INTERCEPT Treated Red Blood Cells in Subjects with Thalassemia Major Requiring Chronic RBC Transfusion[[8]](#footnote-8)) reached its enrolment target of at least 70 patients. Richard Benjamin, Cerus' chief medical officer, says the SPARC study is being conducted in transfusion-dependent thalassemia major patients, who because of their need for blood transfusions have an ‘elevated lifetime risk for exposure to existing and emerging pathogens”. Cerus plans to provide in March an update on timing of its submission for European approval of its Intercept blood system for red blood cells. The company has already reported positive results from a European phase III acute clinical trial in 2015. Cerus has also been in dialogue with the US Food & Drug Administration (FDA) regarding a protocol design for a Phase III pivotal red blood cell study to be conducted in the US.

## Other products

* 1. Akari Therapeutics has been engaged in a Phase II clinical program to provide Coversin to patients with the haemolytic disorder paroxysmal nocturnal haemoglobinuria who are resistant to Soliris. One patient on this protocol for nine months has exhibited consistent suppression of haemolysis[[9]](#footnote-9).
  2. A pilot study[[10]](#footnote-10) to assess the safety and efficacy of intravenous immunoglobulin (specifically CSL Behring’s Privigen) in people with scleroderma has been recruiting participants at Georgetown and Johns Hopkins university hospitals. The placebo-controlled and randomized (3:1) trial, to run for one full year, will study the effects of IVIg on the skin of about two dozen scleroderma patients. Investigators hope this treatment will improve disease outcomes, including skin, muscle, joint, gastrointestinal and lung involvement. One of its inclusion criteria is the failure to respond to standard care over the four months prior to the trial’s start so any observed improvement will be assumed to be due to IVIg. However, larger controlled trials will be needed to demonstrate IVIg’s effectiveness conclusively.

# Regulatory

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

* 1. The FDA approved Shire’s Adynovate[[11]](#footnote-11) [antihemophilic factor (recombinant), pegylated], an extended circulating half-life recombinant Factor VIII (rFVIII) treatment for haemophilia A, in paediatric patients under 12 years of age[[12]](#footnote-12). It also approved Adynovate for use in surgical settings for both adult and paediatric patients[[13]](#footnote-13). Adynovate was first approved by the FDA in November 2015. It provides prophylaxis with twice-weekly dosing.
  2. CSL has received marketing authorisation from the European Commission for its new treatment for haemophilia A, Afstyla, which was designed for greater molecular stability and longer duration of action, and can be used for all age groups.
  3. **The FDA cleared** Sangamo BioSciences’ investigational new drug application (IND) for its SB-525 gene therapy program for the treatment of haemophilia A. This enables clinical development to assess the safety, tolerability and potential efficacy of the drug in adults. Sandy Macrae, CEO of Sangamo, said: "Based on non-human primate studies, SB-525 has demonstrated the potential to be the best-in-class treatment for Hemophilia A." Sangamo is also evaluating SB-FIX, an in vivo genome editing therapy for haemophilia B, in a Phase I/II clinical trial, with sites currently screening patients for the study.
  4. HEMA Biologics announced that the FDA had accepted for consideration the biological licence application (BLA) for its coagulation factor VIIa, recombinant (eptacog beta activated), a potential new treatment for haemophilia A and B patients with inhibitors[[14]](#footnote-14). The BLA was submitted by LFB, SA which manufactures Hema products. If the product is approved by the FDA, HEMA Biologics will have full commercialization rights for North America. The product has not yet received commercial approval from any other regulatory authority.
  5. Portola’s new drug application for its oral, once-daily Factor Xa inhibitor anticoagulant, betrixaban, will receive priority review by the FDA[[15]](#footnote-15). Portola hopes to have betrixaban approved for extended-duration prophylaxis of venous thromboembolism (VTE) in acute medically ill patients with risk factors for VTE.
  6. Portola’s marketing authorization application for betrixaban for extended-duration prophylaxis of VTE in adults with acute medical illness and risk factors for VTE was accepted for review by the European Medicines Agency (EMA)[[16]](#footnote-16).
  7. Yisheng Biopharma[[17]](#footnote-17) has received orphan drug designation[[18]](#footnote-18) from the FDA for its Pika rabies vaccine, which is currently under Phase II clinical development.
  8. The FDA granted orphan drug designation (ODD) to Alexion Pharmaceuticals’ ALXN1210, a longer-acting anti-C5 antibody which is being evaluated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)[[19]](#footnote-19). PNH is a debilitating, ultra-rare, life-threatening blood disorder in which uncontrolled activation of complement, a component of the immune system, results in haemolysis (destruction of a patient’s red blood cells). Martin Mackay, Executive Vice President and Global Head of R&D at Alexion, said: “Data from our ongoing clinical studies have shown rapid, complete, and sustained complement inhibition in treated patients, and we look forward to continuing to evaluate this highly innovative molecule in our Phase III trial of ALXN1210 administered every eight weeks[[20]](#footnote-20)”.
  9. ProMetic Life Scienceshas commenced the rolling submission of its biologics license application (BLA) to the FDA for plasminogen for treatment of patients with plasminogen congenital deficiency[[21]](#footnote-21). ProMetic's plasminogen was granted Orphan Drug and Fast Track Designations by the FDA. The Fast Track designation allows sections of the regulatory application to be submitted and reviewed on an ongoing basis[[22]](#footnote-22). Pierre Laurin, president and CEO of ProMetic, says the company is “on target for an expected commercial launch of plasminogen in the US in 2017."

# 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. Biogen’s global haemophilia business, spun out into a new company, Bioverativ, began trading common shares mid-January on the NASDAQ Global Select Market[[23]](#footnote-23). Biogen said Bioverativ will be an independent, publicly held biotech focused on R&D and commercialization of new therapies designed to address areas of serious unmet need in haemophilia and other rare blood disorders. The spinoff is expected to be completed on 1 February. Biogen’s board in December agreed to give Biogen shareholders one share of the new company’s stock for every two shares of Biogen held as at close of business on 17 January. During the first three quarters of 2016, haemophilia treatments accounted for over 7 per cent of Biogen’s total $US 8.577 billion in revenue. The haemophilia A treatment Eloctate and the haemophilia B drug Alprolix combined totalled $US 605 million in sales compared with $US 554.2 million in sales for the whole of 2015. Bioverativ plans to progress a pipeline of preclinical prospects led by haemophilia A candidate BIVV 001[[24]](#footnote-24) (formerly Biogen’s BIIB073), a once-weekly or less frequent treatment that is expected to enter clinical phases in 2017[[25]](#footnote-25).
  2. Biogen entered into an exclusive, global license agreement with California-based Amunix Operating., to incorporate Amunix XTEN half-life extension technology in developing a recombinant Factor IX candidate. The agreement is part of Biogen’s haemophilia business, Bioverativ, an independent, publicly-traded company from 1 February 2017.
  3. Geoffrey McDonough, CEO of Swedish Orphan Biovitrum (Sobi), will leave the company on 1 July 2017. Håkan Björklund, Chairman of the Board of Sobi, said: “Given the increasing demand and focus of our business in Europe, the Board has decided that Sobi needs more continuous presence in Stockholm than Geoffrey can sustain given his current location in Boston.”
  4. Executive handover occurred at Grifols on 1 January 2017 when Victor Grifols Roura was succeeded by his brother, Raimon Grifols, and his son, Víctor Grifols Deu, who became joint and several chief executive officers of the company. Víctor Grifols continues as non-executive chairman of the board of directors.
  5. bluebird bio Inc has contracted apceth Biopharma GmbH to make its candidate ALD cell therapy Lenti-D[[26]](#footnote-26) and its thalassemia treatment LentiGlobin[[27]](#footnote-27) for the European market at its GMP-certified production facility in Ottobrunn near Munich. Last June bluebird contracted Swiss supplier Lonza to produce the therapies at its cell and gene therapy plant in Pearland, Texas.
  6. Fresenius Kabi has negotiated a 5-year exclusive distribution deal with [Terumo Cardiovascular Group](http://www.massdevice.com/tag/terumo/) to launch Fresenius’ CATSmart auto transfusion system in the US. Auto transfusion systems re-infuse a patient’s own blood lost during surgery. The CATSmart system features continuous-flow technology, three wash programs, an auto-start function and sensor for quick set up and automatic processing.
  7. On December 8, 2016, Catalyst Biosciences entered into a definitive agreement with Wyeth, a wholly-owned subsidiary of Pfizer[[28]](#footnote-28). Wyeth has granted Catalyst an exclusive licence to Wyeth’s proprietary rights that apply to Factor VIIa variants, CB 813a and CB 813d, to research, develop, manufacture and commercialize the products. Wyeth has also transferred and will transfer to the company documentation related to the development, manufacturing and testing of the products, including the Investigational New Drug application. Catalyst agreed to make contingent cash payments to Wyeth in an aggregate amount up to $US 17.5 million, payable upon the achievement of milestones which are clinical, regulatory and commercial in nature. If either product reaches market, Wyeth is also to receive a single-digit royalty on net product sales on a country-by-country basis for a predefined royalty term.
  8. CSL Limited and [Momenta Pharmaceuticals](http://www.biospace.com/company_profile.aspx?CompanyId=652720) havesigned a $US 600 million research collaboration and global licensing deal. They plan to develop and commercialize Fc multimer proteins, including Momenta’s M230[[29]](#footnote-29). M230 is a selective immunomodulator of Fc receptors, and is projected to start in the clinic this year. Craig Wheeler, Momenta’s President and CEO said: “This collaboration and license agreement with CSL validates our belief that M230 is an exciting recombinant product candidate for potential use in autoimmune indications. It was developed using our proprietary Fc biology platform and understanding of how intravenous immunoglobulin (IVIg) works in autoimmune diseases. As the global leader in immunoglobulin therapy, CSL is the ideal development and commercialization partner for us in Fc biology given their expertise in developing plasma-derived medicines and focus on creating disruptive recombination products in the autoimmune space.” Paul Perreault, CEO and managing director of CSL said M230 “offers CSL the potential to further grow and expand our long-term global leadership in helping those patients with autoimmune diseases that are treated with immunoglobulins.”
  9. RaNA Therapeutics acquired the MRT platform, an mRNA therapy platform, from Shire. Shire received an equity stake in RaNA and is eligible for future milestones and royalties on products developed with the technology. The MRT employees from Shire, focussed on the development of this technology since 2008, joined RaNA. Ron Renaud, CEO of RaNA Therapeutics, said: “This acquisition results in the most comprehensive RNA-based therapeutic approach in the industry and significantly expands RaNA’s ability to correct a wide range of disease genotypes regardless of mutation and access new targets not currently addressable by existing modalities.”
  10. When Aptevo, was spun off from Emergent BioSolutions[[30]](#footnote-30) one of the drugs that it took with it was Ixinity, which Emergent had picked up in 2013 with its $US 222 million acquisition of Winnipeg-based Cangene. Aptevo has faced manufacturing issues that interrupted production of Ixinity, its recombinant factor IX treatment for haemophilia B, but says that these have been solved and Ixinity should be back on the market early in the second quarter.

# 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. Australia’s Medibank Better Health Index, a quarterly survey based on interviews with about one thousand people each week, has suggested that in the nine years to 2016, the number of people nationally who suffer iron deficiency and anaemia rose by almost 250,000, to just over 1.1 million. Medibank's chief medical officer Dr Linda Swan said young women aged 18 to 30 are most commonly affected. The index showed Australians with a lack of iron and anaemia were more likely to have exhibited signs of lowered immunity, with 62.2 per cent affected by the common cold in the previous year compared with 46.8 per cent in the general population. The figures for flu were 27.4 per cent and 20.1 per cent respectively.
  2. About 3,000 Scots were infected with hepatitis C and HIV through NHS blood products in the 1970s through to the early 90s. Following the Penrose Inquiry, the Scottish government has provided extra financial support[[31]](#footnote-31).
  3. At a private clinic in Monterey, California, a startup company called Ambrosia is charging people who are concerned about aging a fee of $US 8,000 for a one-off infusion of two litres of plasma from teenagers or young adults. Entrepreneur Jesse Karmazin says that within a month, most participants “see improvements”[[32]](#footnote-32).
  4. In the UK, a nurse who used the wrong type of blood during a transfusion and caused a patient to die was found guilty of gross negligence. who used the wrong type of blood during a transfusion and caused a patient to die was found guilty of gross negligence
  5. In Vietnam, a technique for freezing red blood cells with glycerol at 80 degrees Celsius for 10 years has been awarded the Kova Prize in the category of Creative Ideas for Applied Science. The researchers were doctors from the HCM City Blood Transfusion and Haematology Hospital. Dr Phu Chinh Dung, the hospital’s head, said: “The freezing technique for longer blood storing is useful for patients who have rare blood types and need blood in an emergency”

# Safety and patient blood management

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

## Appropriate Transfusion

* 1. The November-December posting of this bulletin reported that the AABB (formerly the American Association of Blood Banks) had issued updated guidelines for red blood cell transfusion thresholds and optimal storage time[[33]](#footnote-33). Based on evidence from 13 randomized controlled trials, AABB recommended that standard issue red blood cells should continue to be transfused since fresher red blood cells (those stored for fewer than ten days) do not improve clinical outcomes. However, a question was raised about blood in its sixth week of storage[[34]](#footnote-34).
  2. The November-December bulletin also reported that McMaster University researchers had led a large international study showing that “fresher” blood is not necessarily better for transfusion than blood which has been stored for a longer period within regulatory limits[[35]](#footnote-35). It reported a comment from a co-principal investigator of the study that “because there are biochemical, structural and functional changes in the blood during storage, there had been concerns about the use of 'older' blood. This study reassures us that aging is not bad.” That reassurance was qualified by a significant comment: “although further research is needed to evaluate whether red blood cells stored during the last week of storage (35-42 days) are associated with increased mortality”.
  3. Another study[[36]](#footnote-36) has found that red cells stored longer than five weeks may be harmful, increasing patients’ risks of mortality and morbidity. Researchers transfused 60 healthy adult volunteers with one unit of autologous, leukoreduced, packed red blood cells stored 1, 2, 3, 4, 5 or 6 weeks (n=10 per group). They found that red blood cells stored for progressively longer were associated with increased extravascular haemolysis, decreased cell recovery, and increased hepcidin levels. Circulating non transferrin-bound iron was identified in one in ten of the volunteers given red blood cells stored for 5 weeks, compared with seven in nine volunteers who received blood stored for six weeks. The researchers concluded that this could cause patients to be more likely to succumb to pathogenic infections or experience other adverse events.
  4. A study conducted in Sweden and Denmark by [Märit Halmin,](http://ki.se/en/people/mariha2) of the Karolinska Institute in Stockholm, and colleagues[[37]](#footnote-37) found that mortality was not increased in patients receiving red blood cells that had been in storage for 30 to 42 days compared with those transfused with blood stored for 10 to 19 days.
     1. Philip C. Spinella[[38]](#footnote-38) was amongst those sceptical of the finding: "It is interesting that even for patients who were transfused six or more units of RBCs of >35 days of storage that they did not find an association with mortality. This contradicts data that was just presented[[39]](#footnote-39) at the American Society of Hematology" meeting earlier this month. This data [from ASH study] is of higher quality since it is from a prospectively designed randomized controlled trial where the severity of illness was similar between the two study groups".
     2. In the Scandinavian study, 854,862 adult patients between 15 and 90 years of age and registered in the database SCANDAT2 were followed after receiving transfusions from 2003 to 2012. Relative and absolute risks for death in 30 days or 1 year after the first transfusion were assessed in relation to length of blood storage. Halmin told MedPage Today: "The strengths of this study are that we could include so many transfusions, all kinds of patient groups, and a broad population rather than a specific one. This was not a randomized trial, and as such it was important to be really sure that we were not introducing any kind of bias with the storage time; we were very careful not to confound our results in any way."
     3. Risk was measured using three independent analytic methods[[40]](#footnote-40): Halmin and colleagues explained that this was intended to limit confounding factors, bringing greater consensus on red blood cell storage length instead of presenting the disparate results of earlier studies[[41]](#footnote-41).
     4. The discrete exposure group approach grouped all transfusions into episodes with storage categories as follows: 0 to 9, 10 to 19, 20 to 29, or 30 to 42 days, as well as a mixed group of patients who had received RBC units from more than one storage time category. This methodology was seen as similar to two earlier studies[[42]](#footnote-42). The Scandinavian researchers acknowledged that, although grouping transfusion recipients in this way ensured no overlap occurred between groups, it put a significant number of recipients into the mixed category. The probability that a patient received units of only one storage duration decreased with each additional transfusion, so it was likely the most severely ill patients were in the mixed category. The researchers said the time-dependent analysis served as a check on this.
     5. The researchers were aware that mean storage time of blood is dependent on patient blood type. The Instrumental Variable Approach compared mortality in patients with blood group A- and A+, as well as O- and O+, among whom storage time differences were especially large. They took the view that by comparing patients using a genetic factor strongly associated with red blood cell storage but not associated with mortality, they had rendered their findings unlikely to be the result of clinically relevant residual confounding.
     6. Halmin said: "Using these three different approaches and reaching the same results is very robust. These results should lead to a consensus on the length of storage for transfused RBCs and the absence of association with patient mortality".
     7. Spinella did not agree: "While the SCANDAT2 database is very impressive, it does not allow for adjusting for severity of illness. This is essential for the development of accurate regression models that need to adjust for important confounders. The lack of adjusting for severity of illness makes their results very difficult to interpret since the severity of illness can vary substantially within an illness category." He also commented that the study suffered through the lack of reporting on the strength of regression models, which would have given the reader an estimate of the accuracy of those models.

## Treating anaemia

* 1. A study[[43]](#footnote-43) has found that iron sucrose and sodium ferric gluconate complex, the two most commonly used intravenous iron formulations in haemodialysis patients, display similar long-term safety[[44]](#footnote-44).
  2. Researchers at the University of North Carolina at Chapel Hill found that iron deficiency anaemia protects children against the blood-stage of *Plasmodium falciparum* malaria and treating anaemia with iron supplementation removes this protective effect[[45]](#footnote-45).

## Other

* 1. Women giving birth beyond an advanced medical context frequently die from post-partum haemorrhaging. University of British Columbia researcher Dr Christian Kastrup is hoping to reduce the incidence of that by developing “self-propelling treatments” that travel against the flow of blood and act at the source of the bleeding. He says: “There are lots of drugs out there that help to create blood clots, but severe internal bleeding tends to push those agents out with the flow of blood. We’ve been developing different products to solve this problem. For example, we’ve created a gauze that could be put near the affected area that has an agent on it that would bubble and fizz like an antacid tablet, and propel the clotting mechanism to the source of the bleeding.” His team at the University’s Michael Smith Laboratories are testing the feasibility and safety of their ideas and working towards a clinical trial.

# Research (not elsewhere included)

*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. A new analysis[[46]](#footnote-46) found that newborns with congenital cytomegalovirus have an increased risk of developing acute lymphocytic leukemia. The US study found that the risk is even greater in Hispanic children infected perinatally with CMV.
  2. Scientists from the Harvard Medical School reported[[47]](#footnote-47) that a section of a protein in *Clostridium botulinum*, the microbe that causes botulism, can behave like a prion when it is inserted into yeast and *Escherichia coli* bacteria. Previously, prions had been observed only in animals, plants and fungi.

# 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, Zika virus and the tick-borne babesiosis and Lyme disease).*

## Mosquito-borne diseases

* 1. A team at [Johns Hopkins](http://www.upi.com/topic/Johns_Hopkins/) Bloomberg School of Public Health in Baltimore genetically modified *Aedes aegypti* mosquitoes to boost their natural ability to fight dengue infection. Study leader George Dimopoulos, a professor of molecular microbiology and immunology, says: "If you can replace a natural population of dengue-transmitting mosquitoes with genetically modified ones that are resistant to virus, you can stop disease transmission. This is a first step toward that goal." The genetic modifications, while significantly increasing the mosquitoes' resistance to dengue, did not increase the mosquitoes' resistance to the Zika or chikungunya viruses[[48]](#footnote-48).
  2. Researchers from the University of Texas hope they have developed an effective vaccine against chikungunya[[49]](#footnote-49). Instead of using live-attenuated or inactivated chikungunya viruses, they edited a mosquito virus to create a hybrid structurally identical to the natural Chikungunya virus but unable to infect mammal cells. When they tested this vaccine on mice, they found that four days after a single dose, the mice were producing antibodies primed against the chikungunya virus. The antibodies lasted in the body for 290 days. They tested their vaccine on non-human primates and found that it gave them a robust immunity to the disease. “This vaccine offers efficient, safe and affordable protection against chikungunya and builds the foundation for using viruses that only infect insects to develop vaccines against other insect-borne diseases”, said lead researcher Professor Scott Weaver.
  3. European research groups are pooling their expertise to speed up development of an effective and affordable vaccine against the Zika virus. Central to the program is Themis, an Austrian company, whose proprietary technology platform is based on a well-established measles vaccine vector. The ZIKAVAX consortium also includes as co-ordinator the non-profit partnership European Vaccine Initiative, the Institut Pasteur and the Commissariat à l'énergie atomique et aux énergies alternatives (CEA), a French government-funded research organization. The consortium received 5 million EUR funding from the EU's Horizon 2020 program.

## Avian influenza

*Because of the capacity of influenza viruses for reassortment[[50]](#footnote-50), the spread of influenza strains in animals and birds is of interest as one or more strain may eventually develop the potential to cause a pandemic in humans. There are also strains which, while primarily infecting and being transmitted by animals or birds, nevertheless can infect humans, and the concern there is that human-to-human transmission might develop.*

### Avian Influenza in birds, wild and/or domestic

* 1. Recently, outbreaks caused by different highly pathogenic avian influenza (HPAI) H5 subtypes have been reported in both Europe[[51]](#footnote-51) (H5N8) and Asia[[52]](#footnote-52) (H5N1, H5N8[[53]](#footnote-53) and H5N6). H5N6 has been of particular concern, as it has caused 10 human deaths in China since April 2014[[54]](#footnote-54).
  2. In Africa, both wild and domestic birds have been dying from H5 viruses[[55]](#footnote-55), thought to have been introduced from Europe, Asia, the Middle East and North Africa by migratory birds.
  3. As usual, outbreaks of bird flu in supplying countries led to bans by customers. Saudi Arabia banned Polish and Tunisian poultry imports. Beijing banned poultry imports from more than 60 countries and said any countries with highly pathogenic cases would automatically join that list.

### Avian Influenza in humans

* 1. In a statement on its website on 25 December, 2016, the Chinese Centre for Disease Control and Prevention warned that avian influenza A(H7N9) warranted greater attention in the current northern hemisphere winter, because the disease was developing earlier than in previous years, and cases were increasing more quickly in some districts[[56]](#footnote-56).
  2. On 10 January, 2017, the Chinese National Health and Family Planning Commission released data showing that 83 additional human cases[[57]](#footnote-57) of A(H7N9), including 25 deaths, were recorded in December 2016. Among them, 58 reported exposure to poultry or poultry markets while the source of infection of the rest was under investigation[[58]](#footnote-58). “From 2013 to date, 900 human cases have been reported by the Mainland health authorities, 125 of which have been recorded from November 2016 thus far,” a spokesman said. New cases and deaths continued to be reported throughout January. In most instances there was an established connection with poultry[[59]](#footnote-59). In the first week of January, 60 of 637 environmental samples from 21 live poultry markets in 15 Guangdong province cities yielded the H7 virus.
  3. Hong Kong’s seventeenth imported human case of avian influenza A (H7N9) died[[60]](#footnote-60). In all, by 18 January, this season had seen four cases exported from the Mainland to Hong Kong and two to Macao.
  4. A New York veterinarian became infected with bird flu A(H7N2) transmitted from cats housed at Animal Care Centres shelters. The veterinarian was presumably infected while obtaining respiratory specimens from sick cats.
  5. By 24 January the World Health Organization (WHO) had called on all countries to monitor carefully outbreaks of deadly avian influenza in birds and poultry and to report promptly any human cases that could signal the start of a flu pandemic. “The rapidly expanding geographical distribution of these outbreaks and the number of virus strains currently co-circulating have put WHO on high alert,” Dr Margaret Chan had told the UN agency’s executive board in Geneva. She said the new H5N6 strain causing severe outbreaks in Asia was created by gene-swapping among four different viruses. Under the International Health Regulations, a binding legal instrument, WHO’s 194 member states are required to detect and report human cases promptly, Chan said, adding: “We cannot afford to miss the early signals.”

## MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

* 1. By18 January 2017, Saudi Arabia had reported 1537 laboratory-confirmed cases of MERS-CoV infection, including 640 deaths.

## Ebola virus disease

* 1. According to the head of the Russian federal health and epidemic watchdog Rospotrebnadzor, an Ebola vaccine developed in Russia successfully passed the second phase of clinical test.
  2. An Ebola vaccine, which WHO has been developing for 15 years and which is manufactured by Merck, uses a genetically engineered version of vesicular stomatitis virus (VSV), a cattle virus, in which Ebola genes have been inserted[[61]](#footnote-61). While this experimental Ebola vaccine has been shown to be 100 per cent effective in preliminary trials[[62]](#footnote-62), the WHO has warned that it cannot be used as a long-term preventive vaccine. The vaccine has not yet been approved and further trials are underway. Marie-Pierre Preziosi, head of the Initiative for Vaccine Research at the WHO, has warned that it is unknown how long the vaccine lasts, and with current knowledge could only be used to treat people once outbreaks are already occurring. It would be given only to the people most at-risk of being exposed to a sick person once an Ebola outbreak occurred, such as family members, health-care providers, and sanitation workers. It is also not yet known whether the experimental vaccine is safe or effective for pregnant women, children under six, or people who are HIV positive, although. studies to determine the safety and effectiveness of the vaccine for these groups are beginning. Another issue is that there are different strains of Ebola, which means that vaccines that work against one strain of Ebola may not work against another.
  3. Abivax, a French biotechnology company, and Denmark-based ExpreS2ion Biotechnology have entered into an [agreement](http://www.businesswire.com/news/home/20161212005881/en/ExpreS2ion-ABIVAX-Announce-Development-Collaboration-Ebola-Prophylaxis) to collaborate in their development of a treatment for Ebola.
  4. Scientists have found potential evidence of Ebola virus replication in the lungs of a person recovering from infection[[63]](#footnote-63), an advance that may pave the way for new treatment approaches and help better understand how the deadly virus is transmitted.

## Other diseases: occurrence, diagnosis, prevention and treatment

* 1. In the US, the Infectious Disease Research Institute (IDRI) announced that a fusion antigen it developed and patented is being used as part of a Chagas disease[[64]](#footnote-64) diagnostic test created by InBios[[65]](#footnote-65) and approved by the US Food & Drug Administration (FDA). Because Chagas disease can be transmitted by blood transfusions, blood and tissue products, national screening of the blood supply was instituted in the US in early 2007. Now, through the assay developed using IDRI technology, point of care tests will be available in the US to detect Chagas disease infection in individuals.
  2. Kalobios announced that it had received positive guidance from the FDA concerning its development plans for its drug benznidazole. This is an oral anti-parasitic medication used in the treatment of Chagas disease, which is caused by a protozoan parasite Trypanosoma cruzi. While benznidazole is used to treat Chagas disease in some other countries it is not currently approved by the FDA. If so approved, it would be eligible for a Priority Review Voucher. This means the drug would be reviewed within 6 months instead of the standard 10 months[[66]](#footnote-66).
  3. In the US, the Centers for Disease Control and Prevention (CDC) signed a contract worth $US 911 million to stockpile Emergent BioSolutions’ anthrax vaccine, BioThrax, while the Biomedical Advanced Research and Development Authority (BARDA) is buying $US 100 million worth of the product, to be delivered to the stockpile within two years. A separate award of [$US 1.6 billion](http://www.fiercepharma.com/vaccines/emergent-biosolutions-grabs-nuthrax-deal-worth-up-to-1-6b) from BARDA is for Emergent to continue developing and eventually deliver NuThrax, the company’s improved anthrax vaccine candidate. This is currently in phase III, with the company previously saying it expects FDA approval in 2018[[67]](#footnote-67).
  4. In South Australia, the number of reported cases of Q fever[[68]](#footnote-68) in 2016 (27) was three times the number reported five years ago. Although most people infected recover within several months some die of the disease. State health officials have urged people who work with animals to ensure they are vaccinated[[69]](#footnote-69).
  5. Residents of Central Australia were warned in mid-January about the potentially deadly mud disease melioidosis following heavy wet season rains in desert regions across the Northern Territory. Melioidosis is present in the soil all year round, but it comes to the surface after drenching rains. Humans contract the disease through drinking groundwater, getting dirt into cuts and abrasions, or by breathing the contaminated particles after it becomes aerosolised in windy weather. Symptoms include fever, cough and breathing difficulties to begin with, followed by severe pneumonia and sores that will not heal.

1. Funding for the study was provided by the US National Institutes of Health (NIH) and the National Science Foundation (NSF). [↑](#footnote-ref-1)
2. a graduate student in the laboratory of bioengineer and paediatric haematologist Wilbur A. Lam, of the Georgia Institute of Technology and Emory University in Atlanta [↑](#footnote-ref-2)
3. Hereditary Angioedema is a rare and potentially life-threatening genetic condition. It leads to episodes of oedema (swelling) in hands, feet, face, the intestinal wall and airway. This last is particularly dangerous as it can lead to death by asphyxiation. [↑](#footnote-ref-3)
4. In the US Firazyr is used as an acute treatment in adults 18 years of age and older. The only meaningful competitor in the US is Kalbitor (acquired over a year ago by Shire with the acquisition of Dyax), but the market has been dominated by Firazyr given its fast onset and the possibility of self-administration. [↑](#footnote-ref-4)
5. Cinryze is the only drug approved in US for the prophylaxis treatment of HAE. CSL's Beriner has comparable efficacy, but it's not approved in the US for prophylaxis. It’s used outside the US for acute treatment. [↑](#footnote-ref-5)
6. Restoring the proper production of haemoglobin through an allogeneic hematopoietic stem cell transplantation (HSCT) from a healthy half-matched family donor is used to treat this disease; but it can take the patient months to recover to near-normal blood cell levels and immune cell functions so the patient is prey to bacteria, viruses and fungi. Kiadis believes that adding ATIR201 as an immuno-therapeutic adjunctive to HSCT can provide functional, mature immune cells that can fight infections while not eliciting severe Graft-versus-Host-Disease (GVHD), thus bridging the hiatus until the immune system is re-established from stem cells in the transplanted graft. **Manfred Rüdiger, CEO of Kiadis Pharma, commented:** “It is well established that a stem-cell transplant, once engrafted, can be functional for life and so the aim of our approach is to not just ameliorate symptoms or reduce the need for transfusions, but to provide patients with an enduring, life-long cure. Our approach could provide an alternative to various gene-therapy-based strategies which, for example, may suffer from gene silencing or suboptimal expression levels over time.We believe ATIR201***™*** has the potential to make curative HSCT a viable option to many more patients suffering from inborn disorders of the blood like thalassemia.” [↑](#footnote-ref-6)
7. Piga AC, et al. Abstract #851. Presented at: ASH Annual Meeting and Exposition; 3-6 December 2016, San Diego [↑](#footnote-ref-7)
8. The SPARC study is a randomized, crossover trial. Participants receive two periods of transfusion support, one period each of conventional and Intercept-treated red blood cells over 6 - 9 months in total. The primary safety endpoint is immunogenicity. The primary efficacy endpoint is haemoglobin usage, because of its relevance to the ability of transfused red blood cells to oxygenate tissues, persist in circulation, and suppress endogenous erythropoiesis. Haemoglobin consumption is correlated with iron burden, which despite access to chelation therapy is a significant complication for patients. [↑](#footnote-ref-8)
9. Akari provided a update at the American Society of Hematology (ASH) meeting in December [↑](#footnote-ref-9)
10. <https://clinicaltrials.gov/ct2/show/NCT01785056> [↑](#footnote-ref-10)
11. Adynovate is built on the full-length Advate [antihemophilic factor (recombinant)] molecule. [↑](#footnote-ref-11)
12. The approval of Adynovate to treat children under the age of 12 was based on a prospective, uncontrolled, open-label, multi-centre Phase III trial to assess the immunogenicity, safety and efficacy of Adynovate. Adynovate met the primary endpoint with no previously treated children developing inhibitors to Adynovate. No treatment-related serious adverse events were reported. 73 percent of children had zero joint bleeds (n=48/66) while on prophylactic treatment with Adynovate. The median overall annualized bleeding rate (ABR) among paediatric patients treated with Adynovate was 2.0 (mean ABR 3.04; range 2.21-4.19), which was similar to the rates seen in the adult trial. [↑](#footnote-ref-12)
13. The approval to use Adynovate in surgical settings for both adult and paediatric patients was based on interim results of an ongoing Phase III study of perioperative control of haemostasis among 15 patients with severe haemophilia A undergoing surgical procedures. [↑](#footnote-ref-13)
14. The licence application was supported by the report, *Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX* *(PERSEPT 1)*. That study focussed on the potential treatment of episodic bleeding events in 27 patients, adult and adolescent, with inhibitors. Two initial dose regimens were tested in 468 bleeding events. Both study arms met the primary endpoint of haemostatic success (bleeding stopped). Most (85 per cent) of the bleeding events treated with the initial 225 µg/kg dose required no further therapy. The Pain VAS (Visual Analog Scale) showed significant improvement, consistent with the efficacy findings. The results were presented as an oral abstract by Dr Michael Wang, UC Denver in July 2016 at the World Federation of Hemophilia Congress held in Orlando. [↑](#footnote-ref-14)
15. Priority review shortens the FDA review period from the standard 10 months to 6 months, so a final decision should be issued by 24 June, 2017. [↑](#footnote-ref-15)
16. The EMA's Committee for Medicinal Products for Human Use will review the application during its standard 210-day review period. [↑](#footnote-ref-16)
17. headquartered in Beijing, with employees in Singapore and the US also [↑](#footnote-ref-17)
18. Orphan drug designation is granted to novel drugs and biologics which are intended for the safe and effective treatment, diagnosis or prevention of rare diseases or disorders that affect fewer than 200,000 people in the US. Incentives may include tax credits towards the cost of clinical trials and waivers of prescription drug user fees. It also carries a seven-year period of marketing exclusivity in the US after FDA approval for the marketing clearance. [↑](#footnote-ref-18)
19. The European Commission in June 2016 granted orphan drug designation to ALXN1210 for the treatment of patients with PNH. [↑](#footnote-ref-19)
20. Alexion is enrolling patients in Phase III trials of ALXN1210 in patients with PNH as well as in patients with atypical haemolytic uremic syndrome (aHUS), also caused by chronic uncontrolled complement activation. Information on these clinical trials can be found at [www.clinicaltrials.gov](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.clinicaltrials.gov&esheet=51489136&newsitemid=20170106005146&lan=en-US&anchor=www.clinicaltrials.gov&index=1&md5=11917cf667cf62076142ceff61e7ccb3) under the identifiers NCT02946463 and NCT02949128. [↑](#footnote-ref-20)
21. Plasminogen, synthesized by the liver and circulating in the blood, is important in wound healing, cell migration, tissue remodelling, angiogenesis and embryogenesis. One condition often associated with plasminogen deficiency is ligneous conjunctivitis, thick growths on the conjunctiva which, if left untreated, can lead to blindness. They may recur after surgical excision. Another condition can also affect the ears, sinuses, tracheobronchial tree, genitourinary tract, and gingiva. Tracheobronchial lesions can result in respiratory failure. Hydrocephalus has also been found in children. [↑](#footnote-ref-21)
22. The BLA will include data from ProMetic's phase II/III clinical trial. The primary endpoint successfully achieved a targeted increase in the blood plasma concentration level of plasminogen. The secondary endpoint saw a 100 per cent response rate, with all patients who had active visible lesions when enrolled in the trial reportedly finding their lesions healed within weeks of treatment. [↑](#footnote-ref-22)
23. Shares of Bioverativ began trading under the symbol BIVVV on a “when-issued” basis. With regular-way trading from 2 February, the company’s stock symbol will change to BIVV. [↑](#footnote-ref-23)
24. BIVV 001 is an engineered Factor VIII molecule with a region of Fc dimer, D’D3 domains of von Willebrand factor, and polypeptides developed through the XTEN half-life extension technology developed by Amunix and acquired by Biogen. [↑](#footnote-ref-24)
25. Other candidates in the pipeline are BIVV 002 (formerly Biogen’s BIIB085), a subcutaneous haemophilia B candidate that combines Fc dimer and XTEN technology along with R338L Padua Factor IX variant; a Factor VIIIa mimetic bispecific antibody indicated for haemophilia A and inhibitors, whose method of action is undisclosed; lentiviral gene transfer vector-based gene therapies for haemophilia A and haemophilia B, to be developed through a collaboration Biogen [launched in 2015](http://www.genengnews.com/gen-news-highlights/biogen-idec-tiget-launch-gene-therapy-collaboration/81250860?q=TIGET) with a joint venture of Italy’s Fondazione Telethon and Ospedale San Raffaele; candidates for beta thalassemia and sickle cell disease, to be generated through a collaboration that Biogen [launched in 2014](http://www.genengnews.com/gen-news-highlights/biogen-idec-sangamo-launch-up-to-320m-hemoglobinopathy-collaboratio/81249341?kwrd=Sangamo) with Sangamo BioSciences using the latter’s genome-editing technology platform; and “multiple” early-stage programs for sickle cell, whose methods of action are also undisclosed. [↑](#footnote-ref-25)
26. Lenti-D is an autologous gene therapy being developed to stabilise or prevent progression of cerebral adrenoleukodystrophy (ALD). [↑](#footnote-ref-26)
27. LentiGlobin is an autologous gene therapy being developed for people with transfusion-dependent beta-thalassemia and severe sickle cell disease. It works by inserting a functional beta-globin gene into a patient’s own hematopoietic stem cells *ex vivo*. [↑](#footnote-ref-27)
28. following the June 1, 2015 termination of the research and license agreement made on June 29, 2009 between the Company and Wyeth to collaborate on the development of novel human Factor VIIa products. [↑](#footnote-ref-28)
29. Momenta is granting CSL an exclusive, global licence to its intellectual property relating to M230. CSL is paying $ US 50 million upfront. Momenta will also be eligible for up to $US 550 million for clinical, regulatory and commercial milestones. Momenta will fund a proportion of global development and commercialization expenses in return for a share of US. profits, as well as milestones and royaltiesin other countries. Momenta also has an option to co-promote M230 and other collaboration products in the US. [↑](#footnote-ref-29)
30. Emergent, based in Gaithersburg, Maryland, develops and produces vaccines and drugs to counter biological and chemical threats and emerging infectious diseases. It decided to spin off its biosciences operations so each group could focus on its strengths. [↑](#footnote-ref-30)
31. The government reported that 330 people have received lump sums of £30,000; one-off payments of £50,000 have been made to 11 people with both HIV and hepatitis C; a total of 138 people have received annual payments of either £27,000 or £37,000, depending on the circumstances of their illness; and annual payments widows and widowers of some victims will begin in April. Bill Wright, chairman of Haemophilia Scotland said the latter payments would be made only to partners of people who died from illnesses like cirrhosis or liver cancer, which are linked to advanced "stage two" hepatitis C, and that surviving spouses of people who had less advanced "stage one" hepatitis C will not get payments, even if their deaths were "strongly suspected" to be linked to their existing condition. [↑](#footnote-ref-31)
32. Several trials are examining whether introducing young blood can treat disease. Researchers at the University of California, San Francisco, are examining the effects of transfusions in patients with a degenerative disorder called progressive supranuclear palsy. A Chinese study is investigating whether young plasma alleviates the neurologic effects of an acute stroke. In 2014, Tony Wyss-Coray a Stanford University neuroscientist, found that old mice had increased neuron growth and improved memory after about 10 infusions of blood from young mice. Funded by a Hong Kong billionaire, he founded a company, Alkahest, to trial plasma transfusions from young people to treat Alzheimer’s disease. In March 2015, Grifols invested $US 37.5 million in the company**.**  [↑](#footnote-ref-32)
33. [Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, Peterson N, Ramsey G, Rao SV, Roback JD, Shander A, Tobian AAR. “Clinical practice guidelines from the AABB:  red blood cell transfusion thresholds and storage”,*JAMA*. [e-published 12 Oct 2016].](https://www.ncbi.nlm.nih.gov/pubmed/?term=.++Clinical+practice+guidelines+from+the+AABB%3A++red+blood+cell+transfusion+thresholds+and+storage.) [↑](#footnote-ref-33)
34. FDA regulations set maximum storage for red cells as 42 days. This is not universally followed. 'The UK, Ireland, the Netherlands, for instance, have limited storage to 35 days. [↑](#footnote-ref-34)
35. [Heddle NM, Cook RJ, Arnold DM, et al. “Effect of short-term vs. long-term blood storage on mortality after transfusion”. *N Engl J Med.* [e-published 24 October 2016] DOI: 10.1056/NEJMoa1609014](https://www.ncbi.nlm.nih.gov/pubmed/27775503) [↑](#footnote-ref-35)
36. [Rapido F, Brittenham GM, Bandyopadhyay S, La Carpia F, L’Acqua C, McMahon DJ, Rebbaa A, Wojczyk BS, Netterwald J, Wang H, Schwartz J, Eisenberger A, Soffing M, Yeh R, Divgi C, Ginzburg YZ, Shaz BH, Sheth S, Francis RO, Spitalnik SL, Hod EA. “Prolonged red cell storage before transfusion increases extravascular hemolysis”. *J Clin Invest* 2017](https://www.ncbi.nlm.nih.gov/pubmed/27941245);[127(1)](https://www.jci.org/127/1):375-382. doi:[10.1172/JCI90837](https://doi.org/10.1172/JCI90837). Commentary, [Lee JS, Kim-Shapiro DB. Stored blood: how old is too old? J Clin Invest 2017.](https://www.ncbi.nlm.nih.gov/pubmed/27941251)127(1):100–102. doi:10.1172/JCI91309 [↑](#footnote-ref-36)
37. Märit Halmin, Klaus Rostgaard; Brian K. Lee, Agneta Wikman, Rut Norda, Kaspar René Nielsen; Ole B. Pedersen; Jacob Holmqvist, Henrik Hjalgrim, Gustaf Edgren*,* “Length of Storage of Red Blood Cells and Patient Survival After Blood Transfusion: A Binational Cohort Study” *Ann Intern Med.* 2016. DOI: 10.7326/M16-1415 [↑](#footnote-ref-37)
38. # of Washington University in St. Louis and co-author of a December 2015 editorial on blood storage in the *Journal of the American Medical Association:* [Philip C. Spinella,](http://jamanetwork.com/searchresults?author=Philip+C.+Spinella&q=Philip+C.+Spinella)[Jason Acker,](http://jamanetwork.com/searchresults?author=Jason+Acker&q=Jason+Acker)“Storage Duration and Other Measures of Quality of Red Blood Cells for Transfusion”, JAMA. 2015;314(23):2509-2510. doi:10.1001/jama.2015.14714

    [↑](#footnote-ref-38)
39. Johnathan P. Mack, Susan R Kahn, Alan Tinmouth, Dean Fergusson, Paul C Hébert and Jacques Lacroix “Dose-Dependent Effect of Stored Red Blood: Results of a Sub-Group Analysis of the Age of Blood Evaluation (ABLE) Trial”, *Blood* 2016 128:96 [↑](#footnote-ref-39)
40. The Discrete Exposure Group Approach, the Time-Dependent Approach, and the Instrumental Variable Approach. [↑](#footnote-ref-40)
41. Including a 2008 study on patients who had cardiovascular surgery (Colleen Gorman Koch, Liang Li, Daniel I. Sessler, Priscilla Figueroa, Gerald A. Hoeltge, Tomislav Mihaljevic, and Eugene H. Blackstone*, “*Duration of Red-Cell Storage and Complications after Cardiac Surgery”, *N Engl J Med* 2008; 358:1229-1239 [March 20, 2008](http://www.nejm.org/toc/nejm/358/12/) DOI: 10.1056/NEJMoa070403) and a small randomized trial reported in 2012 (Daryl J Kor, [Rahul Kashyap](https://www.researchgate.net/profile/Rahul_Kashyap2), [Rahul Kashyap](https://www.researchgate.net/profile/Rahul_Kashyap2), [Ognjen Gajic](https://www.researchgate.net/profile/Ognjen_Gajic) et al, “Fresh Red Blood Cell Transfusion and Short-Term Pulmonary, Immunologic, and Coagulation Status”, [*American Journal of Respiratory and Critical Care Medicine*](https://www.researchgate.net/journal/1535-4970_American_Journal_of_Respiratory_and_Critical_Care_Medicine) 185(8):842-50,·January 2012. DOI: 10.1164/rccm.201107-1332OC) · [↑](#footnote-ref-41)
42. Sartipy U, Holzmann MJ, Hjalgrim H, Edgren G. “Red Blood Cell Concentrate Storage and Survival After Cardiac Surgery”. JAMA. 2015;314(15):1641-1643. doi:10.1001/jama.2015.8690 and [Edgren G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Edgren%20G%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Kamper-Jørgensen M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kamper-J%C3%B8rgensen%20M%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Eloranta S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Eloranta%20S%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Rostgaard K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rostgaard%20K%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Custer B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Custer%20B%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Ullum H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ullum%20H%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Murphy EL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Murphy%20EL%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Busch MP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Busch%20MP%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Reilly M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Reilly%20M%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Melbye M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Melbye%20M%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Hjalgrim H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hjalgrim%20H%5BAuthor%5D&cauthor=true&cauthor_uid=20158690), [Nyrén O](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nyr%C3%A9n%20O%5BAuthor%5D&cauthor=true&cauthor_uid=20158690). “Duration of red blood cell storage and survival of transfused patients (CME)”. [*Transfusion.*](https://www.ncbi.nlm.nih.gov/pubmed/20158690) 2010 Jun;50(6):1185-95. doi: 10.1111/j.1537-2995.2010.02583x. Epub 2010 Feb 12. Erratum in *Transfusion.* 2010 Aug;50(8):1857. [↑](#footnote-ref-42)
43. [Winkelmayer WC, Goldstein BA, Mitani AA, et al. “Safety of Intravenous Iron in Hemodialysis: Longer-term Comparisons of Iron Sucrose Versus Sodium Ferric Gluconate Complex”*. Am J Kidney Dis.* doi:](http://www.ajkd.org/article/S0272-6386(16)30667-9/abstract)[10.1053/j.ajkd.2016.10.031](http://dx.doi.org/10.1053/j.ajkd.2016.10.031). [Epub ahead of print] [↑](#footnote-ref-43)
44. Wolfgang C. Winkelmayer, of Baylor College of Medicine in Houston, and colleagues, mined the US Renal Data System to identify 2015 HD facilities that used ferric gluconate more than 90 per cent of the time and the same number using iron sucrose, matched by region. Over the period 1999 to 2011, 24,911 patients received iron sucrose and 26,692 ferric gluconate. The groups were similar with respect to age, gender, race, comorbid conditions, body mass index, estimated glomerular filtration rate, average haemoglobin level, and dosages of erythropoiesis-stimulating agents. Over the follow-up period, 10,381 patients died, including 3908 from cardiovascular and 1209 from infectious causes. The team found no substantial differences in all-cause and cause-specific mortality between iron sucrose and ferric gluconate facilities. In a subset of Medicare patients, they found no significant differences in fatal and nonfatal cardiovascular events. The investigators did however find an 8 per cent reduction in the relative hazards of infectious hospitalizations in patients receiving dialysis at centres that mostly used iron sucrose rather than ferric gluconate. They suggested a future randomized trial to probe any harmful or protective effects for the iron formulations, including by dose. Central venous catheter usage and anaphylaxis rate were not assessed in the study. [↑](#footnote-ref-44)
45. The study was published in the journal *EBioMedicine*. [↑](#footnote-ref-45)
46. Stephen Starko Francis et al, “In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia”, *Blood* 2016: blood-2016-07-723148; doi: https://doi.org/10.1182/blood-2016-07-723148 [↑](#footnote-ref-46)
47. # Andy H. Yuan, Ann Hochschild, “A bacterial global regulator forms a prion”, Science 13 Jan 2017: Vol. 355, Issue 6321, pp. 198-201. DOI: 10.1126/science.aai7776

    [↑](#footnote-ref-47)
48. The research was published on 12 January in the journal *PLOS Neglected Tropical Diseases*. [↑](#footnote-ref-48)
49. esse H Erasmus, Albert J Auguste, Jason T Kaelber, Huanle Luo, Shannan L Rossi, Karla Fenton, Grace Leal, Dal Y Kim, Wah Chiu, Tian Wang, Ilya Frolov, Farooq Nasar, Scott C Weaver. “**A chikungunya fever vaccine utilizing an insect-specific virus platform”**. Nature Medicine, 2016; DOI: [10.1038/nm.4253](http://dx.doi.org/10.1038/nm.4253) [↑](#footnote-ref-49)
50. One recent study of reassortment in birds was published 12 December in Influenza and Other Respiratory Viruses. US and Bulgarian researchers undertook monthly avian flu surveillance on 63 foie gras duck farms, 52 of them during the whole study period of November 2008 to April 2012. They also tested samples from nearby resting areas for wild birds. They reported that low-pathogenicity avian flu was common on the farms. They found low-path H3, H4, and H6 strains monthly and low-path H5 sporadically in the younger ducks, and different subtypes—H1, H10, and H11—in the fattening premises (ducks 75 to 100 days old), which suggested to them different routes of introduction. Only 6 of 52 farms were free of avian flu viruses for the entire period. No sick birds were reported on any of the farms, so the flu was categorised as “silent”. The investigators noted only a 0.55 per cent prevalence of avian flu in migratory ducks and a 0.53 per cent prevalence in wild geese. They discovered no evidence of direct transmission of the virus from wild birds. They concluded: "The 'foie gras' duck farms in Bulgaria are an optimal niche where Eurasian-like [avian flu viruses] are maintained and reassorted unapparent to farmers and veterinarians." [↑](#footnote-ref-50)
51. In **mid-December**, H5N8 avian flu was continuing to spread in Hungary; France also reported another cluster of H5N8 outbreaks; there were two new outbreaks of H5N8 in the Netherlands, in wild birds and on a farm; other European countries reported H5N8 in both wild birds and poultry; in the UK almost 5000 turkeys died from H5N8 and more were culled; and Dutch officials reported H5N5 in a dead tufted duck. France found low-pathogenic H5N9 in ducks. France also had outbreaks of H5N1 and H5N2. **In mid-January**, Ireland’s Department of Agriculture confirmed H5N8 in a wild duck in Galway. Bulgaria announced H5N8 had led to the culling of 430,000 birds (mainly ducks) since mid-December. Czech veterinary authorities confirmed that 130,000 birds had been slaughtered since H5N8 was found a week earlier. In the UK, for the second time in a month, the Department for Environment, Food & Rural Affairs and Animal and Plant Health Agency (DEFRA) reported H5N8 avian influenza in a flock of turkeys at a farm in East Lindsey, Lincolnshire. [↑](#footnote-ref-51)
52. In **mid-De**cember, South Korea raised its flu alert level because of concerns over the H5N6 strain and Japan also culled poultry because of it. It had also been found in poultry in China and Vietnam. Both H5N6 and H5N8 had been appearing in waterfowl in Japan and South Korea, following regional migration patterns. In Taiwan, H7N7 and H7N8 avian flu subtypeshad been found in poultry. **In mid-January** India reported that H5N8 was continuing to spread; China reported H5N8 ina flock of domesticated black swans in Wuhan City Zoo, in Hubei Province; and North Korea admitted to an outbreak of avian influenza. Taiwan found H5N2 in ducks as well as chickens. [↑](#footnote-ref-52)
53. On 30 December China’s National Avian Influenza Reference Laboratory identified HPAI H5N8 virus in a dead swan, of which samples were received from Shanxi province. [↑](#footnote-ref-53)
54. On27 December, it was reported that China's Xinjiang region had culled more than 55,000 chickens and other poultry following an outbreak of the highly virulent H5N6 strain that has infected 16,000 birds. The fourth flu outbreak among poultry since October, it brought the total cull since then to more than 170,000 birds. The culling comes amid fears about the spread of avian flu across Asia, with South Korea battling its worst outbreak of H5N6 and Japan and India also killing flocks. [↑](#footnote-ref-54)
55. In mid-January Uganda reported that both wild and domestic birds were dying at an alarming rate from highly pathogenic avian influenza A viruses serotype H5. Since 2014 HPAI H5N1 has been reported in Africa (eg Nigeria) and more recently H5N8 has appeared in West Africa. This strain was already circulating in Asia, Europe, the Middle East and North Africa. One of the migratory birds thought to have introduced the virus is the white-winged tern which spends it summers in central and south east Europe and central Asia. At the beginning of the northern winter it migrates in large flocks to Africa, south Asia, Australia and New Zealand. It is found from sea level up to 2000 metres. [↑](#footnote-ref-55)
56. Researchers from China's Center for Disease Control and Prevention analysed the early, sudden H7N9 spike.and reported their findings in the Western Pacific Surveillance and Response Journal (WPSAR), which appears on the World Health Organization Western Pacific Region Office Web site. The team said an earlier start to the season and the steep increase in cases had raised concerns in both China and the international community. The illness onset for the first case was 28 September, and until the end of November only eight cases were reported, similar to earlier years. However, 106 cases were reported in December alone. They compared patient profiles and illness patterns to earlier seasons, finding little difference. Nearly all patients had severe pneumonia. Most had exposure to live poultry, especially live poultry markets and backyard poultry. Five patients were poultry workers. As in earlier seasons, most were from urban areas, the exception being recent patients from Zhejiang province, most of whom were from rural areas. More counties reported their first-ever H7N9 cases, compared with the past four seasons. [↑](#footnote-ref-56)
57. The 54 male and 29 female patients aged from 23 to 91 from Jiangsu (52 cases), Zhejiang (21 cases), Anhui (nine cases) and Fujian (one case) had their onset from November 22 to December 29, 2016. [↑](#footnote-ref-57)
58. The group of cases included two clusters for which human-to-human transmission can't be ruled out. The first was of two patients from the city of Suzhou in Jiangsu province: a 66-year-old man and his 39-year-old daughter. The father had live poultry market exposure. He died while his daughter developed severe pneumonia. The daughter had helped care for him in the hospital and had close contact with him without personal protection for 3 days. The second cluster was of two men, ages 66 and 62, from the city of Hefei in Anhui province who were patients in the same hospital ward in the middle of December. The older of the two men had been exposed at a live poultry market and died. The other man became severely ill. They had been on the same nephrology ward for 20 hours and had had physical contact when one helped the other get to the bathroom. [↑](#footnote-ref-58)
59. eg roast duck vendor, farmer, visitor or worker at wet markets [↑](#footnote-ref-59)
60. He had visited a wet market in Guangdong and bought a dressed chicken. [↑](#footnote-ref-60)
61. The US National Institutes of Health (NIH) says VSV can cause severe disease in livestock, but poses no threat to humans. Scientists have used the virus as an experimental vaccine delivery system against infectious diseases such as Ebola, Marburg, and Lassa fever viruses for about 10 years. [↑](#footnote-ref-61)
62. The vaccine was recently tested on nearly 12,000 people in Guinea. None of those contracted Ebola, although 23 other people in the area who were not vaccinated contracted the disease. [↑](#footnote-ref-62)
63. Scientists at the Lazzaro Spallanzani National Institute for Infectious Diseases in Italy tracked the presence of Ebola virus genetic material in the lungs and the blood of a healthcare worker during treatment and recovery. They monitored the patient's lung levels of viral RNA fragments known to be associated with Ebola replication and compared these with viral RNA levels in the patient's blood. Viral RNA and viral replication markers were present in the lungs for about five days longer than in the blood. The results suggest that Ebola virus may have been replicating in the lungs, although it is possible that the lungs simply provided a protective environment that allowed RNA to linger longer than it did in the blood. Biava M, Caglioti C, Bordi L, Castilletti C, Colavita F, Quartu S, et al. (2017) “Detection of Viral RNA in Tissues following Plasma Clearance from an Ebola Virus Infected Patient”. *PLoS Pathog* 13(1): e1006065. [DOI: 10.1371/journal.ppat.1006065](http://dx.doi.org/10.1371/journal.ppat.1006065) [↑](#footnote-ref-63)
64. Chagas disease is caused by the parasite *Trypanosoma cruzi.*  Chagas disease is a leading source of heart disease in Latin America, and although it has not been considered endemic in the US, conservative estimates are that Chagas disease-related healthcare costs are in excess of $US 118 million to the U.S. each year. Estimates suggest that between 300,000 and over one million symptomatic cases exist in the US. Given migration patterns, California, Texas, Florida and New York are the States considered to be most heavily affected. [↑](#footnote-ref-64)
65. InBios' Chagas Detect Plus Rapid Test Kit is a non-invasive  [test](https://medicalxpress.com/tags/diagnostic+test/) for use in a primary care setting by personnel trained to obtain whole [blood](https://medicalxpress.com/tags/blood/) or serum samples. The two-step rapid diagnostic test can give results in 20 minutes. In several clinical studies, the test demonstrated greater than 95 per cent sensitivity and specificity in both endemic and non-endemic populations. [↑](#footnote-ref-65)
66. An unusual feature of the Priority Review Voucher program is that vouchers are transferable. In 2016 Retrophin sold their voucher to Sanofi for $US 245 million. Abbvie bought a voucher one for $US 350 million from United Therapeutics. [↑](#footnote-ref-66)
67. Emergent’s pipeline includes another anthrax vaccine, PreviThrax, currently in phase I; VAX161C, a pandemic influenza vaccine in phase I; and UV-4B, a dengue vaccine also in phase 1. Emergent has a $US 21.9 million contract with BARDA in relation to developing a Zika vaccine. [↑](#footnote-ref-67)
68. Q Fever is caused by direct or indirect contact with the bacteria from infected animals. SA Health Chief Medical Officer Professor Paddy Phillips said the main carriers tend to be cattle, sheep or goats, but animals including cats, dogs, camels and kangaroos may also carry the infection. He said: “Q Fever is typically an occupational disease of meat workers, farmers and hobby farmers, kangaroo hunters, shearers and veterinarians. Symptoms include a fever which may last up to four weeks, severe headache, sweats and chills, chest pains when breathing, nausea and vomiting, diarrhoea and abdominal pain. Some people may develop pneumonia and inflammation of the liver, while in rare cases serious complications such as endocarditis – infection of the heart valves – can appear years after initial infection.” Professor Phillips said only about half of the infected people show signs of the illness and onset of symptoms can be sudden. But with an early diagnosis and effective antibiotic therapy, a good outcome can be expected. He said person-to- person spread of Q Fever is extremely rare and it usually occurs when people breathe in bacteria within dust, or make contact with contaminated clothing, wool, hides or straw. [↑](#footnote-ref-68)
69. Vaccination in those previously exposed to Q fever can cause a severe reaction, so the vaccine can be delivered only by trained and authorised doctors, who will first take a blood sample and skin test to see if there has been prior exposure. The State’s Chief Medical Officer said: “Vaccination is recommended for farmers, livestock transporters, workers in abattoirs, agricultural college staff and students, wildlife and zoo workers, shearers and wool sorters, veterinarians, professional dog and cat breeders, tanning and hide workers and laboratory personnel handling veterinary products.” [↑](#footnote-ref-69)