Monitoring International Trends

posted August-September 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

- Alnylam Pharmaceuticals suspended dosing in studies of its haemophilia candidate fitusiran following the death of a patient.
- Spark Therapeutics Inc. reported encouraging preliminary Phase I/II data for its gene therapy candidate SPK-8011 in two patients with haemophilia A. There are two other gene therapies in the clinic for haemophilia A, BMN 270 from BioMarin Pharmaceutical Inc. and SB-525 from Sangamo Therapeutics Inc. Both products are in Phase I/II testing.
- Catalyst Biosciences announced positive initial clinical data from a small ongoing Phase I/II proof-of-concept study of CB 2679d in patients with haemophilia B.
- uniQure N.V. has developed an optimized large-scale process to manufacture its lead gene, therapy candidate, to treat haemophilia B.
- Sancilio Pharmaceuticals completed enrolling patients in a Phase II clinical trial evaluating Altemia (docosahexaenoic acid) as a treatment for children with sickle cell anemia (SCA) and sickle cell disease (SCD).
- Gamida Cell has a new grant to advance clinical trials for CordIn, a therapy to treat sickle cell disease (SCD) and thalassemia.
- Japanese startup Megakaryon says it has established a method to mass-produce platelets from human induced pluripotent stem, or iPS, cells.
- The US Armed Forces Radiobiology Research Institute will conduct a pilot study in nonhuman primates evaluating Pluristem Therapeutics' PLX-R18 as a treatment for acute radiation syndrome prior to and within the first 24 hours of radiation exposure.
- Protalex announced that the company is escalating the dose of PRTX-100 in its US Phase I/II study in adults with persistent/ chronic immune thrombocytopenia

Safety and Patient Blood Management

- A study has concluded: *Allogeneic red blood cell transfusion in major spine surgery could be a risk factor for postoperative infection.*
- Five years in the Johns Hopkins Health System reducing unnecessary blood transfusions improved patient care and earned a 400 per cent return on investment.
- An Australian study reported that novel oral anticoagulants reduce by one-fifth the risk of intraocular bleeding, compared with warfarin in patients with atrial fibrillation or venous thromboembolism.
- A randomized trial suggests that taking a protein pump inhibitor may reduce the frequency of phlebotomies in people with the most common mutation for haemochromatosis.

- A study has shown that Bayer's Xarelto (rivaroxaban) significantly lowered the combined risk of stroke, cardiovascular death and heart attack in patients with chronic coronary or peripheral artery disease.
- Bristol-Myers Squibb and Pfizer have presented observational real-world data analysis on the effectiveness and safety of Eliquis (apixaban) compared with warfarin in select high-risk patients with non-valvular atrial fibrillation.
- A 5-gram dose of idarucizumab quickly and completely reversed the anticoagulant effects of dabigatran in more than 500 patients who either experienced uncontrolled bleeding or who were about to undergo a surgical procedure.,

Regulatory

- Bayer filed a Biological License Application with the FDA seeking marketing approval for its long-acting human Factor VIII therapy, BAY94-9027, for use in haemophilia A.
- The FDA approved new product strengths for Octapharma's Nuwiq (recombinant FVIII), to treat haemophilia A patients.
- Roche's emicizumab prophylaxis has been granted priority review by the FDA for haemophilia A with factor VIII inhibitors
- The FDA granted Global Blood Therapeutics Rare Pediatric Disease designation for GBT440 for the treatment of sickle cell disease (SCD).
- The FDA accepted for review Portola Pharmaceuticals' resubmitted Biologics License Application seeking approval for Factor Xa inhibitor reversal agent AndexXa (andexanet alfa).
- AMAG Pharmaceuticals made a submission to the FDA to broaden the existing label for ferumoxytol (Ferahame).
- The FDA has granted Pluristem clearance to start a Phase I clinical trial evaluating PLX-R18 in patients with incomplete bone marrow recovery following hematopoietic cell transplantation.
- RevMedX won FDA 510(k) clearance for XSTAT 12 and XSTAT 30 devices used to stop severe bleeding from knife and gun-shot wounds in the arms or legs.
- Kedrion Biopharma and Kamada receive FDA Approval of KEDRAB for post-exposure prophylaxis against rabies infection.
- The FDA has granted Orphan Drug Designation to Ra Pharmaceuticals' RA101495 for treating paroxysmal nocturnal hemoglobinuria (PNH).

Company news

- uniQure agreed with Chiesi Group to reacquire the rights to co-develop and commercialize its haemophilia B gene therapy in Europe and other select territories.
- CSL reported a 24 per cent increase in underlying net profit at constant currencies for the year to 30 June 2017.
    i) CSL has paid out $US 352 million to complete its purchase of Ruide, a Wuhan-based business that gives it a stake in Chinese plasma collection and fractionation.
    ii) CSL's key projects include its recombinant production site in Lengnau, Switzerland; new base fractionation capacity at Kankakee and Marburg; additional Haegarda/ Berinert capacity at Marburg; new albumin and Ig capacity at Broadmeadows; new Ig capacity at Bern; and opening new collection centres.
    iii) For the financial year sales of immunoglobulins were up 16 per cent in constant currency terms, with Privigen up 21 per cent and Hizentra up 10 per cent.
    iv) CSL reported a strong demand for idelvion, and transition from Helixate to Afstyla Kcentra sales were up 35 per cent and Berinert up 31 per cent. Sales growth of albumin in China was 13 per cent
    v) CSL said it expects to record a net profit after tax increase of 18 to 20 per cent on a constant currency basis in the next year

vi) CSL Behring is acquiring Calimmune, a US biotechnology company developing *ex vivo* hematopoietic stem cell gene therapy.

- In reporting its second quarter financial results, Cerus highlighted these recent developments amongst others:
  i) Collaboration agreement with Central California Blood Center for the manufacture of pathogen-reduced cryoprecipitate as a novel biologic; and
  ii) Advances in the INTERCEPT red cell program with additional BARDA funding to support clinical trials for a planned FDA submission and commercial manufacturing scale-up.
- Dimension Therapeutics of Cambridge, Massachusetts has agreed to be acquired by RegenxBio of Rockville, Maryland.
- Chinese company 3SBio has accelerated the expansion of its global biologics platform by acquiring the Canadian manufacturing business of Therapure.
- Aptevo Therapeutics announced that it had agreed to sell its three marketed hyperimmune products, WinRho SDF, HepaGam B, and VARIZIG, to Saol Therapeutics. Aptevo will continue to own and market IXINITY, an intravenous recombinant factor IX therapeutic for treating haemophilia B.
- Kedrion Biopharma is in the final stages of a $US 100 million upgrade to its production facility in Melville, New York State.
- Bioverativ has formed a strategic collaboration expanding the use and adoption of leading imaging technologies, including ultrasound and radiolabelled imaging, to improve the diagnosis and management of joint disease in people with haemophilia.
- Swiss biopharmaceutical company Novimmune concerning the latter's pre-clinical bi-specific antibody candidate for haemophilia A.
- Apic Bio is advancing a first-in-its class gene therapy for treatment of alpha-1 antitrypsin deficiency.

Country news

- Cerus Corporation announced the signing of two, new, expanded contracts with Établissement Français du Sang (EFS), the French National Blood Service.
- Canadian Blood Services is seeking $C 855-million over seven years to increase the amount of plasma it collects from unpaid donors.
- In Italy, blood donation was suspended after a number of people became infected locally with chikungunya.
- Zipline, a California-based drone start up, began delivering medical supplies including blood products in Rwanda.

Infectious diseases

- Sanofi announced that the US the Biomedical Advanced Research and Development Authority (BARDA), was decreasing its financial assistance for the company's Zika vaccine project. Sanofi decided not to continue development. Various experimental Zika vaccines are being tested, but Sanofi was the only major pharmaceutical company with a near-term market goal.
- Scientists at Arizona State University created a Zika vaccine based on tobacco plants.
- A study found that the administration of inactivated influenza vaccines via a microneedle patch induces impressive immune responses.
- Rates of influenza vaccination coverage in the US fell among children when the nasal spray vaccine was not recommended for them.
- Westmead Hospital has been participating in an international trial based on blood donated by people who have recovered from influenza or have received the flu shot.
- South Korean scientists have substituted genes from H5N1 avian influenza into an H5N8 avian flu virus and found that in mice it caused greater pathogenicity and up to a 1,000-fold greater virulence. The number of Chinese towns, provinces, and regions

that reported human cases of H7N9 avian influenza from October 2016 was higher than the previous four waves combined. that 759 illnesses were reported in the fifth wave, 281 of them fatal. Fourteen clusters of two or three people were reported in the fifth wave, compared with an average of nine in each of the earlier waves.

- As of 21 September 2017, there had been in Saudi Arabia a total of 1716 laboratory-confirmed cases of MERS-CoV infection, including 694 deaths.
- The FDA has approved benznidazole to treat the tropical parasitic infection Chagas, in children aged 2 to 12.

Table of Contents

1. 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

- Alnylam Pharmaceuticals suspended dosing in all studies of its haemophilia candidate fitusiran following the death of a patient in an open-label extension phase II

study[1]. The company said it would resume dosing after discussion with global regulatory authorities and proper protocol amendments for enhanced patient safety monitoring were in place. The company's share price fell almost sixteen per cent following the announcement.

- The Catalyst Biosciences share price rose more than ten per cent after the company announced positive initial clinical data from a small ongoing Phase I/II proof-of-concept study of CB 2679d in patients with haemophilia B[2]. The company said that a single dose of the drug was more potent than Pfizer's Benefix, the current standard of care, and stayed in the circulation for longer[3]. In June 2017, the investigational drug was granted orphan drug status by the European Commission.
- Spark Therapeutics Inc. reported preliminary Phase I/II data showing that a single intravenous dose of its gene therapy candidate SPK-8011 stabilized Factor VIII activity levels at 14 per cent and 11 per cent of normal in two patients with haemophilia A at weeks 12 and 23, respectively. SPK-8011 is an adeno-associated virus (AAV) vector that delivers the Factor VIII gene[4]. There are two other gene therapies in the clinic for hemophilia A, BMN 270 from BioMarin Pharmaceutical Inc. and SB-525 from Sangamo Therapeutics Inc. Both products are in Phase I/II testing.
- BioMarin Pharmaceutical announced it would expand its development plan for BMN 270, its investigational gene therapy for haemophilia A, to include an extra Phase III study of the 4e13 vg/kg dose. Since the data update from its ongoing open-label Phase I/II study, presented at the International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress, the Factor VIII activity levels in the 4e13 vg/kg cohort had continued to trend upwards[5]. BioMarin will therefore conduct two separate Phase III studies, one with the 4e13 vg/kg dose and one with the 6e13 vg/kg dose. These are expected to begin in the fourth quarter 2017. The company has commissioned its commercial manufacturing facility.
- In May, Sangamo awarded Pfizer Inc. exclusive, worldwide rights to SB-525. The product is a recombinant AAV vector carrying a Factor VIII gene construct driven by a proprietary, synthetic, liver-specific promoter. Sangamo expects initial clinical data from the Phase I/II trial of SB-525 late this year or early in 2018.
- uniQure N.V. has developed an optimized large-scale process to manufacture its lead gene, therapy candidate, to treat haemophilia B. This new platform will allow the Dutch company to boost production of its AMT-060 gene therapy at its Lexington, Massachusetts, facility, in accordance with Good Manufacturing Practices guidelines. This should enable uniQure to meet quickly the requirements of both the FDA and the European Medicines Agency (EMA), the company's CEO, Matt Kapusta, said in a press release.

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[1] The patient reportedly died from blood clotting inside cerebral venous sinus (a thrombotic event).

[2] Catalyst is working with ISU Abxis of South Korea, which uses the name ISU304 for the therapy, to conduct the trial (NCT03186677). The study is being conducted at three clinical sites in South Korea and is expected eventually to include 12 patients with moderate to severe haemophilia B.

[3] This open-label study started with a comparison of the overall response of a single administration of 75 IU/kg BeneFix with a single administration of 75 IU/kg CB 2679d. Three patients with haemophilia B received BeneFix and were observed for 72 hours, followed by CB 2679d, again followed for 72 hours. Catalyst said the trial will also test increasing dosages of CB 2679d – 150 IU/kg and 300 IU/kg – administrated subcutaneously compared with 75 IU/kg intravenous dosage. It will also test the safety and activity of daily subcutaneous injections of CB 2679d (300 IU/kg) for up to six days. Completion of the trial is planned for early 2018.

[4] In July, Spark Therapeutics presented updated interim haemophilia B data supporting consistent and sustained response at the International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress.

[5] Six patients received a single dose of BMN 270 at the 4e13 vg/kg level. Based on data at 28 July 2017, for the three patients who were given the 4e13 vg/kg dose in November/December 2016, at week 32, all were in or near to the normal range of Factor VIII activity levels.

i) AMT-060 gene therapy is based on a viral vector to deliver a therapeutic form of human factor IX gene. The therapy is being evaluated in a Phase I/II trial (NCT02396342) in patients with severe haemophilia B and advanced joint disease. The trial's most recent long-term results show that AMT-060 is safe and well tolerated, while reducing annual spontaneous bleeding rates by 84 percent to an average of 0.5 annual bleeds after gene transfer. These results were subject of an oral presentation[6], given during the 26th Biennial Congress of the International Society on Thrombosis and Haemostasis in Berlin.

ii) The FDA granted AMT-060 its breakthrough therapy designation in January 2017. The EMA awarded the gene therapy its PRIME designation in April 2017.

Treating beta thalassemia and sickle cell disease

- Sancilio Pharmaceuticals completed enrolling patients in a Phase II clinical trial evaluating Altemia (docosahexaenoic acid) as a treatment for children with sickle cell anemia (SCA) and sickle cell disease (SCD). The SCOT trial (NCT02973360) is designed to determine an optimal dose of the therapy as well as evaluating its safety and effectiveness. Children aged 5 to 17 will be randomized to receive either Altemia or a placebo.
- The Israeli government has awarded Gamida Cell a $US 3.5 million grant to advance the development of clinical trials for CordIn, a therapy to treat sickle cell disease (SCD) and thalassemia. The grant follows the recent closing of a $US 40 million financing round and the Jerusalem-based company's recent expansion to the US, after appointing Dr. Ronit Simantov as the company's new US-based chief medical officer. CordIn is Gamida's candidate for the treatment of SCD and thalassemia, as well as bone marrow failure syndromes and genetic metabolic diseases. It's a variation of NiCord, developed as an alternative to bone marrow transplants to treat patients with blood cancers who cannot find a donor with fully matched tissue. The product comes from expanding cells from the umbilical cord. So far clinical trial data has been encouraging, showing successful and swift engraftment as well as the curing of disease symptoms in these hard to-engraft patients. Particularly, interim results from a Phase I/II clinical trial[7] (NCT02504619) appear to suggest that CordIn could effectively overcome the engraftment barriers of umbilical cord blood and has the potential to increase access to curative transplants for SCD.

Artificial blood and blood products

- Japanese startup Megakaryon Corp. says it has established a method to mass-produce blood products by making platelets from human induced pluripotent stem, or iPS, cells. The Kyoto company hopes to begin clinical trials in 2018 and obtain regulatory approval in 2020 for production and sales. It aims to supply up to 20 per cent of blood platelet products used in Japan. Megakaryon was established in September 2011 to commercialize technology to make blood platelets from iPS cells that was developed by researchers including University of Tokyo Prof. Hiromitsu Nakauchi and Prof. Koji Eto of Kyoto University's Center for iPS Cell Research and Application.

[6] "Updated Results from a Dose-escalation Study in Adults with Severe or Moderate-severe Hemophilia B Treated with AMT-060 (AAV5-hFIX) Gene Therapy: up to 1.5 Years Follow-up". A summary appears in the meeting's book of abstracts.

[7] The Phase I?II trial, launched in January 2015, was the first time that a patient with SCD was transplanted with CordIn. The transplant took place at the University of California at San Francisco Benioff Children's Hospital in Oakland, California. The trial is still recruiting patients in the US.

Other products

- Humacyte, completed enrollment of 350 subjects for its Phase III HUMANITY study of HUMACYL, the company's investigational human acellular vessel (HAV). Conducted across 40 sites in the U.S., Europe and Israel, this pivotal Phase III clinical trial evaluates the efficacy and safety of the bioengineered blood vessel as a conduit for hemodialysis in selected patients with End-Stage Renal Disease (ESRD) requiring renal replacement therapy. Humacyte expects 12-month post-implantation patient data from the study to be available in late-2018. The company hopes on the basis of this data to file a Biological License Application with the US Food and Drug Administration (FDA to seek marketing authorization for HUMACYL. To expedite the review process, Humacyte was granted the Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA earlier this year. In addition to this Phase III trial, Humacyte plans to seek regulatory approval for additional clinical applications for its HAV, and the company recently announced the commencement of a US.Phase II clinical trial of the bioengineered vessel as a bypass graft in patients with peripheral arterial disease PAD.
- The US Department of Defense's Armed Forces Radiobiology Research Institute (AFRRI) will conduct a pilot study in nonhuman primates evaluating Pluristem Therapeutics' PLX-R18 as a treatment for acute radiation syndrome prior to and within the first 24 hours of radiation exposure[8]. The AFRRI is part of the Uniformed Services University of Health Sciences. Pluristem's PLX-R18 is generated from placenta-derived mesenchymal-like adherent stromal cells. The cells are designed to release a combination of therapeutic proteins to help treat bone marrow that has been damaged due to acute radiation syndrome, or as a result of cancer, or cancer therapy, or immune-mediated bone marrow failure. Previously, Pluristem reported positive data from an ongoing Phase II-equivalent nonhuman primate trial carried out by the National Institute of Allergy and Infectious Diseases (NIAID), which also investigated PLX-R18 cells as a treatment for acute radiation syndrome. The results confirmed the treatment increased survival rates in irradiated animals[9].
- Protalex announced that following completion of a planned interim analysis of safety and efficacy data from the second dose cohort, the company is escalating the dose of PRTX-100 in its US Phase I/II study of PRTX-100 in adults with persistent/ chronic immune thrombocytopenia[10] (ITP) (PRTX-100-202 Study). One of the three patients treated in the second dose cohort achieved a protocol defined platelet response. Treatment of the first patient in the third cohort at a dose of 6.0 micrograms/kg, double that of the second dose cohort of 3.0 micrograms/kg, is expected soon. The 202 Study is an open-label, dose escalating study that can enrol up to 36 patients in as many as six cohorts. Each patient will receive four weekly intravenous doses of PRTX-100 and will be monitored for up to 48 weeks thereafter. The primary study endpoint of the 202 Study is a platelet response to PRTX-100. Secondary endpoints include safety, immunogenicity, and pharmacokinetics. Enrolment has been taking place at several study sites in the US.

[8] The trial will be carried out in accordance with FDA's Animal Rule pathway, which applies when human efficacy trials are not feasible, in this case due to the ethics of exposing humans to nuclear radiation. Product approval via the Animal Rule pathway can be granted following large animal efficacy studies and human safety data.

[9] The NIAID study is evaluating PLX-R18 administration 24 hours after radiation exposure, while the AFRRI study will evaluate therapy given prior to or within the first 24 hours of radiation exposure, which is more relevant to the needs of the armed forces.

[10] ITP is an autoimmune-mediated condition characterized by bruising and increased bleeding as a result of immune-mediated accelerated destruction of platelets and impaired production of platelets. PRTX-100 is a highly purified form of an immunomodulatory protein known to modify aspects of the human immune system.

- Scientists have used virtual screening software to engineer bispecific antibodies, making a few key changes to natural human immunoglobulin G antibodies. Bispecific antibodies targeting cancer cell protein clusters are currently in clinical trials[11].
- Sage Bionetworks and Celgene have launched an Apple iPhone-based mobile study, Journey PRO, to understand the disease burden carried by patients with chronic anaemia due to beta-thalassemia, myelofibrosis and myelodysplastic syndromes. The expectation is that this tool will be able then to evaluate how effective new treatments will be at reducing the burden of chronic anaemia diseases on patients.

2. Safety and patient blood management

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

Appropriate Transfusion

- The Society for the Advancement of Blood Management's (SABM) Annual Meeting was held in September 2017 in Portland, Oregon. Dr Irwin Gross from Accumen addressed key SABM Standards and Quality Guidelines on 7 September and presented "Transfusion Therapy in Oncology: Red Cells, Platelets, and Alternative Strategies" on 8 September. Trudi Gallagher RN presented "Profound Anemia When Blood Is Not an Option" on 6 September and partnered with another speaker on "Culture's Effect on Success or Failure of PBM Hospital Programs" on 9 September.
- A Danish study[12] reported that women who have had at least one previous cesarean delivery have an increased risk of complications when undergoing a hysterectomy later in life. Women with at least two previous cesarean deliveries had an increased risk of needing a blood transfusion, with an adjusted odds ratio of 1.93 compared with women without a previous cesarean delivery. The study authors pointed out that the risk of intra-abdominal adhesions increase with the number of cesarean deliveries. These adhesions may complicate future surgery, leading to longer operating time.
- A new study[13] examines the connection between blood transfusions and infection for patients undergoing major spinal deformity surgery, and concluded: *Allogeneic red blood cell transfusion in major spine surgery could be a risk factor for postoperative infection.* Researchers examined 56 patients who underwent spinal fusions in eight or more levels. They found:
  i) overall infection rates were 36 per cent in the patients who received transfused blood and 10 per cent among patients who didn't;
  ii) only patients who received blood transfusions reported wound infections;
  iii) smokers were more likely to have an infection as well as receive a transfusion; and

[11] See study by Camilla De Nardis et al., in *Journal of Biological Chemistry*: A new approach for generating bispecific antibodies based on a common light chain format and the stable architecture of human immunoglobulin G1…First Published on June 27, 2017 doi: 10.1074/jbc.M117.793497

[12] Lindquist SA, Shah N, Overgaard C, et al. Association of previous cesarean delivery with surgical complications after a hysterectomy later in life. *JAMA Surg*. 2017 Aug 9. doi:10.1001/jamasurg.2017.2825

[13] isahn, Christian; Jeyamohan, Shiveindra; Norvell, Daniel; Tubbs, R. Shane; Moisi, Marc; Chapman, Jens; Page, Jeni and Oskouian, Rod. (2017). "Association Between Allogeneic Blood Transfusion and Postoperative Infection in Major Spine Surgery". *Clinical spine surgery*. 30. DOI: 10.1097/BSD.0000000000000539.

iv) transfused patients stayed in hospital significantly longer than other patients.

- Researchers reported that a five-year effort across the Johns Hopkins Health System to reduce unnecessary blood transfusions had improved patient care and yielded a 400 percent return on investment, resulting in annual cost savings of more than $US 2 million[14].

Treating anaemia

- French researchers have discovered that the haemoglobin of the lugworm can transport 40 times more oxygen from the lungs to tissues than human haemoglobin. The main hindrance to using the blood of the lugworm as an alternative to human blood is the possibility of its causing an allergic reaction and potentially causing kidney damage. However, lugworm haemoglobin is almost the same as human haemoglobin and doesn't need to be contained within red blood cells. This makes differing blood types inconsequential. Purified lugworm haemoglobin was first trialled in mice. From 2015, ten human kidney transplant patients have been given the extracellular haemoglobin extracted from the lugworm, with an additional 60 participants currently enrolled in the study across France.

Other

- An Australian study [15]reported that novel oral anticoagulants reduce by one-fifth the risk of intraocular bleeding, compared with warfarin in patients with atrial fibrillation or venous thromboembolism.
- Indian scientists have developed a new biomaterial with enhanced blood clotting efficiency to treat injuries[16]. "We have engineered fibrin-inspired peptide-based sealants which have demonstrated superior blood clotting ability than natural fibrin," explained Dr Rituparna Sinha Roy, a member of the research team. Tests showed that the engineered sealant was able to form an interwoven structure resembling a clot but in nearly half the time.
- Researchers at the University of Queensland, and colleagues, have studied the venoms of 16 species of monitor lizard, including the Komodo dragon[17]. Although the venom of the Komodo dragon is crippling, it has been found to be a promising potential treatment for blood clots. Several species of monitor lizard - including Komodo dragons - are vulnerable or endangered species. The medical potential of their venom is "a great example of why we need to conserve all of nature", researcher Bryan Fry concluded.
- A randomized trial[18] in 30 patients has shown that taking a protein pump inhibitor may reduce the frequency of phlebotomies in people with the most common mutation for haemochromatosis (pC282Y). This is thought to be due to acid suppression decreasing non-haem intestinal iron absorption.

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[14] A summary of the blood management program was published 7 September in the Online First edition of *Anesthesiology*, the journal of the American Society of Anesthesiologists. First author of the paper was Steven Frank, professor of anesthesiology and critical care medicine at the Johns Hopkins University School of Medicine.

[15] Sun MT, Wood MK, Chan W, et al. "Risk of Intraocular Bleeding With Novel Oral Anticoagulants Compared With Warfarin: A Systematic Review and Meta-analysis". *JAMA Ophthalmol*. 2017 Jul 6. [Epub ahead of print]

[16] Snehasish Ghosh et al., "Engineered isopeptide bond stabilized fibrin inspired nanoscale peptide based sealants for efficient blood clotting", Scientific Reports 7, article number 6509 (2017) published 26 July 2017.

[17] Bryan G Fry et al., "Enter the Dragon: The Dynamic and Multifunctional Evolution of Anguimorpha Lizard Venoms", *Toxins,* **2017**, *9*(8), 242; doi:10.3390/toxins9080242

[18] "Proton Pump Inhibitors Decrease Phlebotomy Need in HFE Hemochromatosis: Double-Blind Randomized Placebo-Controlled Trial", *Gastroenterology,* Volume 153, issue 3, September 2017, pp 678-680.e2 Clinicaltrials.gov: NCT01524757.

- A study[19] has shown that Bayer's Xarelto (rivaroxaban) significantly lowered the combined risk of stroke, cardiovascular death and heart attack in patients with chronic coronary or peripheral artery disease. In the Phase III COMPASS study, Bayer's Factor Xa inhibitor, (Xarelto) vascular dose, 2.5 mg twice daily, plus aspirin 100 mg once daily reduced the risk of the composite outcome of stroke, cardiovascular death and heart attack by 24 per cent (relative risk reduction) in patients with chronic coronary artery disease or peripheral artery disease. The trial compared this combined approach with aspirin 100 mg once daily alone. Patients included in the study had already received guideline recommended therapy for hypertension, high cholesterol and diabetes. A 5 mg twice daily dose of rivaroxaban was also investigated but the difference in the primary outcome did not reach statistical significance.
- At the European Society of Cardiology Congress in Barcelona, Bristol-Myers Squibb and Pfizer presented observational real-world data analysis on the effectiveness and safety of Eliquis (apixaban) compared with warfarin in select high-risk patients with non-valvular atrial fibrillation. Using data pooled from four large US insurance claims data bases they found that among non-valvular atrial fibrillation patients, Eliquis was associated with a lower risk of stroke/ systemic embolism and lower rates of major bleeding compared with warfarin for the overall population as well as for each of the selected high-risk patient sub-populations.
- Researchers reported[20] that a 5-gram dose of idarucizumab quickly and completely reversed the anticoagulant effects of dabigatran in more than 500 patients who either experienced uncontrolled bleeding or who were about to undergo a surgical procedure., according to findings published online in the July 11 issue of the *New England Journal of Medicine*. Idarucizumab is a monoclonal antibody fragment that binds directly to dabigatran, neutralizing its activity.In October 2015, the FDA approved the use of idarucizumab for the reversal of the effects of dabigatran in patients requiring urgent surgical procedures who have life-threatening bleeding.

3. Regulatory

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

- Prometic Life Sciences announced that the US Food and Drug Administration (FDA) has granted a Rare Pediatric Disease Designation[21] to the company's Ryplazimä, a plasminogen replacement therapy for the treatment of patients with congenital plasminogen deficiency[22]. Ryplazimä had already been granted Orphan Drug and Fast Track Designation by the FDA.

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[19] John W. Eikelboom, et al," Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease**",** *New England Journal of Medicine***,** August 27, 2017DOI: 10.1056/NEJMoa1709118

[20] Online 11 July 2017 in the *New England Journal of Medicine.*

[21] The FDA grants Rare Pediatric Disease Designation for serious or life-threatening diseases primarily affecting patients from birth to 18 years.

[22] Plasminogen is a naturally occurring protein that is synthesized by the liver and circulates in the blood. Plasminogen is vital in wound healing, cell migration, tissue remodeling, angiogenesis and embryogenesis. A common condition associated with plasminogen deficiency is ligneous conjunctivitis, which is characterized by thick, woody growths on the conjunctiva of the eye, which if left untreated, can lead to corneal damage and blindness. Since the growths tend to recur, multiple surgeries may be required. Also characteristic of plasminogen deficiency is hypoplasminogenemia that can affect the ears, sinuses, tracheobronchial tree, genitourinary tract, and gingiva. Tracheobronchial lesions including hyper viscous secretions can result in respiratory failure. Hydrocephalus has also been reported in children with severe hypoplasminogenemia,

- Bayer filed a Biological License Application with the FDA seeking marketing approval for its long-acting human Factor VIII therapy, BAY94-9027, for use in haemophilia A. It allows for dosing at intervals as long as a week. A compound called PEG (polyethylenglycol) is added to the factor VIII protein to prolong the stability of the protein circulating in the blood whilst maintaining its coagulation activity. Bayer's application was supported by positive results for BAY94-9027 shown in a Phase II/III clinical trial called PROTECT VIII (NCT01580293). The PROTECT VIII study was conducted at 97 clinical sites worldwide involving about 140 participants aged 12 to 65. Bayer said trial results "demonstrated protection from bleeds with dosing intervals as few as once every seven days, once every five days, and twice per week". More recent data from the PROTECT VIII KIDS trial (NCT01775618) was presented at the 2016 World Congress of the World Federation of Hemophilia[23], again suggesting safety and long-lasting efficacy in preventing and treating bleeding, this time in patients under 12 years of age. The company said BAY94-9027 was able to keep bleeds under control in all tested administration regimens — twice weekly, every five days, and every seven days. About 92 per cent of the bleeding events reported during the study were controlled with one or two infusions.
- The FDA has approved new product strengths for Octapharma's Nuwiq (recombinant FVIII), to treat haemophilia A patients. The new vial strengths, 2500, 3000 and 4000 International Units (IU) are in addition to the current strengths offered (250, 500, 1000 or 2000 IU). Data presented recently at the International Society on Thrombosis and Haemostasis (ISTH) Congress in Berlin, showed that 57 per cent of those using Nuwiq three times a week were able to reduce their respective schedules to twice a week or less, based on their individual pharmacokinetics analysis.
- Roche's emicizumab prophylaxis has been granted priority review by the FDA for haemophilia A with factor VIII inhibitors. Emicizumab binds the IXa and X factors which are proteins that are needed to activate the natural coagulation cascade and repair the blood clotting process. The FDA is expected to decide on the product's approval by 23 February 2018. The Biologics License Application for emicizumab is based on results from two Phase III studies HAVEN 1 and HAVEN 2. Roche chief medical officer and global product development head Sandra Horning said: *Results of our phase III study in adults and adolescents as well as early phase III results in children showed that emicizumab has significant potential to help people with haemophilia A with inhibitors, who face major challenges in preventing and treating bleeds.* Roche is also seeking approval of emicizumab in Europe and has submitted data from the HAVEN 1 and HAVEN 2 studies to the European Medicines Agency (EMA). The drug will be reviewed by the European regulator under accelerated assessment.
- The FDA granted Global Blood Therapeutics Rare Pediatric Disease designation[24] for GBT440 for the treatment of sickle cell disease (SCD). GBT440 is being developed as a potentially disease-modifying therapy for SCD[25]. Ted W. Love,

[23] Results were presented in a poster, "PROTECT VIII Kids Trial Results: BAY 94-9027 Safety and Efficacy in Previously Treated Children With Severe Hemophilia A."

[24] The FDA defines a rare pediatric disease as a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals age 18 years or younger, and is a rare disease that impacts fewer than 200,000 individuals in the United States. The Rare Pediatric Disease designation provides incentives to advance the development of rare disease drugs and biologics. Additionally, the FDA's Rare Pediatric Disease Priority Review Voucher Program states that a sponsor with a Rare Pediatric Disease designation who receives a New Drug Application (NDA) or Biologic License Application (BLA) approval for a rare pediatric disease may be eligible for a voucher that can be redeemed to obtain priority review for any subsequent marketing application.

[25] GBT440 is an oral, once-daily therapy for patients with SCD. It increases haemoglobin's affinity for oxygen. Since oxygenated sickle haemoglobin does not polymerize, GBT440 should therefore block polymerization and the resultant sickling of red blood cells.

president and CEO of Global Blood Therapeutics, said: *The FDA's Rare Pediatric Disease designation for GBT440, in addition to the previously granted Orphan Drug and Fast Track designations*[26]*, confirm the Agency's recognition that the SCD community faces a critical need for new treatments……. "We have made important progress in our pediatric program this year and look forward to sharing additional updates at the American Society of Hematology Annual Meeting in December*.[27]

- The FDA accepted for review Portola Pharmaceuticals' resubmitted Biologics License Application seeking approval for Factor Xa inhibitor reversal agent AndexXa (andexanet alfa). The FDA's action date is February 2, 2018. Portola had received a Complete Response Letter in August 2016 citing the need for additional manufacturing information and more data to support the inclusion of edoxaban and enoxaparin in the label.
- The FDA has granted Pluristem clearance to start a Phase I clinical trial evaluating PLX-R18 in patients with incomplete bone marrow recovery following hematopoietic cell transplantation.
- Protalex has been awarded a grant of $US 403,000 from the FDA Office of Orphan Products Development to foster clinical development of PRTX-100[28] for the treatment of immune thrombocytopenia[29]. PRTX-100 is a new generation immunomodulatory therapy and has been granted Orphan Drug Designation as a potential treatment for ITP in both the U.S. and Europe. Protalex has been enrolling patients into two Phase I/II dose-escalating studies of PRTX-100 at several sites in the US (the 202 Study) and in Europe (the 203 Study) and has so far seen patients in each completed lower dose cohort achieve a protocol-defined platelet response. Richard J. Francovitch, Protalex's vice president, ITP programs, said: *We recently opened new dose cohorts in both the 202 and 203 studies and look forward to the results as the studies move forward evaluating higher doses of PRTX-100.*
- AMAG Pharmaceuticals made a submission to the FDA to broaden the existing label for ferumoxytol (Ferahame) to include the treatment of all adults with iron deficiency anaemia who are intolerant to or have unsatisfactory response to oral iron. It is currently indicated for the treatment of iron deficiency anemia in adults with chronic kidney disease. The FDA is expected to make a decision on the label expansion by 2 February 2018. AMAG's submission included data from a randomized, double-blind, noninferiority phase III clinical trial designed to compare ferumoxytol with ferric carboxymaltose injection in approximately 2,000 adults.
- RevMedX won FDA 510(k) clearance for XSTAT 12 and XSTAT 30 devices used to stop severe bleeding from knife and gun-shot wounds in the arms or legs. The devices are large syringes that quickly push dozens of tablet-sized highly absorbent pieces of foam into a wound. Once the foam tablets are inside the wound, they

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[26] The European Medicines Agency (EMA) has included GBT440 in its Priority Medicines (PRIME) program, and the European Commission (EC) has designated GBT440 as an orphan medicinal product for the treatment of patients with SCD.

[27] GBT is conducting the HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization) Study, a Phase III clinical trial in SCD patients aged 12 and above. GBT440 is also being studied in the ongoing Phase 1/II GBT440-001 trial and in the ongoing HOPE-KIDS 1 Study, an open-label, single- and multiple-dose study in paediatric SCD patients (aged 6 to 17).

[28] PRTX-100 is a highly purified form of staphylococcal protein A (SpA), which is an immunomodulatory protein known to modify aspects of the human immune system.

[29] Immune thrombocytopenia or ITP is an autoimmune-mediated condition characterized by bruising and increased bleeding as a result of immune-mediated accelerated destruction of platelets and impaired production of platelets. The diagnosis of ITP is based upon a low platelet count, usually less than 100,000 per microliter of blood, in the absence of other possible causes of reduced platelet numbers such as an underlying illness or medication. The two most recently approved drugs used to treat ITP, Nplate (romiplostim) and Promacta/Revolade (eltrombopag), both increase the production of platelets but do not appear to affect the underlying platelet destruction process.

quickly expand, blocking the blood from escaping and delivering pressure onto the wound from within. Each tablet contains a radiopaque marker so it can be easily found using X-ray fluoroscopy during surgery. The devices have previously been FDA approved for use in civilian and battlefield situations, but only to treat junctional wounds around the groin and shoulders.

- Kedrion Biopharma and Kamada received FDA approval of KEDRAB for post-exposure prophylaxis against rabies infection. KEDRAB is a plasma-derived human rabies immune globulin. It represents new entry into $US 100 million-plus US rabies prevention market where only two other products exist. KEDRAB should be administered concurrently with a full course of rabies vaccine. KEDRAB will launch in the US in early 2018.
- The FDA has granted Orphan Drug Designation to Ra Pharmaceuticals' RA101495 for treating paroxysmal nocturnal hemoglobinuria (PNH)[30]. It is administered intravenously once a fortnight. PNH is a life-threatening condition in which red blood cells are destroyed.

4. 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.

- uniQure announced that it had entered into an agreement with Chiesi Group to reacquire the rights to co-develop and commercialize its haemophilia B gene therapy in Europe and other select territories and to terminate their co-development and licence agreement.
- CSL reported a 24 per cent increase in underlying net profit at constant currencies for the year to 30 June 2017. The company has bought back 29 per cent of its shares during the past nine years but said it will not buy back shares this year for the first time since 2008, so as to invest in future growth projects.
    i) CSL has paid out $US 352 million to complete its purchase of Ruide, a Wuhan-based business that gives it a stake in Chinese plasma collection and fractionation.
    ii) CSL's key projects include its recombinant production site in Lengnau, Switzerland, where it plans to produce proteins to treat immune deficiency diseases; new base fractionation capacity at Kankakee and Marburg; additional Haegarda/ Berinert capacity at Marburg; new albumin and Ig capacity at Broadmeadows; new Ig capacity at Bern; opening 25 to 30 new collection centres; and an upgrade to its Enterprise Resource Planning systems.
    iii) For the financial year its total sales of immunoglobulins were up 16 per cent in constant currency terms, with Privigen up 21 per cent and Hizentra up 10 per cent.
    iv) CSL reported a strong demand for idelvion, and transition from Helixate to Afstyla. Kcentra[31] sales were up 35 per cent and Berinert[32] up 31 per cent. Sales growth of albumin in China was 13 per cent
    v) CSL said it expects to record a net profit after tax increase of 18 to 20 per cent on a constant currency basis in the next year

[30] PNH is a life-threatening condition in which red blood cells are destroyed.
[31] Kcentra is used in surgery to stop the action of blood-thinning drugs like warfarin
[32] Berinert is a synthetic form of a protein that occurs naturally in the blood and helps control inflammation in the body

vi) CSL Behring, with an upfront payment of US $91 million, is acquiring Calimmune, a US biotechnology company developing *ex vivo* hematopoietic stem cell gene therapy.

vii) On August 8, 2017, the US International Trade Commission announced its vote to institute an investigation of *Certain Recombinant Factor IX Products* (Inv. No. 337-TA-1066). This follows a July 7, 2017 complaint filed by Bioverativ alleging violation of Section 337 by way of unlawful importation into the US, selling for importation, and/or selling within the US after importation of certain recombinant Factor IX products that infringe one or more claims of US Patent Nos. 9,670,475; 9,623,091; and 9,629,903. The Commission identified CSL Behring LLC of King of Prussia, Pennsylvania, CSL Behring GmbH of Germany, and CSL Behring Recombinant Facility AG of Switzerland as the respondents in this matter.

- Bayer on 30 August 2017 filed a lawsuit at the US District Court for the Northern District of California against Nektar Therapeutics and Baxalta, seeking to protect its pegylated recombinant human factor VIII against a patent challenge. That was the date it also filed its Biological License Application with the FDA for this new treatment for haemophilia A.
- Cerus Corporation entered into a $US 40 million amended growth capital credit facility with Oxford Finance. Cerus received an immediate $US 30 million loan on 31 July 2017 and had the option to draw another $10 million subject to achieving a specified revenue milestone. Kevin D. Green, vice president, finance and chief financial officer of Cerus Corporation, said: *A portion of the proceeds from the initial $US 30 million loan were used to repay the outstanding term loans of approximately $US 17.6 million provided under the original agreement with Oxford. The amended facility provides Cerus with not only additional capital but also deferred amortization for 18 to 24 months.*
- In reporting its second quarter financial results, Cerus highlighted these recent developments amongst others:
  i) Collaboration agreement with Central California Blood Center for the manufacture of pathogen-reduced cryoprecipitate as a novel biologic; and
  ii) Advances in the INTERCEPT red cell program with additional BARDA funding to support clinical trials for a planned FDA submission and commercial manufacturing scale-up.
- Cerus said its CE Mark submission for INTERCEPT red cells is now expected to occur in the second half of 2018 to accommodate new product release assay development; the revised timing also allows for inclusion of Phase III clinical data in thalassemia patients.
- Dimension Therapeutics of Cambridge, Massachusetts has agreed to be acquired[33] by RegenxBio[34] of Rockville, Maryland. RegenxBio will pay $US 3.41 per share in the all-stock deal valued at approximately $US 86 million. Dimension went public at $US 13 per share in 2015. The acquisition agreement comes two months after Dimension shifted its priorities away from its experimental haemophilia B gene therapy, DTX101, in the wake of early clinical trial results that suggested the therapy prompted a possible immune system response. While immunosuppressive steroids can tamp down these responses, such treatment can also diminish the effect of gene therapy. Dimension's stock price tumbled by nearly 50 percent on those January results.

[33] Subject to shareholder agreement Dimension will become a subsidiary of RegenxBio; Dimension shareholders will own approximately 10.9 percent of the combined company, according to the agreement.

[34] Dimension's gene delivery technology was developed by RegenexBio. In 2013, RegenxBio joined with Fidelity Biosciences to form Dimension. Dimension's scientific and technical advisory board was led by James Wilson, a University of Pennsylvania geneticist who was RegenxBio's scientific founder.

- Chinese biopharmaceutical company 3SBio has accelerated the expansion of its global biologics platform by acquiring the Canadian manufacturing business of Therapure[35]. Dr. Jing Lou, Chairman of 3SBio, said: *The acquisition effectively integrates our mammalian cell culture capabilities and Therapure's downstream purification and plasma source technologies.*
- Aptevo Therapeutics announced that it had agreed to sell its three marketed hyperimmune products, WinRho SDF[36], HepaGam B[37], and VARIZIG[38], to Saol Therapeutics for total consideration of up to $US 74.5 million, including an upfront payment of $US 65 million, an additional potential milestone payment of up to $7.5 million related to the achievement of gross profit milestones, and up to $US 2 million related to collection of certain accounts receivable after the closing. Aptevo will continue to own and market IXINITY, an intravenous recombinant factor IX therapeutic for treating haemophilia B.
- Kedrion Biopharma is in the final stages of a $US 100 million upgrade to its production facility in Melville, New York State. The expansion will add about 80 new employees to Kedrion's current workforce of more than 120.
- Bioverativ has formed a strategic collaboration expanding the use and adoption of leading imaging technologies, including ultrasound and radiolabelled imaging, to improve the diagnosis and management of joint disease in people with haemophilia. The collaboration will examine the impact of Bioverativ's extended half-life therapies, ELOCTATE and ALPROLIX, and its investigational therapy BIVV001 [rFVIIIFc-VWF-XTEN], on protection from bleeds and improvement of long-term joint health.
- rivately-held Swiss biopharmaceutical company Novimmune concerning the latter's pre-clinical bi-specific antibody candidate for haemophilia A. The deal will grant Shire rights to develop and commercialise the drug, adding to its own monoclonal antibody capabilities, which it's been focussing on since announcing its new US-based rare diseases innovation centre.
- Apic Bio[39] is advancing a first-in-its class gene therapy for treatment of alpha-1 antitrypsin deficiency, with investments from the venture philanthropy arm of the Alpha-1 Foundation and a private investor with alpha-1 antitrypsin deficiency.

5. Specific country events

- In the US, consumer advocacy group Public Citizen called for the immediate suspension of a large trial sponsored by the National Institutes of Health[40], and comparing blood transfusion strategies after heart attacks. Public Citizen said, in a letter sent to the Office for Human Research Protections and the Veteran Affairs

[35] Therapure offers a range of therapeutic protein development and manufacturing services, including technology transfer and process development, analytical development and testing, scale-up and cGMP manufacturing and aseptic fill/finish and lyophilization. One of its attractions to 3SBio is that Its production lines are established according to US, Canadian and EU biologics cGMP standards.
[36] *WinRho SDF* for autoimmune platelet disorder and haemolytic disease of the newborn;
[37] *HepaGam B* for the prevention of Hepatitis B following liver transplantation and for treatment following hepatitis B exposure
[38] *VARIZIG* for treatment following exposure to varicella zoster virus for individuals with compromised immune systems
[39] Apic Bio is a spin-off from the University of Massachusetts Medical School and is based on gene therapy research by its scientific founders Christian Mueller, Associate Professor of Pediatrics and a member of the Horae Gene Therapy Center at the University of Massachusetts Medical School, Terence R. Flotte, the Celia and Isaac Haidak Professor in Medical Education, dean of the School of Medicine and provost and executive deputy chancellor of the University of Massachusetts Medical School; and colleagues at the Horae Gene Therapy Center. Their research is funded in part by an $US11 million grant from the US National Heart, Lung, and Blood Institute (NHLBI).
[40] National Heart, Lung and Blood Institute. The study is being funded through a $16.1 million grant

Office of Research Oversight, that the Myocardial Ischemia and Transfusion or MINT trial[41] should be halted "because of potentially serious ethical violations".

i) The MINT trial began in April and is expected to be completed in 2021. The trial plan calls for 3,500 hospital patients with acute MI who have blood counts below 10 g/dL to be randomized to either a liberal or restrictive transfusion strategy with red blood cells. The primary endpoint is the composite outcome of all-cause mortality or nonfatal MI at 30 days.
ii) Public Citizen says the trial is unethical and does not adequately protect patients enrolled in the trial. The group claims that the consent form does not fairly describe the trial or explain that the strategies are experimental[42]; and that the trial protocol does not supply important information that would enable institutional review boards to assess the trial sufficiently.
iii) In response to the Public Citizen letter, MINT principal investigator Jeffrey Carson (Rutgers University) provided the following statement: *The Myocardial Ischemia and Transfusion Trial seeks to answer an important question about the optimal amount of blood transfusion that we give to patients with low red blood cell counts who have had a heart attack. Previous small trials do not provide adequate data for accurate predictions, which is why the NIH funded this high-quality large trial. The health and safety of our participants is our top concern. Our protocols and processes have been reviewed by more than 35 institutional review boards across the country, as well as the Data Safety Monitoring Board, which is an independent organization comprised of physicians and ethicists. Each board, independently, has approved it.* Carson was the first author of a 2013 pilot trial with 110 patients which suggested that the more restrictive transfusion strategy might be beneficial[43].
iv) An NIH analysis of 16 randomized trials comparing liberal and restrictive transfusion strategies for heart attack patients found a higher risk of death and major cardiac events associated with a restrictive approach.

- Widespread measles vaccination in the US has sharply decreased measles antibody titre concentrations in plasma donors. Revaccinating donors only briefly boosted the antibody levels[44]. Researchers concluded: *With the success of the measles vaccination program and the ongoing WHO efforts to eliminate and ultimately eradicate measles worldwide, a replacement of the measles antibody titer as a functional potency.*
- On 1 August 2017 Grifols announced that the American Red Cross laboratory in Charlotte, North Carolina was screening blood samples collected in New Jersey, Pennsylvania, Maryland, Maine, Vermont, and New Hampshire with the Procleix *Babesia* assay under an Investigational New Drug (IND) study.
- The Saudi Health Ministry said it had held 16,000 units of blood and blood products ready for treating Hajj pilgrims.
- Cerus Corporation announced the signing of two, new, expanded contracts with Établissement Français du Sang (EFS), the French National Blood Service, for the

[41] https://clinicaltrials.gov/ct2/show/NCT02981407?term=NCT02981407&rank=1
[42] The director of Public Citizen's health group, Michael Carome's press release: *One of the most troubling ethical lapses in the MINT trial is the failure of the consent form to fully disclose to potential subjects the possible risks of using a restrictive blood transfusion strategy. A reasonable person who is considering enrolling in this trial certainly would want to know about prior research results that strongly suggest that use of a restrictive strategy in heart attack patients increases the chances of dying or having another heart attack, and yet the consent form makes no mention of these risks*.
[43] This was a pilot study for the MINT trial, published in the American Heart Journal in June 2013. Of the 110 patients recruited for the study, seven died after a restrictive strategy compared with one who died after a liberal approach.
[44] "Measles Virus Neutralizing Antibodies in Intravenous Immunoglobulins:is an Increase by Re-Vaccination of Plasma Donors possible? "

INTERCEPT Blood System. One contract covers the supply of INTERCEPT Platelet kits while the other is for the purchase of additional Illuminators to help support the roll-out to new regions. The initial term of this platelet kit supply agreement is two years with two one-year extension options, supporting INTERCEPT platelet production in all EFS regional centres. In January 2017, the Ministry of Health informed EFS of its decision that the INTERCEPT Platelet system should be deployed for the control of bacterial infections transmitted by transfusion, in accordance with the December 2016 recommendation by France's regulatory authority, the French National Agency for Medicines and Health Products Safety (ANSM). The EFS produces approximately 330,000 units of platelets annually across 12 regional centres in continental France and 3 overseas territories. The INTERCEPT Blood System for platelets has been used in France since 2006, and is currently used in the Alsace region, as well as throughout overseas French territories including the islands of La Reunion, Guadeloupe, and Martinique. Use in the island territories was to meet the need to maintain a safe platelet supply during outbreaks of chikungunya, dengue and Zika in these tropical regions. INTERCEPT is used by the French Army.

- Canadian Blood Services is seeking $C 855-million over seven years to increase the amount of plasma it collects from unpaid donors. Provincial, territorial and federal governments were provided with a business plan seeking 40 new plasma-collection centres so that Canada could become 50 per cent self-sufficient in plasma for immunoglobulin, rather than the 17 per cent it currently achieves.
  i) CBS is concerned about the rise of a paid-plasma industry that it fears could undermine Canada's voluntary blood-donation system. Some provinces have banned paid plasma collection, but others allow it, including Saskatchewan and New Brunswick, which have two new paid-plasma clinics operated by Canadian Plasma Resources (CPR), which is hoping to open a total of 10 locations across the country.
  ii) CBS spends more on buying plasma derived drugs than it does on its fresh-blood program. It spent over $C 623 million for the drugs in 2016, up from about $C 459 million two years earlier. Much of the increase is accounted by the demand for immunoglobulin.
  iii) Canada's federal government has appointed an expert panel to examine the security and sustainability of the national immunoglobulin supply. The panel is expected to submit its report by the end of March 2018.
- In Italy, blood donation was suspended after a number of people became infected locally with chikungunya.
- Zipline, a California-based drone start up, began delivering medical supplies including blood products in Rwanda, and in 2018, it will start deliveries to over 1,000 health care facilities in Tanzania. Zipline is setting up four distribution centres that will each have as many as 30 fixed-wing drones.

6. 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).

Zika

- Sanofi announced that the US the Biomedical Advanced Research and Development Authority (BARDA), an arm of the Department of Health and Human Services, had informed it in mid-August that it was decreasing its financial assistance for the company's Zika vaccine project. *Consequently, Sanofi does not intend to continue development of, or seek a license from, the Walter Reed Army Institute of Research for the Zika vaccine candidate at this time*, the company said. Various experimental Zika vaccines are being tested[45], but Sanofi was the only major pharmaceutical company with a near-term market goal.
- Scientists at Arizona State University have created a Zika vaccine based on tobacco plants.
- A case-control study in Brazil[46] reinforced the connection between Zika infection and Guillain-Barre syndrome (GBS) and found that older adults were the hardest hit
- Researchers reported
  i) that prior exposure to dengue virus could decrease a patient's immune response to Zika, and potentially even promote infection[47];
  ii) that testing peptides in saliva may be a quick way to diagnose the Zika virus[48];
  iii) that in monkeys Zika doesn't appear to be transmitted through saliva[49];
  iv) that men who contract Zika virus have lower sperm counts for 1 to 2 months after infection[50]; and
  v) that adults infected with the Zika virus can develop a number of serious neurological conditions, most often inflammation and swelling of the brain and spinal cord[51].

Influenza

- A recent study reported in *The Lancet* tested the efficacy, safety and participant satisfaction of influenza vaccination via microneedle patch, and concluded that the administration of inactivated influenza vaccines via such a microneedle patch induces impressive immune responses and shows potential as an alternate method for delivery[52].
- A US study[53]showed that rates of influenza vaccination coverage fell among children when the nasal spray vaccine was not recommended for children aged 2 to 17 years.

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[45] Smaller companies are still working on a Zika vaccine, as are scientists at the US National Institute of Allergy and Infectious Diseases.

[46] By a team from Brazil's health ministry and the US Centers for Disease Control and Prevention (CDC), published at the end of August in *PLoS Neglected Tropical Diseases*.

[47] T.F. Rogers et al., "Zika virus activates de novo and cross-reactive memory B cell responses in dengue-experienced donors," *Science Immunology*, 2:eaan6809, 2017. Published 18 August 2017.

[48] D. Zuanazzi et al., "Postnatal Identification of Zika Virus Peptides from Saliva", *Journal of Dental Research.* Published August 21, 2017, https://doi.org/10.1177/0022034517723325

[49] See *Nature Communications*, 21 August 2017

[50] Guillaume Joguet et al., "Effect of acute Zika virus infection on sperm and virus clearance in body fluids: a prospective observational study", *Lancet Infectious Diseases,* published: 21 August 2017 DOI: http://dx.doi.org/10.1016/S1473-3099(17)30444-9

[51] *JAMA Neurology,* online 14 August 2017

[52] Rouphael, G.N., et al. "The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial".

[53] Benjamin Fogel and Steven Hicks, "Influenza vaccination rates in children decline when the live attenuated influenza vaccine is not recommended", *Vaccine,* Volume 35, Issue 39, 18 September 2017, Pages 5278-5282.
https://doi.org/10.1016/j.vaccine.2017.07.067

For the 2016-17 season, the Centers for Disease Control and Prevention (CDC) recommended against using the live attenuated influenza vaccine sold as FluMist because of issues with effectiveness. Earlier studies had shown ease of administration as a primary factor in parental decisions about vaccinating their children against influenza.

- Westmead Hospital has been participating in an international 320-patient trial involving the use of blood donated by people who have recovered from influenza or who have received the flu shot. Their antibodies are extracted, and this hyperimmune immunoglobulin is given to flu patients by intravenous drip over two hours. The product used in the trial has come from the US.

Avian influenza

Because of the capacity of influenza viruses for re-assortment, 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.

- South Korean scientists have substituted genes from H5N1 avian influenza into an H5N8 avian flu virus and found that in mice it caused greater pathogenicity and up to a 1,000-fold greater virulence[54].
- The number of Chinese towns, provinces, and regions that reported human cases of H7N9 avian influenza from October 2016 was higher than the previous four waves combined, researchers from China and the US Centers for Disease Control and Prevention (CDC) reported[55]. They said
  i) that 759 illnesses were reported in the fifth wave, 281 of them fatal;
  ii) that the newly emerged Yangtze River Delta low pathogenic lineage accounted for most of the activity[56];
  iii) that the highly pathogenic strain which had emerged in poultry, was found in 27 of the 759 human cases, in those from rural areas, people with early hospital admission, and in those who had been exposed to sick or dead poultry; and
  iv) that fourteen clusters of two or three people were reported in the fifth wave, compared with an average of nine in each of the earlier waves.

MERS-CoV

- As of 21 September 2017, there had been in Saudi Arabia a total of 1716 laboratory-confirmed cases of MERS-CoV infection, including 694 deaths.

Ebola virus disease

- Integrated BioTherapeutics (IBT) and The Scripps Research Institute (TSRI) have together been awarded a $US 6.6 million, 5-year grant by the US National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) to develop a vaccine that protects against all ebolaviruses. IBT's Chief Scientific Officer, M. Javad Aman, who is co-principal investigator for the collaboration, said: *To meet this*

[54] Su-Jin Park, "Altered virulence of Highly Pathogenic Avian Influenza (HPAI) H5N8 reassortant viruses in mammalian models", *Virulence,* online: 5 September 2017 http://dx.doi.org/10.1080/21505594.2017.1366408

[55] Kile JC, Ren R, Liu L, et al. Update: Increase in Human Infections with Novel Asian Lineage Avian Influenza A(H7N9) Viruses During the Fifth Epidemic — China, October 1, 2016–August 7, 2017.

[56] In February2017, World Health Organization (WHO) flu vaccine advisors recommended new candidate vaccine viruses for the Yangtze River Delta lineage, for which current H7N9 candidate vaccine viruses showed limited protection.

challenge, we have assembled a unique team of experts in immunogen design, structural biology, vaccine development, and animal models of filovirus infection.

- Two new studies published in *Clinical Infectious Diseases* observed survivors of Sierra Leone's Ebola outbreak to understand how often the disease causes disabilities and how it affects major organs[57]. They found that Ebola survivors have seven times the disability rate of their close contacts, and the virus likely causes muscle damage.

Other diseases: occurrence, diagnosis, prevention and treatment

- The FDA has approved benznidazole to treat the tropical parasitic infection Chagas, or "kissing bug" disease, in children aged 2 to 12. Chagas disease is caused by a parasite called *Trypansosoma cruzi*. According to the World Health Organization about six to seven million people worldwide are infected, mostly in Latin America, with an estimated 300 000 infected people in the US according to the FDA. This chronic debilitating condition is caused by the transmission of infected faeces of blood-sucking bugs. It can also be contracted through transfusion of infected blood, by organ transplantation or congenitally from an infected mother to her foetus.
- A vaccine to prevent Lyme disease is being fast-tracked[58] for approval by the FDA to address the most rapidly growing vector-borne disease in the US. Known in its preapproval phase as VLA15, it is a product of French vaccine-maker Valneva[59]. Only 180 participants in a preliminary clinical trial have received the inoculation so far. Valneva said its vaccine appears to be effective against the six most common types of *B. burgdorferi* that are prevalent in the US and Europe. Under the fast-track designation, the company will advance to a larger clinical study of the vaccine early in 2018.

[57] Soushieta Jagadesh et al., "Disability among Ebola survivors and their close contacts in Sierra Leone: a retrospective case-controlled cohort study." *Clinical Infectious Diseases*, cix705, https://doi.org/10.1093/cid/cix705 Published: 20 August 2017 and Simone Lanini et al., "Relationship between viremia and specific organ damage in Ebola patients: a cohort study", *Clinical Infectious Diseases*, cix704, https://doi.org/10.1093/cid/cix704 Published: 20 August 2017

[58] With fast-tracked products the FDA will accept less data for approval and studies of the vaccine can continue after it goes on the market.

[59] A US- developed vaccine was licensed to Baxter with the licence now is held by Shire. It was developed by Dr. Benjamin Luft, the Edmund D. Pellegrino Professor of Medicine at Stony Brook University and a specialist in infectious diseases.