Monitoring International Trends

**posted June-July 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 put financial or other pressures on the Australian sector.

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

**Products**

* + Two international conferences provided an opportunity for companies to report research results and trial data on their products and pipeline.
    1. The International Society on Thrombosis and Haemostasis (ISTH) held its Congress in Berlin in July. Amongst the presentations:
       1. Octapharma reported recent data for Nuwiq in treating haemophilia A.
       2. Spark Therapeutics presented updated interim haemophilia B data supporting consistent and sustained response to its gene therapy.
          1. Bio Products Laboratory presented new Phase III data demonstrating that prophylactic Coagadex prevents or reduces bleeding episodes in children with moderate to severe hereditary Factor X deficiency.
    2. The European Hematology Association (EHA) met in Madrid in June. Amongst the presentations:
       1. bluebird bio announced new data from the ongoing HGB-205 clinical study evaluating its LentiGlobin gene therapy product candidate in patients with transfusion-dependent β-thalassemia and severe sickle cell disease.
       2. Amgen reported from an open-label extension study evaluating the safety and efficacy of Nplate (romiplostim) in children with immune thrombocytopenia.
  + CSL Behring says haemophilia A patients on Afstyla use less factor replacement.
  + Fitusiran, a gene therapy targeting antithrombin, has been found effective as a monthly injection in adults with haemophilia A or B.
  + Scientists using the gene-editing technique CRISPR have managed to switch on production of foetal haemoglobin. This has a very strong affinity for oxygen, and can compensates disorders where adult haemoglobin is defective.
  + Platelet Biogenesis has financing to support preclinical studies for its stem cell-based bioreactors. Clinical trials are expected to begin in around three years.

**Safety and Patient Blood Management**

* + Hong Kong confirmed the first local case of Japanese encephalitis transmitted by blood transfusion in hospital.
  + The US army launched a clinical trial for a new freeze-dried plasma product.
  + Researchers confirmed that one of the main causes of hospital-acquired anaemia is the cumulative blood loss from repeated blood tests.

**Regulatory**

* [Chugai](https://www.chugai-pharm.co.jp/english/" \t "_blank) filed a new drug application for its anti-coagulation factor IXa/X humanized bispecific monoclonal antibody emicizumab in Japan for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A with factor VIII inhibitors.”
  + The US Food and Drug Administration (FDA) received:
    1. CSL’s supplemental Biologics License Application (BLA) for Hizentra [Immune globulin subcutaneous (Human) 20% liquid] for the treatment for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.
    2. NovoNordisk’s biologics license application for Rebinyn (coagulation factor IX [recombinant)], glycoPEGylated) for on-demand treatment and control of bleeding episodes and the perioperative management of bleeding in adults and children with haemophilia B.
    3. Shire’s investigational new drug (IND) application for its recombinant factor VIII (FVIII) gene therapy candidate, SHP654, for the treatment of haemophilia A.
    4. Bioverativ’s investigational new drug (IND) application for BIVV001, a long-acting factor VIII therapy for haemophilia A, with once weekly or longer dosing.
    5. a new drug application for fostamatinib disodium(Tavalisse, Rigel Pharmaceuticals), for treating patients with chronic or persistent immune thrombocytopenia (ITP).
  + The FDA granted seven years of orphan drug exclusivity to CSL Behring’s Haegarda (C1 Esterase Inhibitor Subcutaneous [Human]), the first and only subcutaneous treatment option for prevention of hereditary angioedema (HAE) attacks. HAEGARDA was approved by the FDA on June 22, 2017 for routine prophylaxis to prevent HAE attacks in adolescent and adult patients, and marketing exclusivity will continue till June 22, 2024.
  + The European Medicines Agency (EMA):
    1. granted orphan therapy designation (to speed up the approval pathway) to Catalyst Bio’s "next-generation" Factor IX, CB 2679d.
    2. granted an orphan designation to Sangamo Therapeutics and Pfizer’s SB-525, a gene therapy candidate for haemophilia A.
    3. validated Shire’s marketing authorization application (MAA) for Veyvondi to prevent and treat bleeding episodes and peri-operative bleeding in adults with von Willebrand Disease (VWD).

**Company news**

* + CSL Limited agreed to acquire 80 per cent equity of plasma-derived therapies manufacturer Wuhan Zhong Yuan Rui De Biological Products Co. Ltd.
  + Grifols was expelled from the Pharmaceutical Research and Manufacturers of America association as its research and development spending was less than the minimum requirement for membership.
  + Korean biopharmaceutical firm [**Green Cross**](http://www.theinvestor.co.kr/companies_detail.php?q=Green%20Cross%20Corp.(006280)&mode=stock&stockcode=006280) announced it will invest US$ 92.66 million in upgrading facilities in its home country.
  + **Shire has bought global rights to develop and commercialize a bispecific antibody from Novimmune that could improve the treatment of haemophilia A.**

**Country news**

* + The UK Prime Minister ordered an inquiry into how patients died or were left permanently damaged after transfusions of government-supplied imported blood products in the 1970s and 1980s.
  + In the US, a cow in Alabama was found to be suffering from bovine spongiform encephalopathy (BSE) or “mad cow disease”.

**Infectious diseases**

* + A clinical trial of a vaccine against the chikungunya virus (developed by Themis Bioscience of Vienna) enrolled healthy adult volunteers at three sites in the US.
  + Scientists have studied the immune response to a different part of the flu virus from the one researchers currently use for seasonal flu vaccines. This part is often the same between different strains. The first human tests suggest that this new strategy can produce good protection against multiple strains of flu.
  + Sequirus has produced a cell-based influenza vaccine on a commercial scale using a virus that has been grown in cells.
  + The number of human infections with avian influenza A(H7N9) virus and the geographical distribution in the fifth epidemic wave (i.e. from 1 October 2016) has been greater than earlier waves. The World Health Organization (WHO) says this suggests that the virus is spreading, and that further intensive surveillance and control measures in both the human and animal health sectors are vital.
  + As of 2 August 2017, there had been in Saudi Arabia a total of 1680 laboratory-confirmed cases of MERS-CoV infection, including 681 deaths. Some of the cases caught the disease in Saudi hospitals; others were infected after contact with camels.
  + Merck’s Ebola vaccine rVSV-ZEBOV has been shown to elicit a quick immune response. Its protective qualities have been found to last for at least a year.
  + Ebola virus RNA has been detected in semen more than two years after resolution of acute Ebola virus infection.
  + In a Phase III trial in West Africa, Merck’s Ebola vaccine rVSV-ZEBOV showed it can elicit a quick immune response. Now a study in the US has found that the vaccine's protective qualities can last for at least a year.
  + Ebola virus RNA has been detected in semen more than two years after resolution of acute Ebola virus infection.
  + Abivax hopes to develop a hyperimmune candidate against Ebola.
  + Queensland had a busy Ross River virus season. Pentosane polysulfate sodium is being trialled to reduce the severity and duration of joint pain.
  + A number of saleyards workers in Geelong have tested positive for the presence of Q fever antibodies.

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# Products and treatments

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

## Treating bleeding disorders

* + The International Society on Thrombosis and Haemostasis (ISTH) held its 2017 Congress in Berlin in July. Octapharma sponsored two scientific symposia, one of which explored recent data and real-world experiences with Nuwiq[[1]](#footnote-1) in the treatment of haemophilia A. “Towards Life Without Limitation, Growing Experience with Nuwiq in Patients with Haemophilia A”, was held on 9th July, demonstrating the value of personal prophylaxis[[2]](#footnote-2).
  + At the ISTH Congress Spark Therapeutics presented updated interim haemophilia B data supporting consistent and sustained response to its gene therapy[[3]](#footnote-3). Data demonstrated a 99-per cent reduction in annualized infusion rate (AIR) and a 96-percent reduction in annualized bleeding rate (ABR) in 10 participants as of June 5, 2017. The company said five trial participants are now at least one-year post investigational SPK-9001 administration, including one participant out approximately 18 months; all have discontinued routine factor IX concentrate infusions and have sustained increases in factor IX activity levels[[4]](#footnote-4). A separate data analysis[[5]](#footnote-5) suggested a one-time infusion of SPK-9001 resulted in meaningful health-related quality of life improvements in several measures.
  + Also at the ISTH Congress, Bio Products Laboratory presented new Phase III data demonstrating that prophylactic Coagadex (Coagulation Factor X, Human) dosing prevents or reduces bleeding episodes in children with moderate to severe hereditary Factor X deficiency[[6]](#footnote-6).
  + Bioverativ unveiled a series of poster presentations on their pipeline of blood disorder drugs at the ISTH Congress. Tim Harris, the Executive Vice President of Research and Development at Bioverativ, said 10 poster presentations highlighted new data from the ASPIRE (Eloctate) and B-YOND (Alprolix) extension studies, including the first and only longitudinal study on joint health in the field of extended half-life therapies (Eloctate). He said these collective data demonstrate favourable outcomes in joint health with prophylactic use of Eloctate and Alprolix in severe haemophilia A or B. Harris said the company was also studying the formation and treatment of inhibitors. He mentioned preclinical programs, including BIVV002, an investigational, recombinant factor IX therapy designed for potential subcutaneous dosing once weekly or longer for people with haemophilia B. Bioverativ recently strengthened its pipeline with the acquisition of True North Therapeutics, a private, clinical-stage enterprise working in the field of rare, benign haematology[[7]](#footnote-7).
  + Fitusiran, or ALN-AT3SC, is an investigational gene therapy being developed by [Alnylam Pharmaceuticals](http://www.alnylam.com/) for the treatment of haemophilia A and B, and rare bleeding disorders. It targets the protein antithrombin at its point of production, the liver, and inhibits its activity. This is expected to increase the levels of thrombin, restoring the clotting balance and preventing bleeding events. Once-monthly injections have been found to be effective in adults with haemophilia A or B[[8]](#footnote-8).
  + Bio Marin has reported the latest data from a handful of haemophilia A patients who have received its gene therapy BMN 270, and has outlined the company’s strategy for Phase III trials. Although the product’s future is still uncertain, the company is completing a manufacturing facility for it.[[9]](#footnote-9)
  + CSL Behring says analysis has shown that haemophilia A patients on Afstyla use less factor replacement[[10]](#footnote-10).

## Treating beta thalassemia and sickle cell disease

* + Beta thalassemia and sickle cell disease are blood disorders which are targets for gene therapy. Beta thalassemia reduces the production of haemoglobin, while sickle cell disease involves atypical haemoglobin which can distort red blood cells. New medical technology from Carnegie Mellon University uses state-of-the-art peptide nucleic acid molecules, based on a synthetic nucleotide technology. The peptide nucleic acid (gamma-PNA with a polyethylene glycol group on the side chain) is delivered together with donor DNA to repair a malfunctioning gene. The repair has been successfully demonstrated in mice[[11]](#footnote-11), and the hope is this will lead to human trials.
  + A team of scientists led from the University of New South Wales has introduced a beneficial natural mutation into blood cells using the gene-editing technique CRISPR, and managed to switch on production of foetal haemoglobin. The additional foetal haemoglobin has a very strong affinity for oxygen, and picks up the work of the defective adult haemoglobin. The study was reported in the journal *Blood.* Senior author and UNSW molecular biologist Professor Merlin Crossley said: “With CRISPR gene-editing we can now precisely cut and alter single genes within our vast genome. Because this mutation already exists in nature and is benign, this ‘organic gene therapy’ approach should be effective and safe to use to treat, and possibly cure serious blood disorders. However, more research is still needed before it can be tested in people. To turn the new gene editing approach into a therapy for blood disorders, the mutation would have to be introduced into blood-forming stem cells from the patient. A large number of stem cells would have to be edited in order to repopulate the patients’ blood with genetically enhanced cells.”
  + Researchers have developed an accurate, cheap test for diagnosing sickle cell anaemia. The test is based on a lateral flow strip, and could be used where other testing methods are not accessible[[12]](#footnote-12). Further testing is required to ensure reliability under field conditions such as high temperatures.
  + Celgene Corporation and Acceleron Pharma have completed target enrolment in the MEDALIST and BELIEVE Phase III studies of luspatercept in patients with beta-thalassemia and myelodysplastic syndromes (MDS). The Companies expect to report top-line results from the clinical trials in the middle of 2018. Michael Pehl, President, Hematology and Oncology for Celgene, said: “Patients suffering from both diseases have limited treatment options to improve their underlying anaemia. We believe that luspatercept may be a potentially paradigm-changing treatment option for patients and physicians alike.” Habib Dable, President and Chief Executive Officer of Acceleron, said: “The rapid pace of patient recruitment in our global Phase III trials reflects the clear need for new MDS and beta-thalassemia therapies that can significantly reduce or eliminate dependence on red blood cell transfusions".
  + At the European Hematology Association (EHA) 22nd Congress in Madrid in June bluebird bio announced new data from the ongoing HGB-205 clinical study evaluating its LentiGlobin gene therapy product candidate in patients with transfusion-dependent β-thalassemia (TDT) and severe sickle cell disease (SCD). Primary investigator of the HGB-205 study, Marina Cavazzana[[13]](#footnote-13) said: “We are beginning to see evidence of the long-term durability of benefit from treatment with LentiGlobin, with some TDT patients even transitioning off of chelation therapy. It is exciting to see the outcome in the patient with TDT with the longest follow-up in HGB-205, who has gone from years of regular transfusions to 3.5 years without a single blood transfusion after a one-time treatment with LentiGlobin gene therapy.”

## Artificial blood and blood products

* + Harvard University spinout [Platelet BioGenesis](http://plateletbiogenesis.com/) of Boston has achieved $US 10 million in Series A financing[[14]](#footnote-14) to advance its platelet manufacturing technology. The finance will support preclinical studies for the company’s stem cell-based bioreactors. Clinical trials are expected to begin in around three years. Cofounder and Chief Business Officer Sven Karlsson said: “By manufacturing platelets, we extend shelf life, eliminate the need for bacterial and viral screening, make them more affordable and produce them on demand.” [[15]](#footnote-15)

## Other products

* + Australian biotech company [Trimph](http://www.trimph.com.au/)[[16]](#footnote-16) has completed a first-in-human trial of its bone ‘glue’ —billed as the only bone graft substitute in the world to be applied in liquid form. The intellectual property behind the bone glue technology, developed at the [University of Sydney](http://sydney.edu.au/), has been granted patents in the US and EU.  The glue is easily applied, expected to facilitate implant procedures in rural areas, and reducez both costs and recovery time.
  + Amongst the data presented by Amgen at the EHA Congress[[17]](#footnote-17) were reports from an open-label extension study evaluating the safety and efficacy of Nplate (romiplostim) in children with immune thrombocytopenia (ITP)[[18]](#footnote-18)
  + Also at the EHA Congress, Agios Pharmaceuticals reported updated data from its pyruvate kinase-R (PKR) activator demonstrating the potential for the first disease-modifying treatment for patients with pyruvate kinase (PK) deficiency. This is a rare, potentially debilitating, congenital anaemia.

# Safety and patient blood management

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

## Appropriate Transfusion

* + In Hong Kong, the Centre for Health Protection (CHP) of the Department of Health on 21 July 2017 confirmed the first local case of Japanese encephalitis (JE) transmitted by blood transfusion in hospital. The patient had received a number of blood transfusions. Residual samples of the blood transfused to the patient in the incubation period were retrieved. Two tested positive, both from the same donation. The CHP identified the blood donor who was asymptomatic all along. While JE is principally mosquito-borne, based on the nature of similar flaviviruses, blood transfusion and organ transplant are considered to be potential modes of transmission of the virus. Since most infections are mild or asymptomatic, the confirmation of transmission via blood transfusion has important implications for blood screening policy for transfusion, particularly where the virus is endemic.
  + LabCorp is offering its ADAMTS13 test to distinguish diseases associated with life-threatening, acute thrombotic microangiopathy (TMA). This is a serious syndrome in which small blood vessels develop blood clots, resulting in the mechanical destruction of red blood cells. The syndrome can arise from medical conditions and medications. Some of the conditions if not treated can result in thrombotic thrombocytopenia purpura (TTP), organ failure and/or death. Patients with TMA may therefore begin treatment for TTP while awaiting test results identifying the cause of their TMA. This involves plasma exchange, which if not clinically necessary, places them at risk, increases the cost of care, and wastes plasma. The new ADAMTS13 test is claimed to provide faster, more accurate results than other available tests, to rule in or out the diagnosis of TTP and to support the earlier institution of appropriate treatment.
  + Freeze-dried plasma offers logistical advantages on the battlefield and is used by France, Germany and other NATO countries. The US army has been working to get FDA approval and researchers recently launched a clinical trial for a new freeze-dried plasma product. Medical centres in the US currently use fresh frozen plasma, which takes up to 45 minutes to thaw. Freeze-dried plasma is a powder which has to be reconstituted. The powder can be stored at ambient temperatures, which means a freezer is not required. It has a long shelf life. Andrew Atkinson, product manager at the US Army Medical Materiel Development Activity (USAMMDA) says it “is a product that we can push farther forward on the battlefield, closer to the point of injury”. USAMMDA is collaborating with Teleflex Incorporated to create a product called RePlas. The army submitted an investigational new drug application and partnered with Cincinnati Children’s Hoxworth Blood Center to begin clinical trials. After receiving FDA permission, the Cincinnati research team began to recruit patients for a Phase I clinical trial[[19]](#footnote-19). The researchers expect to have results in the middle of 2018. Teleflex expects that if FDA approval is eventually forthcoming, the non- military market will include urban and rural trauma centres, and US embassies.

## Treating anaemia

* + Researchers at the University of Texas Southwestern Medical Center, in a study of six North Texas hospitals, found a high rate of hospital-acquired anaemia.  Dr Anil Makam[[20]](#footnote-20) said: “The two main reasons that we found for why people develop anemia in the hospital are undergoing a major surgery or being in the hospital for a long time. While it’s intuitive why people lose blood during a major surgery, it’s often underappreciated the cumulative blood loss from repeated blood tests while people are in the hospital — especially if they’re there for a long period of time.”
  + A team of researchers at Baylor College of Medicine and other institutions carried out a clinical trial that compared new and traditional treatments for iron-deficiency anaemia and determined that the traditional treatment can more effectively treat the anaemia in young children.[[21]](#footnote-21) The results appeared in [*JAMA*](http://jamanetwork.com/journals/jama/currentissue).

## Other

* + [Sulin Zhang](http://www.esm.psu.edu/department/directory-detail.aspx?q=SUZ10&LandOn=Gen), professor of [engineering science and mechanics](http://www.esm.psu.edu/) at Penn State, and colleagues[[22]](#footnote-22) have received a grant from the Penn State Institute for CyberScience (ICS) to develop a modelling platform to predict the deformability and morphological changes of diseased and aged red blood cells (RBC). Zhang said: “This project will offer key molecular insight into the principles underlying RBC deformability and provide rational guidance to the development of novel diagnostic sensors, anti-malaria therapies and new protocols for blood storage”.
  + Taiwanese scientists found a blood thinner drug based on venom from the Wagler's pit viper to be effective in mice[[23]](#footnote-23).

# Regulatory

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

* + [Chugai Pharmaceutical Co.,](https://www.chugai-pharm.co.jp/english/) announced that it had filed a new drug application for its anti-coagulation factor IXa/X humanized bispecific monoclonal antibody emicizumab (genetic recombinant, Development Code: ACE910) to the Ministry of Health, Labour and Welfare (MHLW) in Japan for the planned indication of “Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with congenital factor VIII deficiency (haemophilia A) with factor VIII inhibitors.”[[24]](#footnote-24)
  + CSL Behring announced that the FDA had accepted for review the company’s supplemental biologics license application (BLA) for Hizentra [Immune globulin subcutaneous (Human) 20% liquid] for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.
  + CSL Behring announced that the FDA had granted the Company seven years of orphan-drug exclusivity for HAEGARDA (C1 Esterase Inhibitor Subcutaneous [Human]), the first and only subcutaneous treatment option for prevention of hereditary angioedema (HAE) attacks.[[25]](#footnote-25) HAEGARDA was approved by the FDA on June 22, 2017 for routine prophylaxis to prevent HAE attacks in adolescent and adult patients, and marketing exclusivity will continue through June 22, 2024.
  + Bayer announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had issued a positive opinion[[26]](#footnote-26) on a label update regarding the use of 15 mg once daily of the oral Factor Xa inhibitor Xarelto (rivaroxaban)[[27]](#footnote-27) in combination with a P2Y12 inhibitor for the treatment of patients with non-valvular atrial fibrillation (AF) who require oral anticoagulation and undergo percutaneous coronary intervention (PCI) with stent placement. The final decision of the European Commission is expected by the end of 2017.
  + Kamada announced that it had submitted to the FDA for review a proposed pivotal Phase III protocol for its proprietary inhaled Alpha-1 Antitrypsin (AAT) therapy for the treatment of Alpha-1 Antitrypsin Deficiency (AATD).
  + **Shire PLC** announced that it has filed an investigational new drug (IND) application with the FDA, seeking approval for its recombinant factor VIII (FVIII) gene therapy candidate, SHP654, for the treatment of patients with haemophilia A. The IND was supported by data from pre-clinical and Phase I studies, which showed the potential utility of the candidate. The company presented additional data on the candidate at the ISTH Congress in Berlin. The gene therapy developed by the company treats haemophilia A by delivering a functional copy of FVIII to the liver. This in turn activates the body's immune system to generate FVIII. The company plans to initiate a global multi-center study to evaluate safety and test SHP654 doses to boost FVIII activity levels and reduce bleeding.
  + The FDA has approved the biologics license application for Rebinyn (coagulation factor IX [recombinant] glycoPEGylated, Novo Nordisk) for on-demand treatment and control of bleeding episodes and the perioperative management of bleeding in adults and children with haemophilia B. The approval follows a meeting of the agency’s Blood Products Advisory Committee in April. Rebinyn is an extended half-life factor IX molecule. Novo Nordisk expects to launch the product in the US in the first half of 2018. The FDA’s approval of Rebinyn was based on data from a Phase III clinical program that enrolled children and adults with severe or moderately severe haemophilia B. The trade name for the same product in Europe is Refixia. The European Commission has granted Novo Nordisk marketing authorisation for Refixia for the treatment of adolescents and adults with haemophilia B[[28]](#footnote-28). The authorisation covers all 28 European Union member states.
  + Catalyst Bio is working on a so-called "next-generation" Factor IX called CB 2679d, which has been shown in preclinical studies to help regulate haemostasis more potently than recombinant Factor IX. Recently, CBIO [announced](http://ir.catalystbiosciences.com/phoenix.zhtml?c=254141&p=irol-newsArticle&ID=2277614) that the EMA has granted CB 2679d orphan therapy designation, which will potentially allow for a sped-up pathway to approval. This comes before the intended initiation of Phase I/II studies in South Korea and elsewhere to evaluate the efficacy and safety of CB 2679d.
  + The FDA has accepted the new drug application for fostamatinib disodium (Tavalisse, Rigel Pharmaceuticals), an oral investigational drug candidate for treating patients with chronic or persistent immune thrombocytopenia (ITP). The application is supported by data from a Phase III clinical program that included three studies — two randomized, placebo-controlled studies and an open-label extension study. The FDA set an action date of April 17, 2018.
  + A month after FDA staff and an advisory committee endorsed Pfizer's biosimilar for Amgen's Epogen, the agency has rejected the drug for the second time. The FDA complete response letter (CRL) mentioned concerns about the same Pfizer fill-finish plant whose problems led the FDA to deny approval of a copy of Teva’s Copaxone that was to be finished there.
  + Shire announced that the EMA had validated its marketing authorization application (MAA) for Veyvondi to prevent and treat bleeding episodes and peri-operative bleeding in adults (age 18 and older) diagnosed with von Willebrand Disease (VWD)[[29]](#footnote-29), the most common inherited bleeding disorder. Currently available in the US as Vonvendi [von Willebrand factor (Recombinant)], Veyvondi is the first and only recombinant von Willebrand factor (rVWF) treatment for adults living with VWD. Veyvondi is formulated without the addition of any exogenous raw materials of human or animal origin, resulting in a product that contains only trace amounts of FVIII.
  + Kamada decided to withdraw the marketing authorization application (MAA) for its inhaled formulation of Alpha-1 Antitrypsin (AAT) in the EU. The European Medicines Agency (EMA) concluded that the data submitted was insufficient for the approval and supplementary data will be required from additional clinical study.
  + The FDA has approved Endari for patients five years of age and older with sickle cell disease, to reduce severe complications.
  + The EMA granted an orphan designation to Sangamo Therapeutics and Pfizer’s SB-525, a gene therapy candidate for haemophilia A. The FDA had already granted the therapy a Fast Track designation. SB-525 relies on a recombinant virus to deliver a human factor VIII cDNA construct and a proprietary, synthetic liver-specific promoter to the nucleus of liver cells with a single infusion. A Phase I/II trial is currently evaluating SB-525 in adults, with initial data from the study expected in late 2017 or early 2018.
  + Bioverativ has made an investigational new drug (IND) application to the FDA for BIVV001 (rFVIIIFc-VWF-XTEN), an investigational long-acting factor VIII therapy for haemophilia A patients designed for once weekly or longer dosing. Senior Vice President Rob Peters said: “BIVV001 is the first molecule of its kind to fuse four different proteins together to address the challenges of hemophilia A. We are encouraged by our extensive preclinical data which show improved pharmacokinetics that are independent of von Willebrand factor, and look forward to commencing our Phase I/IIa clinical trial later this year.”

# 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.*

* + Shareholders of Biotest AG accepted the voluntary public tender offer by the Creat Group, by fulfilling the minimum acceptance condition of 75 per cent of Biotest ordinary shares outstanding.
  + CSL Limited has agreed to acquire 80 per cent equity of plasma-derived therapies manufacturer Wuhan Zhong Yuan Rui De Biological Products Co. Ltd. (“Ruide”) from Humanwell Healthcare Group Co. Ltd. for $US 352 million. The transaction will provide CSL with a strategic presence in the Chinese domestic plasma fractionation market[[30]](#footnote-30), building on the leadership position that CSL Behring has built over the past two decades as a supplier of albumin to China. Within the Ruide joint venture, CSL will contribute capabilities across the full range of plasma products currently produced by CSL in markets outside China.
  + Spanish company Grifols generates over 60 per cent of its sales in the US. However, the PhrMA association – Pharmaceutical Research and Manufacturers of America – the main industry association in the US and one to which Grifols’ susidiary Grifols USA belonged, has decided to expel the Catalan company along with another 21 pharmaceutical firms. **The companies have not complied with the new requirements for research imposed by the PhrMA.** To be a member, **firms need to set aside at least 10 per cent of total sales to R&D,** while the average spending on research has to be at least $US 200 million a year (180 million euros) over the last three years. According to Grifols’ latest accounts, it spent only **4.9 per cent of its sales on R &D.**
  + Swedish Orphan Biovitrum (SOBI) has signed a deal with authorities in Ireland to supply Alprolix (rFIXFc) for a minimum of two years, with the opportunity to extend for up to two further years. The haemophilia B drug was [approved](https://www.thepharmaletter.com/article/sobi-and-biogen-receive-european-approval-for-alprolix-for-haemophilia-b) by European regulators in 2016.
  + Swedish Orphan Biovitrum announced that the company had made all payments and transfers of value to healthcare professionals and organisations from 2016 publicly available, including sponsorships to attend meetings, grants and donations, speaker fees, consultancy and advisory boards in accordance with the European Federation of Pharmaceutical Industries and Associations (EFPIA) Disclosure Code. The information was made available on [Sobi´s corporate web site](http://media.ne.cision.com/l/sfryrqfx/www.sobi.com/About-Sobi/Corporate-responsibility-/Transparency), starting 31 May 2017.
  + Swedish Orphan Biovitrum announced its results for the second quarter 2017. Total revenue increased 12 per cent over the second quarter, 2016.
  + Korean biopharma [**Green Cross**](http://www.theinvestor.co.kr/companies_detail.php?q=Green%20Cross%20Corp.(006280)&mode=stock&stockcode=006280) announced on 2 June it will invest $US 92.66 million in upgrading facilities in its home country. The company will make its existing plant, in Ochang, North Chungcheong Province, an integrated manufacturing facility for finished products of plasma derivatives and vaccines[[31]](#footnote-31), which account for more than half of its revenue. Construction is expected to be completed in 2019. Currently, the Ochang plant has the largest single-plant capacity in Asia for treating blood plasma (1.4 million litres).
  + On 11 July CSL Behring announced at the [Peripheral Nerve Society's annual meeting](https://www.pnsociety.com/i4a/pages/index.cfm?pageid=3277) the winners of its annual [Interlaken Leadership Awards](http://www.interlakenleadershipawards.com/). There are two 2017 recipients of this program which provides monetary grants and/or product supply for investigational use to support research focusing on the potential role of immunoglobulin therapy in the treatment of neurological/neuromuscular disorders. Dr. Maarten Titulaer, a neurologist at Erasmus University Medical Center, Rotterdam, will examine intravenous Ig (IVIG) treatment for autoimmune epilepsy with neuronal antibodies. Dr. Jean-Philippe Camdessanché from Institut NeuroMyoGène, Faculty of Medicine CHU de Saint-Etienne, will study the identification, validation, and characterization of novel auto-antigens in chronic inflammatory demyelinating polyneuropathy (CIDP).
  + **Shire has bought global rights to develop and commercialize a bispecific antibody from Novimmune that could improve the treatment of haemophilia A.**The antibody is generated through the collaboration that binds FIXa and FX coagulation factors simultaneously, and compensates for the lack of coagulation factor VIII that causes hemophilia A. Because it targets a process alternative to administering recombinant factor VIII, it may be effective in patients who have developed inhibitors to rFVIII. The antibody is currently in the preclinical stage. Shire is still trailing Roche, whose antibody emicizumab significantly reduced bleeding episodes in Phase III trials.
  + Rubius Therapeutics has raised $US 120 million to develop its novel drug-making technology which genetically engineers red blood cells so they can produce drugs for a range of diseases. Rubius has so far made and tested about 200 red cells, each producing different proteins, and plans to use them as catalysts for medicines to fight rare blood disorders such as haemophilia, cancers, enzyme deficiencies, and autoimmune and infectious diseases.

# Specific country events

* + The UK Prime Minister ordered an inquiry into how at least 2400 people in Britain died from hepatitis C and Aids-related conditions after receiving transfusions of government-supplied imported blood products in the 1970s and 1980s, and how thousands more were left with permanent damage.
  + Sex workers and gay men will now be allowed to donate blood in England and Scotland three months after having sex instead of a year, under equalities reforms announced by the Westminster government. All blood that is donated in the UK undergoes a mandatory test for HIV, Hepatitis B and C, and certain other viruses. In Northern Ireland, where health is a devolved issue, preparatory work is said to have begun to reduce the deferral period for gay men to donate blood, with a final decision awaiting approval by a Stormont minister.
  + In the US, a cow in Alabama was found to be suffering from bovine spongiform encephalopathy (BSE) or “mad cow disease”. The US Department of Agriculture said that the animal “at no time presented a risk to the food supply, or to human health in the United States”. The discovery occurred a little more than a month after American beef producers began sending beef to China after a 14-year suspension.
  + To mark World Sickle Cell Awareness Day on 19 June, the American Society of Hematology (ASH) announced the launching of an effort to develop clinical practice guidelines for management of the disease. There will be five panels of haematologists, other clinicians, people living with sickle cell disease, and experts in developing evidence-based guidelines. One panel will review the use of blood transfusions to improve red blood cell counts and mitigate complications, while another will be concerned with the only current cure for SCD: stem cell transplantation. The process will also consider new evidence available since the publication of the National Heart, Lung, and Blood Institute (NHLBI) guidelines. The new guidelines are expected to be published in 2019.

# Legal Matters

*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.*

* + Shire claimed Roche had been making **misleading statements about the new Roche haemophilia drug emicizumab – and in a court in Hamburg, Germany, Shire won a preliminary injunction blocking its rival from making such statements**[[32]](#footnote-32)**.**
  + Bioverativ launched a suit against CSL Behring in the District Court of Delaware alleging CSL had actively breached three of its patents. Bioverativ sought an injunction against CSL selling its products, and damages equivalent to three times the amount of any money the court found Bioverativ had lost from CSL's alleged breach of the patents. The legal dispute centres on CSL's new drug Idelvion, which Bioverativ says is similar to its drug Alprolix. Bioverativ says its Alprolix drug was registered with the FDA two years before CSL obtained FDA approval for Idelvion in March 2016.

# 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

* + A report in the journal *PLoS Neglected Tropical Diseases* [[33]](#footnote-33) suggested that human travellers are much more likely than stowaway mosquitoes to import illnesses like Zika, yellow fever, malaria and dengue to a new part of the world via aircraft.
  + A clinical trial of a vaccine against chikungunya virus (developed by Themis Bioscience of Vienna) enrolled healthy adult volunteers at three sites in the US. The Phase I/II trial was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.[[34]](#footnote-34) A 2014 Phase II trial of this MV-CHIKV vaccine conducted in Austria by Themis Bioscience showed that the experimental vaccine was safe and induced an immune response. It is a measles vaccine virus modified to produce chikungunya virus proteins. Other chikungunya vaccine candidates are also under investigation in different trials, including one that uses virus-like particles (VLPs) to induce an immune response in recipients. NIAID sponsored the Phase I trial of the VLP vaccine candidate; a [Phase II trial](https://www.niaid.nih.gov/news-events/nih-sponsored-clinical-trial-chikungunya-vaccine-opens) began in 2015. Indian vaccines manufacturer, Bharat Biotech began Phase I human clinical trials of an indigenously developed chikungunya vaccine to evaluate its safety, tolerability and immunogenicity.

## Influenza

* + Australian Influenza Surveillance Report and Activity Updates are published at <http://www.health.gov.au/flureport> . Global reports may be found at <http://www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/en/>
  + Scientists from the US National Institutes of Health (NIH), the US Frederick National Laboratory for Cancer Research, and the University of Melbourne studied the immune response to a different part of the flu virus from the one researchers currently use for seasonal flu vaccines. They focussed on a part of the virus that is often the same between different strains. The first human tests suggest that this new strategy can produce good protection against multiple strains of flu[[35]](#footnote-35).
  + Biondvax, having received in March a grant from the Israeli government to set up a manufacturing plant for its universal flu vaccine, was awarded a loan from the European Investment Bank which can finance its Phase III trials. A recent report in the journal *Vaccine* noted that the Biondvax vaccine, M-001, when used as primer to trivalent influenza vaccine, can protect against future flu strains. Plasma samples from elderly participants given M-001 before the seasonal flu vaccine in 2011 (during a phase III study) demonstrated improved antibodies against a flu strain in the 2014/15 season.
  + FluGen, Johnson and Johnson and Sanofi Pasteur are also working on a universal flu vaccine.
  + Sequirus, a unit of CSL, has produced a cell-based influenza vaccine on a commercial scale using a virus that has been grown in cells. Compared with the traditional method of producing flu vaccine using chicken eggs, this method offers improved process control and increased (faster) output. The company says that influenza viruses isolated and grown in cells can be a better match for influenza viruses in circulation. The Sequirus plant at Holly Springs, North Carolina, was built in partnership the US Biomedical Advanced Research and Development Authority (BARDA) to prepare for pandemic threats.

### Avian influenza

*Because of the capacity of influenza viruses for reassortment, 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 flu of various strains continues to be reported in both commercial and wild flocks around the world. Reports continue of human cases of H7N9 in mainland China, though with less frequency than during the northern hemisphere winter. Most cases have had exposure to live poultry or poultry markets.
  + The number of human infections with avian influenza A(H7N9) virus and the geographical distribution in the fifth epidemic wave (i.e. from 1 October 2016) has been greater than earlier waves. The World Health Organization (WHO) says this suggests that the virus is spreading, and that further intensive surveillance and control measures in both the human and animal health sectors are vital. In July, China began vaccinating poultry against the H7N9 virus.
  + A study reported in the Journal of Infectious Diseases showed that immunocompromised macaques were more likely to develop treatment-resistant strains of H7N9 avian flu than healthy animals, even after receiving high doses of antivirals -oseltamivir (Tamiflu)[[36]](#footnote-36).
  + In a study reported in *PLOS Pathogens[[37]](#footnote-37)*, scientists analyzed genome mutations that could occur in the H7N9 strain of avian influenza focussing on a gene that codes for the H7 type of hemagglutanin, a surface protein that allows the virus to attach to bird cells for infection. They found a number of H7 mutations which, when introduced experimentally, resulted in hemagglutanin molecules that had switched from binding bird cells to strongly binding human cells. They recommended monitoring the flu strain for these mutations in the real world.

## MERS-CoV

* + As of 2 August 2017, there had been in Saudi Arabia a total of 1680 laboratory-confirmed cases of MERS-CoV infection, including 681 deaths. Some of the cases caught the disease in Saudi hospitals; others were infected after contact with camels.

## Ebola virus disease

* + In a Phase III trial in West Africa, Merck’s Ebola vaccine rVSV-ZEBOV showed it can elicit a quick immune response. Now a study in the US has found that the vaccine's protective qualities can last for at least a year.[[38]](#footnote-38)
  + Ebola virus RNA has been detected in semen more than two years after resolution of acute Ebola virus infection[[39]](#footnote-39).
  + The Canadian Government is providing $C 5 million for the Canadian Science Centre for Human and Animal Health in Winnipeg to expand its top-level containment labs, which deal with Ebola and MERS[[40]](#footnote-40).
  + Abivax hopes to develop a hyperimmune candidate against Ebola. Bpifrance and Région Occitanie /Pyrénées-Méditerranée have agreed to provide a loan of €390,000 ($US436,820) to the company for the development of a cocktail of polyclonal antibodies.

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

* + The US National Institutes of Health (NIH) announced the development of a platform (SHERLOCK) capable of detecting small amounts of nucleic acid (DNA and RNA) sequences, which will help when it comes to detecting viral or bacterial infections within a population during infectious disease outbreaks.
  + Tulane University has two grants through the US National Institutes of Health’s National Institute of Allergy and Infectious Diseases (NIAID) in relation to Lassa fever. The first grant, worth $US 5.72 million, will support the evaluation of an antibody drug combination while the second grant, worth $US 6.32 million, will go towards designing a Lassa virus vaccine.
  + Queensland had a busy Ross River virus season. There is no vaccine, but pentosane polysulfate sodium is being trialled as a treatment to reduce the severity and duration of joint pain.
  + The City of Greater Geelong announced 25 saleyards workers had shown positive results for the presence of Q fever antibodies, out of 42 tested. The disease is transmitted from animals to humans and can cause fever, chills, headaches and muscle pain, and in some cases long-term liver and heart problems. Acute cases require treatment with antibiotics. Half the people who contract Q fever may not exhibit symptoms. The airborne bacteria that cause Q fever can survive in the environment for a long time, and can withstand disinfectants and harsh conditions. Dust and hay can carry the bacteria. The Australian Services Union alleged workers were not being vaccinated for the disease, although vaccination is considered best practice for those working with animals[[41]](#endnote-1)[[42]](#footnote-41). Abattoir workers, farmers and shearers are at the highest risk of developing the disease.
  + In New Zealand, Auckland recorded 148 cases of mumps this calendar year, up to 7 July.

1. Nuwiqis a naturally long-acting, fourth generation recombinant factor VIII protein produced in a human cell line. Octapharma says the lack of non-human epitopes makes Nuwiq an exciting prospect for reducing rates of inhibitor development. The safety and efficacy of Nuwiq has already been the subject of seven clinical trials. Nuwiq is approved for use in the treatment and prophylaxis of bleeding across all age groups of previously treated patients with haemophilia A in the EU, US, Canada, Australia, Latin America and Russia. [↑](#footnote-ref-1)
2. The most recent data, reported during the ISTH symposium, focused on using Nuwiq to treat previously untreated patients (PUPs) as well as on a pharmacokinetic (PK)-based personalised approach to optimising dosage during haemophilia treatment (NuPreviq). Presentations included “*Focus on PUPs; latest Nuwiq efficacy, safety and immunogenicity data in the NuProtect study*” (Ellis J. Neufeld); “*Nuwiq in practice: experience from a German treatment centre, the Universitätsklinikum Bonn*” (Natascha Marquardt); “*The NuPreviq Approach: Optimising PK-guided Personalised Prophylaxis with Nuwiq*”(John Pasi); and “*Nuwiq in action: an Italian multicentre experience using the NuPreviq approach in practice*”( Massimo Morfini). There were also four poster presentations focusing on Nuwiq in the scientific sessions. [↑](#footnote-ref-2)
3. The interim data were presented today by Lindsey George, a physician in the Division of Hematology at Children's Hospital of Philadelphia and investigator in the ongoing Phase 1/2 clinical trial of SPK-9001 for hemophilia B. [↑](#footnote-ref-3)
4. It was reported in December 2016 that two of the 10 participants experienced an asymptomatic, transient elevation in liver enzymes, associated with a decline in factor IX activity in one of those participants, potentially indicative of an immune response to the Spark100 vector capsid. Elevations in alanine aminotransferase (ALT) occurred several weeks post infusion, and returned to baseline with a tapered course of oral corticosteroids. Both participants continued to demonstrate stable factor IX activity levels, now 18 and 12 weeks' post-cessation of steroids, respectively.  Neither of these participants has experienced a bleed nor taken factor concentrates. [↑](#footnote-ref-4)
5. presented as a poster by Sylvia von Mackensen, senior scientist at the Institute of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Germany. [↑](#footnote-ref-5)
6. Hereditary factor X deficiency is a rare bleeding disorder. Patients often have inadequate amounts of circulating factor X. Factor X deficient patients are at risk of bleeding and are managed similarly to hemophilia patients. TEN02 ([ClinicalTrials.gov NCT01721681](https://clinicaltrials.gov/ct2/show/NCT01963143)) was an open-label, multicenter, nonrandomized, Phase III, prospective study conducted in children <12 years with a diagnosis of moderate or severe congenital factor X deficiency (basal plasma factor X activity <5 IU/dL at diagnosis) and either a history of severe bleeding or an *F10* gene mutation causing a documented severe bleeding type. The poster from the TEN02 study was published in a special July issue of [*Research and Practice in Thrombosis and Haemostasis*](http://onlinelibrary.wiley.com/doi/10.1111/rth2.2017.1.issue-S1/issuetoc) and can also be found on the 2017 [International Society on Thrombosis and Haemostasis Congress](http://www.professionalabstracts.com/isth2017/iplanner/#/presentation/2048) website. [↑](#footnote-ref-6)
7. One acquisition from True North Therapeutics is BIVV009 (formerly TNT009), a first-in-class monoclonal antibody in development for cold agglutinin disease (CAgD). This is a rare chronic autoimmune haemolytic condition that can lead to severe anaemia, frequent blood transfusions, fatigue, and an increased risk of life-threatening thrombotic events such as pulmonary embolism and stroke. BIVV009 has breakthrough therapy designation from the FDA for the treatment of haemolysis in patients with primary CAgD, and orphan drug designation from the FDA and the European Medicines Agency. Late-stage clinical development planning for BIVV009, including a registrational program, is underway. [↑](#footnote-ref-7)
8. Phase 1 Trial Results on Fitusiran Show Promise for Hemophilia A and B

   See K. John Pasi et al., “[Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy](http://www.nejm.org/doi/full/10.1056/NEJMoa1616569)” in [The New England Journal of Medicine](http://www.nejm.org/). [↑](#footnote-ref-8)
9. BioMarin R&D chief Hank Fuchs commented: “We are striving to make a big difference for patients with severe hemophilia A by developing a treatment that not only has the potential to eliminate bleeds, but also has the potential to eliminate the requirement for recombinant Factor VIII infusions for hemophilia A patients related to trauma, surgery and day-to-day activities.” [↑](#footnote-ref-9)
10. Researchers calculated average product consumption per patient in IU (International Unit) per kg, comparing Afstyla, which is dosed two to three times per week, with octocog alfa, dosed three to four times per week. Among patients on prophylaxis, Afstyla led to 6.4 per cent lower consumption among children, and 16.7 percent lower use among adolescents and adults, compared with octocog alfa. These numbers included instances in which patients, despite treatment, started bleeding. Excluding such bleeding events, the difference between the two drugs was 4.8 per cent in children, though it remained at 16.7 percent among adults and adolescents. In patients treated on-demand, the differences were greater. Afstyla-treated children used 41.3 percent less factor than those on octocog alfa, while adolescents and adults used 27.2 percent less. The clotting factor Afstyla — developed by Korean [SK Chemicals](http://www.skchemicals.com) and licensed to CSL Behring in 2009 — is designed to be more stable once injected into the body. It has a strong molecular bond that forms one single chain instead of the naturally occurring light and heavy chains. Since the molecule does not degrade as quickly as earlier clotting factors, patients can take it less frequently CSL Behring says that once activated, the man-made factor is identical to natural factor VIII. [↑](#footnote-ref-10)
11. The trial involved the use of a donor strand of DNA encoding the sequence for a functional haemoglobin subunit beta gene and a stem cell factor that enhances gene editing. The research was reported in *Nature Communications*, under the title "In vivo correction of anaemia in β-thalassemic mice by γPNA-mediated gene editing with nanoparticle delivery." [↑](#footnote-ref-11)
12. The study, “[Towards a point-of-care strip test to diagnose sickle cell anemia](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0177732),” was published in [*PLOS One*](http://journals.plos.org/plosone). [↑](#footnote-ref-12)
13. Professor of Medicine at Paris Descartes University and Research Director at the Centre for Clinical Research in Biotherapy, Necker Hospital, and at the Institute of Genetic Diseases, Imagine, Paris. [↑](#footnote-ref-13)
14. From [Qiming](http://www.qimingvc.com/index.html) US Healthcare Fund, [Vivo Capital](http://vivocapital.com/), [eCoast Angels](http://www.ecoastangels.com/) and other investors. [↑](#footnote-ref-14)
15. The company’s bioreactor uses induced pluripotent stem (iPS) cells to generate megakaryocytes (bone marrow cells that only produce platelets). The megakaryocytes are placed in the top portion of the reactor and bathed in a medium. Platelets transfuse through a porous membrane and collect in the bottom. Because megakaryocytes can be frozen, they can be easily stockpiled and thawed to meet increased demand. [↑](#footnote-ref-15)
16. [Trimph](http://www.trimph.com.au/)’s first product, TrimphDent, was developed specifically for dental applications. It offers an instant scaffold that helps the host bone tissue to preserve its volume and structure, and it accelerates the healing process after tooth extraction. TheTrimphDent technology would also be applicable in osteoarthritis, bone defects traumas, and Trimph plans to expand the use of the technology to the US$3.2 billion orthopaedic market as well. [↑](#footnote-ref-16)
17. June 22-25, 2017 [↑](#footnote-ref-17)
18. *Safety and Efficacy of Long-Term Open-Label Dosing of Subcutaneous (Sc) Romiplostim in Children With Immune Thrombocytopenia (ITP)* and *A Single-Arm, Open-Label, Long-Term Efficacy and Safety Study of Subcutaneous (Sc) Romiplostim in Children With Immune Thrombocytopenia (ITP)* are currently available on the [EHA website](https://www.ehaweb.org/congress-and-events/22nd-congress/key-information/). [↑](#footnote-ref-18)
19. The first clinical trial aims to establish the safety and efficacy of RePlas. The 24 participants will be treated with their own plasma, both frozen and freeze-dried, to serve as their own control condition. The scientists will administer three increasing doses, to assess how different amounts of freeze-dried plasma function in the body. [↑](#footnote-ref-19)
20. an assistant professor of Internal Medicine and Clinical Sciences and a member of the Center for Patient-Centered Outcomes Research at UT Southwestern Medical Center [↑](#footnote-ref-20)
21. First author was [Dr. Jacquelyn Powers](https://www.bcm.edu/people/view/jacquelyn-powers/88758098-4d09-11e6-8d9a-005056b104be), assistant professor of pediatrics-hematology at Baylor College of Medicine and Texas Children’s Cancer and Hematology Centers. Powers and her colleagues compared low doses of the traditional treatment, ferrous sulfate, with low doses of an iron polysaccharide complex preparation, designed to have a pleasant taste and be tolerated better. The researchers determined which of the two medications would more efficiently restore normal blood levels of haemoglobin, in young children with iron-deficiency anaemia, after 12 weeks of treatment. The 80 children were between 9 and 48 months old. One group received one daily low dose of ferrous sulfate, while the other received the same daily dose of the iron polysaccharide complex, all administered at home. After 12 weeks, the researchers compared the levels of hemoglobin between the two groups. “We expected the newer medication, the iron polysaccharide complex, would restore the hemoglobin more effectively because it was designed to have improved taste and be tolerated better, and this might help patients to stick to the treatment,” Powers said. “But the results surprised me; ferrous sulfate, the traditional medication, treated iron-deficiency anemia more effectively in our trial. The results of the trial also show that a low dose can treat the anemia effectively, and that the adverse gastrointestinal effects, such as abdominal pain, constipation, vomiting and diarrhea, were no different between the two treatments. Our trial provides pediatricians with evidence that one daily low dose of ferrous sulfate drops at bedtime on an empty stomach is a better treatment for young patients with iron-deficiency anemia.” [↑](#footnote-ref-21)
22. [Weihua Guan](http://www.eecs.psu.edu/departments/directory-detail.aspx?q=WZG111&LandOn=Gen), assistant professor in the School of Electrical Engineering and Computer Science; [Manuel Llinás](http://bmb.psu.edu/directory/mul27), professor of biochemistry and molecular biology in the Eberly College of Science; and Leann Tilley, professor of biochemistry and molecular biology at The University of Melbourne, Australia. [↑](#footnote-ref-22)
23. A team led by Tur-Fu Huang, a pharmacology researcher at National Taiwan University, investigated the venom of the *Tropidolaemuswaglerix* snake -- a Southeast Asian species known as Wagler's pit viper or the Temple viper. The venom contains a protein called trowaglerix. Designing a molecule based on trowaglerix, the researchers blocked GPVI -- a protein that sits on the surface of blood platelet cells and is crucial to allowing these cells to clump together and form clots. The study was published June 8 in the journal *Arteriosclerosis, Thrombosis and Vascular Biology*. [↑](#footnote-ref-23)
24. The most common adverse reactions observed include hypersensitivity reactions (including cases of rash, urticarial and angioedema) and headache. As with all therapeutic proteins, there is a potential for immunogenicity. Emicizumab is an investigational bispecific monoclonal antibody, which was developed using Chugai’s proprietary antibody engineering technologies. The drug is designed to bind factors lXa and X, and promotes the interaction between factors lXa and factors X. Therefore, emicizumab provides the cofactor function of factor Vlll in people with hemophilia A, who either lack or have impaired coagulation function of factor Vlll1. In August 2016 emicizumab received an Orphan Drug Designation from the MHLW for the prevention and reduction of bleeding episodes in patients with congenital factor VIII deficiency with inhibitors. In September 2015, the drug was designated as a Breakthrough Therapy by the FDA for the prophylactic treatment of people who are 12 years or older with haemophilia A with factor VIII inhibitor. The current filing is based on the results of HAVEN 1 study (NCT02622321) and the interim analysis of HAVEN 2 study (NCT02795767), conducted under a collaboration between Chugai, Roche and Genentech. They have been carried out in haemophilia A patients with factor VIII inhibitors in order to evaluate the efficacy, safety and pharmacokinetics of the once-weekly subcutaneous injection of emicizumab, while HAVEN 1 is for adult and adolescent patients (12 years of age or older) and HAVEN 2 is for paediatric patients (younger than 12 years of age). The data of HAVEN 1 study was published in [the online version of The New England Journal of Medicine (NEJM)](http://www.nejm.org/doi/full/10.1056/NEJMoa1703068) in July 2017. [↑](#footnote-ref-24)
25. HAE is a rare and potentially life-threatening genetic condition caused by deficient or dysfunctional C1-INH, a protein in the blood that helps to control inflammation. Inadequate amounts can lead to the accumulation of fluid in body tissues, causing considerable swelling. HAE attacks can spread to multiple sites. HAEGARDA is a self-administered, plasma-derived concentrate of C1-esterase inhibitor. Bill Campbell, Senior Vice President and General Manager, North America, CSL Behring, said: “HAEGARDA represents an important advance in the care of HAE, having been shown to reduce the number of HAE attacks by a median of 95 percent (relative to placebo) with subcutaneous delivery”. [↑](#footnote-ref-25)
26. Positive CHMP Opinion is based on data from the Phase IIIb PIONEER AF-PCI study [↑](#footnote-ref-26)
27. Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) and is marketed under the brand name Xarelto. Xarelto is variously approved for seven indications, protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other novel oral anticoagulant:  
    • The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors   
    • The treatment of pulmonary embolism (PE) in adults   
    • The treatment of deep vein thrombosis (DVT) in adults   
    • The prevention of recurrent PE and DVT in adults  
    • The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery   
    • The prevention of VTE in adult patients undergoing elective knee replacement surgery   
    • The prevention of atherothrombotic events (cardiovascular death, myocardial infarction or stroke) after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers and no prior stroke or transient ischaemic attack (TIA) when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine  
    Whilst licences may differ from country to country, across all indications Xarelto is approved in more than 130 countries. [↑](#footnote-ref-27)
28. Refixia is the European brand name for nonacog beta pegol, N9-GP. Refixia is indicated for prophylaxis, and for on-demand treatment of bleeding and surgical procedures in adolescent (>12 years of age) and adult patients with haemophilia B (congenital factor IX deficiency). The efficacy and safety evaluation was based on 115 patients across the five paradigm clinical trials, and the marketing authorisation follows the positive opinion from the Committee for Medicinal Products for Human Use (CHMP), under the European Medicines Agency (EMA), provided 24 March 2017. Novo Nordisk expects to launch Refixia in the first European countries in the fourth quarter of 2017. [↑](#footnote-ref-28)
29. Veyvondi was studied in patients, 18 to 64 years of age, in a multi-centre, open label, non-randomized study assessing safety, efficacy and pharmacokinetics, with and without rFVIII. It was also studied in patients, 18 years and older, in a prospective, uncontrolled, international, multi-centre, open label, non-randomized study assessing control of haemostasis before, during or after surgical procedures, with or without rFVIII. The most common adverse reaction observed was generalized pruritus (itching). The EMA filing is based on data from these two Phase III clinical trials reported publicly in December 2015 and December 2016, respectively. [↑](#footnote-ref-29)
30. China’s plasma products market was exceeded $US 3.3 billion in 2016, with a 15 per cent annual growth rate for the past five years. China has the fastest growing immunoglobulin market in the world, and in volume, it is at the moment second only to the US. [↑](#footnote-ref-30)
31. While the Ochang factory has been focusing on producing blood derivatives, the plant that manufactures vaccine products is located in Hwasun, South Jeolla Province. [↑](#footnote-ref-31)
32. Shire challenged alleged "incomplete and misleading statements" about clotting-related adverse events that were seen with Roche's drug in the HAVEN-1 trial. It also said Roche's comments were "disparaging" to one of its own products, the bypassing agent Feiba. TheHAVEN 1 trial tested emicizumab in people 12 years of age or older with haemophilia A and factor VIII inhibitors. - an immune reaction that can limit the effectiveness of conventional drugs for the disease. [↑](#footnote-ref-32)
33. [bit.ly/2uzjUJf](http://bit.ly/2uzjUJf), online July 3, 2017. [Volume 17, No. 8](http://www.thelancet.com/journals/laninf/issue/vol17no8/PIIS1473-3099(17)X0008-X), p854–866, August 2017. Based on calculations of how many mosquitoes get onto commercial aircraft, how many are infected and how many survive long enough at the destination to bite someone, the study estimates human travellers are 200 times more likely to spread dengue virus and 1,000 times more likely to introduce *P. falciparum*, the parasite that causes malaria. [↑](#footnote-ref-33)
34. see [ClinicalTrials.gov](https://www.clinicaltrials.gov/) using the identifier [NCT03028441](https://www.clinicaltrials.gov/ct2/show/NCT03028441). [↑](#footnote-ref-34)
35. Sarah F.Andrews et al., “Preferential induction of cross-group influenza A hemagglutinin stem–specific memory B cells after H7N9 immunization in humans”, Science Immunology  14 Jul 2017:  
    Vol. 2, Issue 13, eaan2676 DOI: 10.1126/sciimmunol.aan2676 [↑](#footnote-ref-35)
36. The immunocompromised monkeys had higher morbidity and mortality than the others, and while oseltamivir treatment at two different doses reduced A(H7N9) virus titres in all the infected monkeys, it did not suppress the virus enough to prevent the emergence of resistant variants. [↑](#footnote-ref-36)
37. de Vries RP, Peng W, Grant OC, Thompson AJ, Zhu X, Bouwman KM, et al. (2017) [Three mutations switch H7N9 influenza to human-type receptor specificity.](http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006390) *PLoS Pathog* 13(6): e1006390. <https://doi.org/10.1371/journal.ppat.1006390> [↑](#footnote-ref-37)
38. [D Gray Heppner Jr](javascript:void(0);), et al., “Safety and immunogenicity of the rVSV∆G-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study”, *The Lancet Infectious Diseases*, [Volume 17, No. 8](http://www.thelancet.com/journals/laninf/issue/vol17no8/PIIS1473-3099(17)X0008-X), p854–866, August 2017. DOI: <http://dx.doi.org/10.1016/S1473-3099(17)30313-4> [↑](#footnote-ref-38)
39. William A Fischer II et al., “Ebola Virus RNA Detection in Semen More than Two Years After Resolution of Acute Ebola Virus Infection”, *Open Forum Infectious Diseases,* 22 July 2017. <https://doi.org/10.1093/ofid/ofx155> [↑](#footnote-ref-39)
40. The funds will be used to convert current Level 3 Containment space at the National Microbiology Laboratory to the highest level of biosafety. The facility already holds a Containment Level 4 lab, which will be expanded by the investment. Construction will be completed by 2020. [↑](#footnote-ref-40)
41. [↑](#endnote-ref-1)
42. Q fever is carried by goats, sheep, cattle, kangaroos, wallabies, camels, rodents, cats, dogs and birds. While abattoir employment is a prime source, contact with animal urine, faeces, birth products, wool or hides can also transmit the disease. [↑](#footnote-ref-41)