Monitoring International Trends

**posted April 2016**

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

* Potential new product developments and applications;
* Global regulatory and blood practice trends;
* Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
* Other emerging risks that could potentially put financial or other pressures on the Australian sector.

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

* + A study of the on demand treatment of 37 von Willebrand disease patients showed their bleeding episodes were successfully managed using Baxalta’s BAX 111. (Section 1)
  + Scientists in Korea used mice models of haemophilia A to demonstrate the viability of induced pluripotent stem cells as a cure for the bleeding disorder. (Section 1)
  + uniQure is continuing to trial its gene therapy AMT-060 in haemophilia B patients. (Section 1)
  + Results presented at the American Society for Hematology (ASH) Annual Meeting suggested that treatment with hydroxyurea for stroke prevention among children with sickle cell anaemia appeared to be a viable alternative to chronic transfusion therapy. (Section 1)
  + Kamada announced the initiation of a Phase II clinical trial with its proprietary Alpha-1 Antitrypsin for the prevention of lung transplant rejection. (Section 1)
  + CSL plans to begin in 2017 a phase III trial of CSL 112, designed to prevent acute vascular events following on from a heart attack. (Section 1)
  + The US Food and Drug Administration (FDA) has approved Bayer's Kovaltry, an unmodified, full-length factor VIII compound for the treatment of haemophilia A in children and adults. (Section 2)
  + Bio Products Laboratory (BPL) received marketing authorization from the European Medicines Agency (EMA) for Coagadex which is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency. (Section 2)
  + [Swedish Orphan Biovitrum](http://www.sobi.com/) (Sobi) and its partner Biogen received a positive opinion from the Committee for Orphan Medicinal Products (COMP) of the EMA recommending the European Commission (EC) maintain the orphan designation for Alprolix, a recombinant factor IX Fc fusion protein therapy for the treatment of haemophilia B. (Section 2)
  + The EC [designated](http://seekingalpha.com/pr/16432562-biomarin-receives-european-orphan-drug-designation-bmn-270-first-investigational-aav-factor) BioMarin Pharmaceutical's [BMN 270](http://www.biomarin.com/products/pipeline/bmn-270/) an orphan drug for the treatment of haemophilia A. BMN 270 is a gene therapy designed to restore factor VIII levels in plasma. (Section 2)
  + The CEO of CSL Ltd., Paul Perreault, sees “smart” acquisitions as a way to spur growth. (Section 3)
  + Baxter International is selling some of its shares in Baxalta to pay down debt. (Section 3)
  + [Grifols](file:///C:\search\search-7.1213540%3ftag_company=Grifols&article=true) has acquired a 49 per cent stake in the US-based [Interstate Blood Bank](file:///C:\search\search-7.1213540%3ftag_company=Interstate%20Blood%20Bank&article=true) (IBB) for $US 100 million (€88m). The company has also entered into an option agreement to purchase the remaining 51 per cent stake for an additional $US 100 million, and has agreed to pay $US 10 million to exercise the call option. IBB collects plasma. (Section 3)
  + **LFB American Plasma, the newly established US subsidiary of the French biopharmaceutical LFB Group, announced an agreement with ImmunoTek BioCenters regarding a long-term plasma supply.** (Section 3)
  + Biogen is reported to be looking to sell its haemophilia portfolio. (Section 3)
  + A study found that for patients who underwent total knee arthroplasty (TKA) procedures, the highest transfusion risk was in patients with comorbidities, and patients who underwent simultaneous bilateral TKA or revision surgery. (Section 5)
  + A US study concluded that while passive adoption of restrictive transfusion guidelines reduced blood product use on general medicine floors, the effect was greatly improved after implementation of a local, targeted intervention to improve patient safety. (Section 5)
  + In the US, the wide variation among doctors and between hospitals for blood transfusions during colorectal surgery has triggered a call for proctocols. (Section 5)
  + Researchers from Blood Systems Research Institute in San Francisco and Canadian Blood Services' Centre for Innovation lab in Edmonton reported that certain red blood cell manufacturing methods may be less damaging to cells than others. (Section 5)
  + Scientists have found how to make the blood-thinning drug heparin using human cells. (Section 6)
  + The [Irish Blood Transfusion Service](file:///C:\search\search-7.1213540) is facing legal action from donors cleared to give blood despite being anaemic. (Section 7)
  + The US Centers for Disease Control and Prevention (CDC) said on 13 April: "There is still a lot that we don't know, but there is no longer any doubt that Zika causes microcephaly”. (Section 8)
  + Scientists have [developed a model](http://dx.plos.org/10.1371/journal.ppat.1005547) of infection to see how viruses affect foetal brain development. They found that viruses can delay or even prevent the differentiation of stem cells into mature brain cells. (Section 8)
  + Zika virus has now been linked to a third possible neurological problem, in addition to microcephaly and Guillain-Barré syndrome (GBS). This third suggestion is the autoimmune disorder, acute disseminated encephalomyelitis (ADEM). (Section 8)
  + The University of California at Davis national Primate Research Center has commenced a study on the effects of the [Zika virus](https://theaggie.org/2016/02/23/zika-virus-case-confirmed-in-yolo-county/) on primates. (Section 8)
  + Stanford scientists are investigating a discarded drug that helps human cells in a lab dish fight off viruses like Ebola, dengue and Zika, which use RNA rather than DNA as their genetic material. (Section 8)
  + A team at the Mayo Clinic has been collaborating with the Butantan Institute in Brazil, to develop a vaccine for the Zika virus. (Section 8)
  + [GeoVax Labs is collaborating](http://www.geovax.com/) with the CDC to evaluate its Zika vaccine. (Section 8)
  + In Jakarta, backyard poultry husbandries and slaughterhouses were closed following an outbreak of avian influenza A (H5N1). A (H5N1) is being reported in bird flocks in a number of countries, with human cases in Egypt. (Section 8)
  + By 12 April the known global total for human cases of A (H7N9) was 776, with recent cases being reported from Zheijiang, Jiangsu and Fujian in China. (Section 8)
  + Scientists continue working to improve flu vaccines. (Section 8)
  + Human infections with A (H5N6) in mainland China were concentrated in Guangdong province. (Section 8)
  + As at noon on 11 April Saudi Arabia had experienced 1371 laboratory confirmed cases of MERS-CoV infection, including 587 deaths. There were nine currently active cases. (Section 8)
  + A case of classical BSE (bovine spongiform encepalopathy) was confirmed in a cow in France. (Section 8)
  + A man infected with the Lassa fever virus was admitted to hospital in Germany. He had had contact with the body of a person who died in Cologne after contact with Lassa fever patients in Togo.
  + Measles was diagnosed in Airlie Beach, Queensland, brought in by a Swiss tourist who travelled via India. A significant outbreak of measles in Melbourne began in Brunswick. (Section 8)
  + Sydney had its second outbreak of legionnaires’ disease this year, possibly centred round St George Hospital. (Section 8)
  + An attendee at a festival near Casino, NSW, contracted diphtheria, a disease easily prevented by vaccination. (Section 8)

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# Products

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

## Haemophilia

* 1. A study of the on demand treatment of 37 von Willebrand disease patients showed their bleeding episodes were successfully managed using Baxalta’s BAX 111. The researchers did not report any thrombotic events or severe allergic reactions. No patients reported anti von Willebrand factor binding or neutralizing antibodies to von Willebrand factor. One patient experienced chest discomfort and increased heart rate during infusion.
  2. Scientists from Korea’s Institute for Basic Science and Yonsei University used mice models of haemophilia A in order to demonstrate the viability of iPSCs[[1]](#footnote-1) as a cure for the bleeding disorder[[2]](#footnote-2).
  3. uniQure announced that it had treated the first patient in the second cohort of its ongoing AMT-060-01 Phase I/II trial. The main goal of the second cohort is to assess the safety of a higher dose of uniQure's AMT-060 gene therapy in haemophilia B patients with a severe or moderately-severe disease phenotype. Secondary objectives of the trial include evaluation of factor IX activity levels as well as evaluation of annualized bleeding rates and recombinant factor IX usage.

## Other

* 1. At the International Symposium on Intensive Care and Emergency Medicine in Brussels, Biotest announced further encouraging results of a phase II trial with IgM Concentrate (IgM enriched immunoglobulin). The randomized, double-blind, placebo-controlled phase II trial (CIGMA trial) was performed in 160 hospitalised patients with severe community acquired pneumonia (sCAP)[[3]](#footnote-3). Coordinating investigator Tobias Welte (Head of Clinic for Pneumology, Hannover Medical School, said: "sCAP is still a global problem because of the high mortality rates. The observed reduction of mortality is extraordinary. A successful phase III trial would be a breakthrough therapy option in this field."
  2. Results presented at the American Society for Hematology (ASH) Annual Meeting and Exposition suggested that treatment with hydroxyurea for stroke prevention among children with sickle cell anaemia appeared to be a viable alternative to chronic transfusion therapy[[4]](#footnote-4). The ability to use a pill, rather than chronic transfusion therapy, for stroke prevention in these patients is “really, really huge,” according to **Venee Tubman,** a paediatric haematologist/oncologist at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center.
  3. Kamada announced the initiation of a Phase II clinical trial with its proprietary Alpha-1 Antitrypsin (AAT) for the prevention of lung transplant rejection. The trial is being conducted in collaboration with Baxalta, which has distribution rights to Kamada’s intravenous (IV) AAT for all indications in the US, Canada, Australia and New Zealand.
  4. ADMA Biologics presented a poster titled “Protective Levels of Neutralizing Antibodies to Influenza are Present in an IVIG (RI-002) Containing Standardized and Elevated Levels of Neutralizing Antibodies to RSV*[[5]](#footnote-5)* and Can Protect Influenza Infected Cotton Rats,” at the Clinical Immunology Society 2016 Annual Meeting, held April 14-17, 2016, in Boston.. RI-002 is ADMA’s lead product candidate. It includes significantly elevated levels of neutralizing antibodies to five different strains of influenza as tested in a laboratory of the Centers for Disease Control (CDC). The data presented demonstrated that RI-002 prevents infection in cotton rats challenged with influenza and suppresses inflammatory cytokines induced by influenza.
  5. Stannsoporfin is InfaCare Pharmaceutical’s heme oxygenase inhibitor that inhibits the formation of bilirubin and is in development for the treatment of hyperbilirubinemia in newborns. The company has completed enrolment in its Phase IIB Jasmine study, a multicentre, single dose, randomized, double blind, placebo controlled, parallel group study evaluating the safety and efficacy of two doses of Stannsoporfin in conjunction with phototherapy in neonates, versus phototherapy alone[[6]](#footnote-6).
  6. Reconstituted HDL infusion therapies like CSL's CSL112 are designed to prevent acute vascular events in the immediate time frame after a heart attack. They are intended as a different kind of therapy from oral anti-cholesterol agents, which elevate HDL over weeks to months, and are therefore intended for long-term use. Study Aegis-1 is comparing two doses of CSL112, 6g or 2g, administered in four weekly infusions, against placebo. The primary endpoints concern liver toxicity, with levels of alanine aminotransferase, bilirubin and serum creatinine being tracked during the first 29 days of the study. (CSL abandoned CSL111, an earlier HDL mimetic, after it showed transient elevations of liver enzymes.) The secondary endpoint, designed to assess the drug's efficacy, is the time to first occurrence of a major adverse cardiovascular event (MACE). The patients are considered high-risk, having had a heart attack during the previous week. In an investor presentation last December, the group said Aegis-1's data monitoring committee had confirmed safety to-date. Promisingly, CSL112 did not show liver enzyme elevation in phase II. CSL plans to begin a phase III trial in 2017. This study will also include high-risk patients and have MACE as its primary endpoint.

# Regulatory

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

* 1. The US Food and Drug Administration (FDA) has approved Bayer's Kovaltry (octocog alfa; antihemophilic Factor [recombinant]), an unmodified, full-length factor VIII compound for the treatment of haemophilia A in children and adults. The approval is based on results from the LEOPOLD[[7]](#footnote-7) clinical trials, which supported the approval of Kovaltry for routine prophylaxis to reduce the frequency of bleeding episodes. Kovaltry can be used two or three times per week in adolescents and adults, and two or three times per week or every other day in children. Kovaltry is a follow on to Bayer’s Kogenate. It was approved in Europe and Canada earlier this year, and approved in Japan at the end of March. Kogenate FS for haemophilia A patients is already well-established in the US market. It is produced in Bayer's Berkeley facilities, where Kovaltry also will be made and tested.
  2. Kedrion Biopharma has gained approval from the FDA to package plasma-derived [Koāte Double Viral Inactivation (DVI) Antihaemophilic Factor (human)](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.koate-dviusa.com%2F&esheet=51308143&newsitemid=20160328005367&lan=en-US&anchor=Ko%C4%81te%C2%AE+Double+Viral+Inactivation+%28DVI%29+Antihemophilic+Factor+%28human%29&index=3&md5=6013a4cbe6cbd92f853c330ea7ec4a91) with Mix2Vial, a needle-free transfer device. The new packaging is designed to offer haemophilia A patients optimized safety and convenience when reconstituting Koāte-DVI. Before the availability of Mix2Vial, the reconstitution of Koāte-DVI required the use of a double-ended transfer needle and three steps (instead of two) to prepare the product for infusion.
  3. Bio Products Laboratory (BPL) received marketing authorization from the European Medicines Agency (EMA) for Coagadex which is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency[[8]](#footnote-8). Coagadex is the first and only treatment licensed specifically for this rare bleeding disorder in Europe[[9]](#footnote-9). It was approved based upon data generated from two small open-label, multicentre, prospective studies[[10]](#footnote-10).
  4. BPL announced on 8 April the submission of a Biologics License Supplement (BLS) to the FDA for the use of Gammaplex 10%, Immune Globulin Intravenous (Human) in patients with primary immunodeficiencies. The application was supported by a two-phase, crossover bioequivalence study between the 10% immune globulin treatment being investigated and BPL’s approved immunoglobulin treatment, Gammaplex 5%. The study marks the first time that a 5% and a 10% immune globulin therapy have been directly compared in a registration trial in patients with primary immunodeficiencies. Gammaplex 10% is currently under review by the FDA, and not yet available in the US.
  5. [Swedish Orphan Biovitrum AB](http://www.sobi.com/) (Sobi) announced that the European Commission (EC) has approved the transfer of the marketing authorisation for Elocta (efmoroctocog alfa) from Biogen to Sobi, making Sobi the marketing authorisation holder of Elocta in the EU.
  6. The German Institute for Quality and Efficiency in Health Care (IQWiG) examined Swedish Orphan Biovitrum’s Elocta (efmoroctocog alfa), assessing whether this new drug offers an added benefit over the appropriate comparator therapy both in prevention and in on-demand treatment for people with haemophilia A. It said such an added benefit could not be derived from the dossier, because it did not contain adequate study data.
  7. [Swedish Orphan Biovitrum](http://www.sobi.com/) (Sobi) and its partner Biogen received a positive opinion from the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) recommending the European Commission (EC) maintain the orphan designation[[11]](#footnote-11) for Alprolix (eftrenonacog alfa), a recombinant factor IX Fc fusion protein therapy for the treatment of haemophilia B. The COMP's recommendation was then referred to the EC which is responsible for granting marketing authorisation for medicines in the EU. An application for marketing authorisation was submitted to EMA in June 2015. In February 2016, Sobi and Biogen received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of EMA for Alprolix. If approved and the orphan designation is confirmed, Alprolix will remain on the Community Register of Orphan Medicinal Products and receive orphan designation.
  8. The European Commission has approved Novartis’ Revolade (eltrombopag) as a first-in-class therapy for children aged one and over with chronic idiopathic thrombocytopenic purpura (ITP) who have not responded to other treatments. In ITP, blood does not clot as expected. Patients have a low number of platelets and suffer from purple bruises or tiny red or purple dots on the skin as well as nosebleeds, bleeding from the gums during dental work, or other bleeding that's hard to stop. Their immune system is thought to attack and destroy their platelets.
  9. The European Commission [designated](http://seekingalpha.com/pr/16432562-biomarin-receives-european-orphan-drug-designation-bmn-270-first-investigational-aav-factor) BioMarin Pharmaceutical's [BMN 270](http://www.biomarin.com/products/pipeline/bmn-270/) an orphan drug for the treatment of haemophilia A. BMN 270 is a gene therapy designed to restore factor VIII levels in plasma.

# Market structure and company news

*The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.*

* 1. CEO of CSL Ltd., Paul Perreault, sees “smart” acquisitions as a way to spur growth. “When I think about M&A[[12]](#footnote-12) as part of our strategy, it is really about adding value,” Perreault told a Bloomberg event in Melbourne. “It’s not about bolt-ons…. If you cannot add value, you probably shouldn’t be buying it.” Perreault said China was a “strategic imperative” for the company as its market opened up to treatments for conditions such as haemophilia. The country has as many as 65,000 sufferers of the bleeding disease, though only about 6,000 are being treated. “We have products that can help people in China, but the hard part is finding a way in,” Perreault said. While the company’s recombinant-protein-based medicines may offer a way in, “it will be a while before recombinants may take a big share of the Chinese market.” The company will not seek to diversify away from its core blood-plasma and vaccines business into fashionable areas, like immune therapies for cancer, and it would not rush to spin off the bioCSL unit, Perreault said.
  2. Baxter International is selling some of its shares in Baxalta to pay down debt. Baxter's stake in Baxalta will be reduced from approximately 13.8 percent to 5.1 percent as a result of the sale.
  3. Kamada announced the submission of a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA) for the Company’s inhaled alpha-1 antitrypsin (AAT) therapy as a treatment for AAT deficiency[[13]](#footnote-13).
  4. Shire Pharma Canada announced that Cinryze[[14]](#footnote-14) is now available in Canada to adult and adolescent patients with hereditary angioedema (HAE)[[15]](#footnote-15) who may benefit from routine prevention. The Canadian Blood Services (CBS) will distribute Cinryze throughout the country, except for Québec.
  5. [Grifols](file:///C:\search\search-7.1213540%3ftag_company=Grifols&article=true) has acquired a 49 per cent stake in the US-based [Interstate Blood Bank](file:///C:\search\search-7.1213540%3ftag_company=Interstate%20Blood%20Bank&article=true) (IBB) for $US 100 million (€88m). The company has also entered into an option agreement to purchase the remaining 51 per cent stake for an additional $US 100 million, and has agreed to pay $US 10 million to exercise the call option. The principal business of the Memphis-headquartered IBB is the collection of plasma for the plasma fractionation industry. The deal is subject to clearance from US anti-trust authorities.
  6. LFB American Plasma, the newly established US subsidiary of the French biopharmaceutical LFB Group, announced an agreement with ImmunoTek BioCenters regarding a long-term plasma supply, an agreement which includes the development of several new plasma collection sites in the US. In 2015, LFB Group announced the decision to construct a new fractionation plant in the north of France (Arras region) with an annual capacity of 3 million litres. The agreement with ImmunoTek will allow LFB to scale up plasma production rapidly on completion of the future fractionation plant. ImmunoTek currently has thirty centres in the planning stage for pharmaceutical customers.  *“*The development of a safe and reliable plasma supply chain continues to be an integral focus point for growing biopharmaceutical companies*,”* says Jerome Parnell III, CEO and President of ImmunoTek. “Synergy between LFB’s growth objectives and ImmunoTek’s experience to scale plasma volume will translate into a robust long-term relationship between both companies*.*”
  7. Reuters reported that Biogen is looking to sell its haemophilia portfolio, reportedly to concentrate on other therapeutic areas.
  8. Portola Pharmaceuticals announced a clinical collaboration with Bayer, the manufacturers of Xarelto, to include its own Factor Xa inhibitor rivaroxaban in a clinical development program in Japan. Portola is developing an FDA designated breakthrough therapy called andexanet alfa to reverse anticoagulation in patients taking Factor Xa inhibitors such as Xarelto. The group also entered into separate agreements with Bayer and Janssen Pharmaceuticals, Inc. to support studies of the antidote in the U.S. and Europe.

# Country-specific events

*The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia’*s *visitors and immigrants come.*

* 1. [Verax Biomedical](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.veraxbiomedical.com%2F&esheet=51317308&newsitemid=20160411005680&lan=en-US&anchor=Verax+Biomedical&index=1&md5=58338c03bc7a058327946ed4bce2130b) announced it had renewed its exclusive commercialization agreement with Fresenius Kabi USA, which permits Fresenius Kabi USA to market, sell and distribute Verax's [PanGenera Detection (PGD) test](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.veraxbiomedical.com%2Fproducts%2Fplatelet-pgd-test.asp&esheet=51317308&newsitemid=20160411005680&lan=en-US&anchor=PanGenera%C2%AE%C2%A0Detection+%28PGD%29+test&index=4&md5=8a0d7d39ca77ea4963c44af4ecda4a68), a rapid in vitro diagnostic test used to detect bacterial contaminants in donated platelets. Verax says its Platelet PGD test is the only rapid test on the market cleared by the FDA for all commonly available US platelet types. The FDA now permits the life of platelet supplies to be extended to [seven days](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.veraxbiomedical.com%2Fproducts%2F7-day-platelet-dating.asp&esheet=51317308&newsitemid=20160411005680&lan=en-US&anchor=seven+%287%29+days&index=5&md5=ce473216a029fd87bdf758825c11e166), instead of the previously permitted five days, for apheresis platelets in plasma that have been safety tested using the Verax PGD test.
  2. In the UK, some MPs from all political parties have called on the government to take seriously the concerns of those who were infected with fatal viruses by the NHS. Some 6,000 people contracted HIV or hepatitis C from infected blood products used by the NHS up until 1991. More than 2,000 have so far died. A government consultation has been under way looking at how “unfit for purpose” systems of support for victims can be reformed. A large crowd of victims and families of the dead protested outside Parliament waving placards declaring “Sentenced to death” and “2,000 dead, who cares?”
  3. In the UK the Office of National Statistics reported that the mismatch between strains included in the seasonal vaccine and strains that actually circulated contributed to the largest spike in deaths in a generation.

# Safety and patient blood management

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

## Appropriate Transfusion

* 1. A recent study[[16]](#footnote-16) found that for patients who underwent total knee arthroplasty (TKA) procedures, the highest transfusion risk was in patients with comorbidities, and patients who underwent simultaneous bilateral TKA or revision surgery. Their higher transfusion risk correlated with higher hospitalisation costs.
  2. A US study[[17]](#footnote-17) in a large, urban academic medical centre concluded that while passive adoption of restrictive transfusion guidelines reduced blood product use on general medicine floors, the effect was greatly improved after implementation of a local, targeted intervention to improve patient safety.
  3. In the US, research on the wide variation among doctors and between hospitals for blood transfusions during colorectal surgery has triggered a “call to action” for protocols to clear up this long-debated area of medicine[[18]](#footnote-18). The authors used a large, state-maintained database to conduct the retrospective study of more than 125,000 cases of colorectal surgeries between 2001 and 2013. They reported that transfusion rates before, during and after surgery ranged from 2.4 per cent to 58.7 per cent among surgeons, and from 2.9 per cent to 32.8 percent among individual hospitals. Even among the most experienced and high-volume surgeons, transfusion rates varied. The authors said that, since perioperative blood transfusions have been strongly associated with post-operative infections such as pneumonia, sepsis, and surgical-site complications, surgeons need a more considered method of deciding when to use blood transfusions.
  4. Researchers from Blood Systems Research Institute in San Francisco and Canadian Blood Services' Centre for Innovation lab in Edmonton reported that certain red blood cell manufacturing methods may be less damaging to cells than others. The scientists examined the levels of microparticles and mitochondrial DNA (mtDNA) present in blood that can indicate cellular damage. Studying red blood cell units manufactured using nine different processes, they observed differences in the extent of damage across the nine methods. The findings appeared first in *Vox Sanguinis* online. Dr. Sonia Bakkour, lead researcher and staff scientist in the molecular transfusion lab at Blood Systems Research Institute, had presented the team's preliminary findings at the AABB annual meeting last October. "Working with the American team at Blood Systems Research Institute was key to this research because of the wide variations in blood manufacturing processes present in the US," explained Dr. Jason Acker, senior development scientist with Canadian Blood Services' Centre for Innovation." Dr. Michael Busch, senior vice president and co-director of Blood Systems Research Institute, said more testing of the apheresis collections equipment, blood bags, leukoreduction filters and other variations in manufacturing methods was needed to determine what single element or combination of elements in the various red blood cell manufacturing processes result were responsible for differences. "We think that our research could lead to finding 'the best' way to manufacture red blood cells," predicted Acker. "It's clear now that manufacturing methods matter. We and our respective research sponsors -- Health Canada, US National Institutes for Health, Heart, Lung and Blood Institute are keen to explore what's in the blood bag or in the filters or in the tubing, for example, that can be minimized or eliminated, improving the outcome in patients who receive blood transfusions."[[19]](#footnote-19)

## Treating anaemia

* 1. AMAG Pharmaceuticals has enrolled the first patient in the head-to-head, Phase III clinical trial evaluating the safety of Feraheme (ferumoxytol) compared with Injectafer (ferric carboxymaltose injection) in adults with iron deficiency anaemia (IDA). This trial is the final study before the company files a supplemental new drug application with the FDA to broaden the use of Feraheme beyond the current chronic kidney disease indication to include all adult IDA patients who have failed or cannot tolerate oral iron treatment.
  2. The China Food and Drug Administration accepted Rockwell Medical’s product submission for Triferic and has begun the review process for regulatory approval of the drug as an iron maintenance therapy in patients with chronic kidney disease on haemodialysis. The drug approval process in China requires the company to file a clinical trial application, which is based on the same information that was included in the new drug application Rockwell filed with the US FDA. Robert L. Chioini, founder, chairman and CEO of Rockwell said: “We plan to work with our Chinese partner, Wanbang Biopharma, to provide any additional clinical information required to complete the registration process for Triferic commercialization in China. We expect that the Chinese dialysis market will become the largest in the world over the next few years and that Triferic, once CFDA approved, should generate substantial revenue for Rockwell.” Triferic, which was commercially launched in September 2015, attracted $US 200,000 in [revenue](http://www.nephrologynews.com/rockwell-reports-profit-loss-poor-sales-of-triferic-for-q4-2015/) in 2015, which didn’t reach analyst expectations.
  3. Keryx Biopharmaceuticals reported a positive outcome from the final trial of oral anaemia treatment ferric citrate to treat iron deficiency anaemia in adults with stage 3-5 non-dialysis dependent chronic kidney disease. The study compared treatment with ferric citrate to a placebo in 234 patients who had failed to respond to existing iron therapies. This phase III trial met its primary and all secondary endpoints.

## Other

* 1. Portola Pharmaceuticals’ share price fell significantly when, in a late stage study, its long-acting oral anticoagulant missed the main goal of preventing blood clots in acutely ill patients. Betrixaban, designed for the prevention of venous thromboembolism (VTE), or blood clots, was tested against an injectable standard therapy in patients hospitalized for serious conditions such as heart failure, stroke, and pulmonary disease. There was no statistical difference in major bleeding between the patients treated with betrixaban and those given the injectable, enoxaparin, in the 7,513-patient trial, the company said. Although the number of fatal bleeds was balanced between the two therapies, there were fewer brain haemorrhages in patients on betrixaban. Portola claimed that overall, a "positive net clinical benefit" with betrixaban was observed. Chief Executive Bill Lis said the totality of the efficacy and safety data in such a high-risk patient population was robust enough to support the submission of a marketing application for the drug later this year.
  2. Portola entered a collaboration with Bayer in a clinical development program in Japan. Portola is developing an FDA designated breakthrough therapy called andexanet alfa to reverse anticoagulation in patients taking Factor Xa inhibitors such as Bayer’s Xarelto.
  3. At the American College of Cardiology 65th Annual Scientific Session and Expo in Chicago, Boehringer Ingelheim presented the results of a new interim analysis of data from the continuing phase III RE-VERSE AD patient study. It said the study demonstrated that a single 5g dose of idarucizumab immediately reversed the anticoagulant effect of dabigatran, the active ingredient in Pradaxa, in all patients evaluated. Idarucizumab was the first specific reversal agent for a non-vitamin K antagonist oral anticoagulant approved by the FDA and European Medicines Agency (EMA) in 2015, and is marketed as Praxbind.
  4. Phthalates are banned in toys and some other products, in both the US and EU, due to their potential toxic effects. They are not banned in medical devices.such as plastic IV tubes and catheters, although in 2002 the FDA recommended reducing exposure to phthalates in medical devices. EU funded [researchers](http://cordis.europa.eu/news/rcn/124910_en.html) have now linked them to the development of attention deficit hyperactivity disorder in critically ill children. Research led by Soren Verstraete, from Leuven, Belgium found a “*clear match between previously hospitalized children’s long-term neurocognitive test results and their individual exposure to the phthalate DEHP during their stay in intensive care*.”[[20]](#footnote-20) Verstraete said the development of alternative plastic softeners for use in indwelling medical devices should be considered as a matter of urgency.

# Research

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

* 1. Scientists at the University of Colorado, have used nanoscale quantum dots (minuscule semiconductor particles with specific light-absorption properties) to [kill drug-resistant superbugs](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4542.html) without harming the surrounding healthy tissue.
  2. Researchers at The Ottawa Hospital have used infused mesenchymal stem cells to treat septic shock. Stem cell production is being scaled up for a larger trial.
  3. A product being developed by University of Arizona College of Medicine (Tucson) researchers may extend the window for treatment of rattlesnake bite. Some toxins in pit viper venom destroy fibrinogen, and the therapy is intended to prevent or delay a dangerous result of destruction of fibrinogen, the increase in the risk of bleeding within the body. The product is a combination of carbon monoxide and iron.
  4. The survival rate in children with sickle cell disease (SCD) is higher where there is medical intervention, and the earlier this is available the better. Then in early adulthood, the risk of adverse effects increases. Research reported in *JCI Insight*[[21]](#footnote-21) details the results of a longitudinal study of SCD model mice that links impaired activity of the antioxidant regulator Nrf2[[22]](#footnote-22) to intravascular red blood cell destruction and other adverse SCD-associated effects. Solomon Ofori-Acquah and colleagues at the University of Pittsburgh confirmed that the severity of haemolytic anaemia, vascular inflammation, and lung injury increases with age in SCD mice; however pharmacological activation of Nrf2 in young mice improved survival and reduced age-related adverse effects. They found expression of Nrf2 in non-blood cells was crucial for protection against tissue damage. They concluded that Nrf2 augmentation should be further explored for treating SCD.
  5. Scientists have found how to make the blood-thinning drug heparin using human cells, a safer alternative to current heparin production methods, which rely on animal by products such as pig intestines from sources which have been found to be of variable quality. John Whitelock, head of the Graduate School of Biomedical Engineering at the University of New South Wales, led the research. He said: “When we started this study, we were very surprised that in this century people would still be using an animal extract to produce a drug. What we’ve done is looked at the way our cells naturally make heparin in our bodies, taken that gene, and expressed it in cells in the laboratory. The result is a natural product that is not synthetic, which makes it safer than the animal-sourced material.” Whitelock presented the research at the American Society for Biochemistry and Molecular Biology Annual Meeting during Experimental Biology 2016. The study was funded by the University of New South Wales and the Australian Research Council.
  6. A report in the American Journal of Pathology provides evidence from both mouse and human studies that SHARPIN, a protein involved in regulating inflammation, has anti-septic effects. Liliana Schaefer[[23]](#footnote-23) explained: "Sepsis has been linked to enhanced activity of the enzyme caspase 1 and aberrant expression of pro-inflammatory interleukins 1β and 18. SHARPIN binds to caspase 1 and inhibits its activation. Our study proposes that the caspase 1/SHARPIN interaction may be a key pharmacological target in sepsis and, perhaps, in other inflammatory conditions where SHARPIN is involved”[[24]](#footnote-24).

# 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.*

* 1. In the US a federal jury in Minnesota has ruled against a transgender woman in a case over discrimination at a plasma collection centre. Although the jurors agreed that CSL Plasma turned away Lisa Scott because she is transgender, they also believed the company had a legitimate business reason to do so. The verdict may be appealed.
  2. The [Irish Blood Transfusion Service](file:///C:\search\search-7.1213540) is facing legal action from donors who were cleared to give blood despite being anaemic. Donors indicated their intention to sue after faulty testing equipment failed to detect their low haemoglobin levels.

# 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 Virus

* 1. Dr Tom Frieden, director of the US Centers for Disease Control and Prevention (CDC) said on 13 April: "There is still a lot that we don't know, but there is no longer any doubt that Zika causes microcephaly”. Dr. Sonja Rasmussen, director of the CDC's Division of Public Health Information and Dissemination said it appears that the mosquito-borne Zika virus causes a particularly severe form of microcephaly that does terrible damage to infants' brains. The CDC made its announcement following what it described as a painstaking evidence review led by Rasmussen that was published on an expedited basis in *The New England Journal of Medicine*[[25]](#footnote-25). Until then, the CDC had said Zika appeared to be associated with microcephaly, which results in an unusually small head and brain, but had been careful not to draw a direct causal link between the virus and the birth defect. That's because "this is an unprecedented association" between a mosquito-borne virus and a horrifying birth defect, Frieden explained, and the agency wanted to proceed with caution. However, there's still much that needs to be learned about Zika's effect on foetal development, said Rasmussen, who's also editor-in-chief of the CDC's Morbidity and Mortality Weekly Report. For example, no one knows the exact risk of brain-related birth defects to the baby of a mother infected with Zika, she said, because some Zika-infected women have given birth to apparently healthy babies. Researchers also don't know if Zika will wind up causing learning disabilities to these apparently healthy children later in life, or if Zika also causes birth defects beyond those that are brain-related, Rasmussen added.
  2. Regardless of whether Zika is transmitted mother to child, viruses like HIV, [rubella](http://www.medicaldaily.com/rubella-gone-americas-become-first-region-eliminate-viral-infection-331394), measles, and cytomegalovirus (CMV) are all capable of congenital transmission. Scientists have [developed a model](http://dx.plos.org/10.1371/journal.ppat.1005547) of infection to see how viruses affect foetal brain development. They found that viruses can delay or even prevent the differentiation of stem cells into mature brain cells by activating a specific signalling pathway. Stephane Chavanas, of the Universite de Toulouse in France, and colleagues developed an infection model based on human neural stem cells that normally produce neurons at a rapid rate. They observed that CMV infection significantly reduced the number of neurons the stem cells could generate[[26]](#footnote-26).
  3. Zika virus has now been linked to a third possible neurological problem, in addition to microcephaly and Guillain-Barré syndrome (GBS). Two patients out of six who tested positive for the virus were diagnosed with the autoimmune disorder acute disseminated encephalomyelitis (ADEM)[[27]](#footnote-27), according to a small study presented at a meeting of the American Academy of Neurology in Vancouver. Four of the patients were diagnosed with GBS[[28]](#footnote-28), Co-author Maria Lucia Brito Ferreira of the Restoration Hospital in Recife, Brazil, said “much more research will need to be done to explore whether there is a causal link between Zika and these brain problems”.
  4. The University of California at Davis National Primate Research Center has commenced a study on the effects of the [Zika virus](https://theaggie.org/2016/02/23/zika-virus-case-confirmed-in-yolo-county/) on primates. Led by virologist Koen Van Rompay, the researchers investigate any developmental impacts of Zika virus and eventually test potential vaccines.
  5. Thermo Fisher Scientific offered the first test kits available in the US to enable serological detection of the Zika virus in research applications. The kits are manufactured by Euroimmun AG. The company says that the highly specific viral antigen used in the assays virtually eliminates cross reactivity with other flavivirus antibodies that are known to interact with the Zika virus, enabling reliable differentiation from viruses such as dengue fever and chikungunya.
  6. Creative Testing Solutions of Phoenix, Arizona claimed on 12 April to be the first testing laboratory in the US to implement a Zika test to ensure the safety of the US blood supply. At that time the CTS laboratory in Tampa, Florida was testing only Puerto Rico blood donations for Zika, since that was the only US state or territory collecting blood in an area with active local transmission of mosquito-borne Zika infections. "The speed at which this test was implemented is unprecedented in blood donation screening history," said Dr. Phillip Williamson, vice president of Operations and Scientific Affairs, who led the team that implemented the Zika test in conjunction with the test manufacturer and under the FDA investigational new drug (IND) mechanism. "Previously, a similar process was enacted to address the need for West Nile virus screening. We accomplished in 6 weeks the same process that took approximately 12 months for WNV." The aggressive implementation timetable was possible because the new Zika test was based on a Nucleic Acid Amplification (NAT) testing platform already in use at all Creative Testing Solutions laboratories. NAT testing technology has been in use for more than two decades to screen blood donations for hepatitis B and C, HIV and, more recently, West Nile virus.
  7. Stanford scientists are investigating a discarded drug that helps human cells in a lab dish fight off viruses. The drug targets viruses like Ebola, dengue and Zika, which use RNA rather than DNA as their genetic material. The drug boosts the human body's ability to resist the virus rather than taking on the virus directly[[29]](#footnote-29).
  8. Dr. Gregory Poland and his team at the Mayo Clinic have been collaborating with the Butantan Institute in Brazil, to develop a vaccine for the Zika virus.
  9. [GeoVax Labs](http://www.geovax.com/) entered into a Research Collaboration Agreement with the CDC to evaluate the immunogenicity and protective efficacy of its Zika virus vaccine. GeoVax had announced on 3 February that it had begun a program to develop a vaccine for the prevention of Zika virus infections using its novel MVA-VLP vaccine platform, and that it had entered into a collaborative relationship with researchers at the University of Georgia to speed development of the vaccine.

## Other mosquito-borne diseases

* 1. New research shows that *Plasmodium knowlesi*, a form of malaria common in monkeys in South East Asia, is capable of flourishing in people even though so far it rarely does[[30]](#footnote-30).
  2. Inovio Pharmaceuticals announced that its novel dMAb antibody and DNA vaccine targeting the chikungunya virus provided 100 per cent protection against a lethal virus challenge in mice[[31]](#footnote-31).
  3. "Control of dengue has certainly been a public health priority for many years. But getting there has not been easy," Stephen S. Whitehead, a researcher at the US National Institutes of Health said of new vaccine candidate TV003,which has been initially tested using a "human challenge model."[[32]](#footnote-32) Researchers gave TV003 to 24 adult volunteers in Maryland and Vermont, while another 24 adults received a placebo as a control. After one injection of TV003, 92 per cent of participants in the vaccine group developed antibodies to all four types of dengue virus. The only side effect associated with the vaccine was a rash around the injection site, which resolved itself in five to 10 days. The participants were artificially infected, six months after receiving TV003, with a highly weakened version of dengue virus Type 2. None of the vaccinated adults became infected, whereas 80 per cent of the people in the control group developed a rash and all of them had detectable dengue virus in their blood. The researchers are now testing whether the TV003 vaccine can protect people from the three other types of dengue virus, beginning with Type 3.

## Influenza: strains, spread, prevention and treatment

* 1. In Indonesia, the administration shut down backyard poultry husbandries and slaughterhouses in the capital following an outbreak of avian influenza (H5N1) in South Jakarta.
  2. Vietnam reported to the World Organization for Animal Health (OIE) a new outbreak of highly pathogenic H5N1 avian flu in poultry which began on 1 April.
  3. By 12 April the known global total for cases of H7N9 was 776, with recent cases being reported from Zheijiang, Jiangsu and Fujian in China.
  4. H5N6 human infections in mainland China were concentrated in Guangdong province.
  5. Further H5N1 cases in humans were reported in Egypt.
  6. A number of companies and institutions are working to improve flu vaccines.
  7. Sanofi Pasteur and the University of Georgia announced that through the use of novel computationally optimized broadly reactive antigen (COBRA) technology, they have elicited a response against multiple seasonal and pandemic [H1N1](http://www.fiercevaccines.com/tags/h1n1) influenza virus strains in mice[[33]](#footnote-33). [Sanofi Pasteur](http://www.fiercevaccines.com/tags/sanofi-pasteur) project head Dr. Tim Alefantis said the vaccine technology focusses on the haemagglutinin protein, found in all licensed flu vaccines. He said: “So we're really trying to leverage the strength of the current vaccine and use the COBRA technology to increase the breadth."
  8. Others working on next-generation flu vaccines inlude Israel-based BiondVax, Wisconsin-based [FluGen](http://www.fiercevaccines.com/tags/flugen), Johnson & Johnson, and the [Scripps Research Institute](http://www.fiercevaccines.com/tags/scripps-research-institute). BiondVax announced that it has completed recruitment in a 224-patient Phase IIb clinical trial of its candidate, M-001. That trial will test the candidate when used ahead of an avian influenza vaccine and is being conducted in conjunction with EU universal vaccine consortium UNISEC.
  9. Vaxart has developed technology for a tablet formulation of recombinant vaccines, which are usually developed as an injectable. The company’s Phase I study of its H1 influenza vaccine generated broad antibody and T-cell responses after just one dose with the oral tablet medication. Last October, Vaxart was [awarded a $US 14 million grant](http://www.vaxart.com/NRfiles/VaxartBARDA102815.pdf) by the US Office of Biomedical Advanced Research and Development Authority (BARDA) to fund a Phase II challenge study. In this study; Vaxart’s vaccine will be tested against a traditional injectable and a placebo. Data from the Phase II trial is expected in 2017. Vaxart is exploring the same delivery platform to develop a tablet vaccine for the Zika virus.
  10. The US government recently committed $US 38 million to fund two projects to improve flu vaccines. One will set out to develop a room-temperature stable recombinant flu vaccine, the other will map flu virus changes over time.
  11. Bone marrow-derived stromal cells are already undergoing clinical trials for sepsis and acute respiratory distress syndrome in the US. Now University of Hong Kong scientists have begun laboratory testing an experimental treatment for H5N1 using mesenchymal stromal cells.

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

* 1. As at noon on 11 April Saudi Arabia had experienced 1371 laboratory confirmed cases of MERS-CoV infection, including 587 deaths. There were nine currently active cases.

## Other diseases: occurrence, prevention and treatment

* 1. Measles was diagnosed in Airlie Beach, Queensland, brought in by a Swiss tourist who travelled via India. As the tourist participated in a variety of tourist activities, secondary cases were expected to be widely scattered. People born after 1965 who could not verify they have had two doses of MMR vaccine were advised to see their GP. A significant outbreak of measles in Melbourne began in Brunswick, and then spread to other suburbs.
  2. A funeral worker in Germany was admitted to Frankfurt University Hospital with Lassa fever, after contact with the body of a person who died in the Cologne University Hospital after contact with Lassa patients in Togo.
  3. Sydney has had its second outbreak of legionnaires’ disease this year, possibly centred round St George Hospital.
  4. An attendee at a festival near Casino, NSW, over Easter contracted diphtheria, a disease easily prevented by vaccination.
  5. Texas and CDC have formed a task force with interests in Texas to tackle Chagas disease and the "kissing bug" that spreads the parasite that causes it[[34]](#footnote-34). Conditions in the Rio Grande Valley are ideal for the parasite Trypanosoma cruzi. Chagas disease may later cause intestinal and cardiac complications, including sudden death.
  6. Scientists at the [the University of Queensland](http://www.uq.edu.au/) [School of Chemistry and Molecular Biosciences](http://www.scmb.uq.edu.au/) and at the [University of California San Francisco](https://www.ucsf.edu/) have found a new way to inhibit the growth of the bacterium that causes tuberculosis (TB). They investigated the impact of compounds related to cholesterol on the tuberculosis-causing bacterium *Mycobacterium tuberculosis.* Cholesterol was already known to affect the virulence and infectivity of TB, and this research showed that the bacterium is given modified cholesterol instead, then it cannot use it as its energy source and so it stops growing.
  7. An article in *The Journal of Molecular Diagnostics[[35]](#footnote-35)* introduces an advanced assay that offers better sensitivity than currently available tests for detecting a prion disease affecting elk.
  8. Scientists from the University of Leeds say they have discovered the method that HIV and Ebola viruses use to bond to cells and spread throughout the body. They hope that this could allow interruption of the process. The study was published in the *Angewandte Chemie* journal.
  9. The European Union Reference Laboratory confirmed on 23 March a case of classical BSE (bovine spongiform encepalopathy). The cow affected was from a French farm.
  10. A man infected with the Lassa fever virus was admitted to the isolation unit of the Frankfurt University Hospital. As an employee in a funeral home he had had contact with the body of a person who died, having been in contact with Lassa fever patients in Togo.

1. Induced pluripotent stem cells [↑](#footnote-ref-1)
2. [Chul-Yong Park](javascript:void(0);) et al., “Functional Correction of Large Factor VIII Gene Chromosomal Inversions in Hemophilia A Patient-Derived iPSCs Using CRISPR-Cas9”, Cell Stem Cell, 23 July 2015. (DOI: <http://dx.doi.org/10.1016/j.stem.2015.07.001>). The researchers collected urinary cells from patients with the chromosomal inversions causing haemophilia to make the iPSCs. They then used Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) associated protein 9 to apply Cas9 nucleases to the iPSCs. [↑](#footnote-ref-2)
3. In the phase II study patients were randomized to two groups. One group received standard antibiotic therapy and placebo (control group). The other group received IgM Concentrate in addition to standard therapy. As published previously, in the control group 28 per cent of patients died within 28 days). In the IgM Concentrate treatment group, the mortality was 22 per cent. Further analyses were performed to identify the patient group that benefits most from IgM Concentrate therapy. More than 75 per cent of patients showed a considerable elevation of inflammation markers before the start of treatment and these patients responded to IgM treatment to a greater extent. In these patients, IgM Concentrate led to a relative reduction of mortality of more than 50 per cent. [↑](#footnote-ref-3)
4. Ware RE et al. [Abstract 3](https://ash.confex.com/ash/2015/webprogram/Paper79359.html). Presented at: ASH Annual Meeting and Exposition; Dec. 5-8, 2015; Orlando, Florida. Russell Ware is director of the division of haematology at Cincinnati Children’s Hospital and professor in the department of paediatrics at the University of Cincinnati. [↑](#footnote-ref-4)
5. RSV (respiratory syncytial virus) is a common virus that leads to mild, cold-like symptoms in otherwsie healthy adults older healthy children. It is more serious in young babies, especially those in high-risk groups. [↑](#footnote-ref-5)
6. The study enrolled 91 term and near term newborns of 35 weeks gestational age and older, across 20 centres in the US. The neonates had blood type incompatibilities with their mothers, had evidence of haemolysis (breakdown of red blood cells) and bilirubin levels requiring intervention in accordance with American Academy of Pediatrics (AAP) guidelines. [↑](#footnote-ref-6)
7. Long-Term Efficacy Open-Label Program in Severe Haemophilia A Disease [↑](#footnote-ref-7)
8. Factor X deficiency is a serious condition. Patients are at increased risk of bleeding or experiencing excessive or prolonged bleeding. Severely affected patients, often children, have an increased risk of bleeding inside the brain, in the lungs or in the gastrointestinal tract, which can be life-threatening. Hereditary Factor X deficiency affects approximately 700 patients in Europe. [↑](#footnote-ref-8)
9. Professor Flora Peyvandi, Director of Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Professor of Internal Medicine- IRCCS Maggiore Hospital, University of Milan, said: “Until now, we have focused on treating Factor X deficiency with blood infusions of plasma or a concentrate of clotting factors. We have wanted a specific Factor X therapy to treat these vulnerable patients. Therefore, the approval of Coagadex in the EU today is a significant advance for patients.” Dr Steve Austin, Haemophilia Centre Director of St George’s University Hospitals NHS Foundation Trust, London, said: “Having been involved in the clinical development programme of Coagadex, I am delighted that this therapy has now been approved. For the first time, patients with this rare bleeding disorder can receive a specific therapy that has been proven safe and effective in clinical studies.” [↑](#footnote-ref-9)
10. The first study was in patients with moderate to severe hereditary factor X deficiency who were treated on-demand for spontaneous or traumatic bleeding episodes. The primary efficacy endpoints were pharmacokinetic measures including recovery rate and half-life, and secondary endpoints included overall assessment of efficacy and the number of infusions needed to treat a bleed. The criteria for treatment success were satisfied in the study, and the pharmacokinetic parameters were consistent with previously published data. Two patients in the study reported six adverse events such as fatigue, infusion site erythema, infusion site pain and back pain. The second study covered five patients undergoing seven surgical procedures. Coagadex was assessed by the investigator as excellent in controlling blood loss during and after surgery. All patients undergoing major surgery had only mild factor X deficiency. There were no treatment-related adverse events reported in surgical patients in the second study. [↑](#footnote-ref-10)
11. To receive orphan designation in the EU, the new drug must be for the treatment of a life-threatening or chronically debilitating condition that affects no more than five in 10,000 people in the EU and for which no satisfactory treatments exist or, where they do exist, the new medicine will be of substantial benefit to patients. It can also be awarded if a new medicine is not expected to make a sufficient return to justify the investment. Designation as an orphan within EU confers benefits such as a 10-year period of market exclusivity following marketing authorisation. [↑](#footnote-ref-11)
12. Mergers and acquisitions [↑](#footnote-ref-12)
13. Amir London, CEO of Kamada, said: “The EMA has agreed to evaluate the totality of the data from our innovative Phase II/III study, and based upon orphan designation of the drug, prior discussions with regulators, the strength of these data, the support we get from the key opinion leaders and the patient community, and the persistent unmet need in this chronic disease, we are highly optimistic of a favourable outcome. Importantly, the combination of lung function measurements, which are the gold standard for pulmonary diseases, and symptom improvements, along with the safety profile of the product, gives us confidence these data meet the risk/benefit balance required by EMA.” [↑](#footnote-ref-13)
14. Cinryze is a highly purified, pasteurized and nanofiltered plasma-derived C1 esterase inhibitor product administered intravenously. [↑](#footnote-ref-14)
15. HAE is a rare and potentially life-threatening genetic disorder that causes acute swelling attacks in different parts of the body [↑](#footnote-ref-15)
16. [Nichols CI, et al.inJ Arthroplasty. 2016;doi:10.1016/j.arth.2015.10.013.](http://www.arthroplastyjournal.org/article/S0883-5403%2815%2900908-0/abstract?showall=true=) [↑](#footnote-ref-16)
17. Scott Hasler, Amanda Kleeman, Richard Abrams, Jisu Kim, Manya Gupta, Mary Katherine Krause, and Tricia J. Johnson, in ***Am J Manag Care.* 2016;22(4):295-300**  [↑](#footnote-ref-17)
18. Christopher T Aquina et al., “[Large Variation in Blood Transfusion Use After Colorectal Resection: A Call to Action](http://journals.lww.com/dcrjournal/Abstract/2016/05000/Large_Variation_in_Blood_Transfusion_Use_After.8.aspx)”, in the journal [*Diseases of the Colon and Rectum*](http://www.ncbi.nlm.nih.gov/pubmed/27050603)*,* May 2016, Volume 59, Issue 5. [↑](#footnote-ref-18)
19. See: A.L. Hansen, J.D.R. Kurach, T.R. Turner, C.Jenkins, M.P.Busch, P.J. Norris, J. Dugger, P.A. Tomasulo, D.V.Devine, J.P.Acker, “**The effect of processing method on the in vitrocharacteristics of red blood cell products”,** Vox Sanguinis, 2015; 108 (4): 350 DOI: [10.1111/vox.12233](http://dx.doi.org/10.1111/vox.12233); and S. Bakkour, J.P. Acker, D.M. Chafets, H.C. Inglis, P.J. Norris, T.H. Lee, M.P. Busch, “**Manufacturing method affects mitochondrial DNA release and extracellular vesicle composition in stored red blood cells”,** Vox Sanguinis, 2016; DOI: [10.1111/vox.12390](http://dx.doi.org/10.1111/vox.12390) [↑](#footnote-ref-19)
20. The research involved nearly 450 children, from newborns to age 16, who were treated in paediatric intensive care units and whose care involved from one to 12 medical tubes; along with 100 healthy for comparison. Measurement of blood levels of DEHP metabolites found no detectable levels in the blood samples of healthy children but “sky high” levels in children admitted with catheters. Four years later the previously critically ill children underwent neurocognitive tests and a strong association between high exposure to phthalates and development of attention deficit hyperactivity disorder was established. The findings were validated with a different group of 221 paediatric ICU patients. Results were presented in Boston to to The Endocrine Society’s 98th annual meeting. [↑](#footnote-ref-20)
21. ##### [Samit Ghosh et al.,](http://insight.jci.org/articles/view/81090) “[Nonhematopoietic Nrf2 dominantly impedes adult progression of sickle cell anemia in mice](http://insight.jci.org/articles/view/81090)”, published April 7, 2016: *JCI Insight.* 2016;[1(4)](http://insight.jci.org/1/4):e81090. doi:[10.1172/jci.insight.81090](http://dx.doi.org/10.1172/jci.insight.81090).

    *JCI Insight* is published by the American Society of Clinical Investigation. [↑](#footnote-ref-21)
22. Nuclear factor erythroid-2–related factor 2 (Nrf2) [↑](#footnote-ref-22)
23. Professor of Pharmacology at the Institut fur Allgemeine Pharmakologie und Toxikologie of the Klinikum der Goethe-Universität Frankfurt am Main [↑](#footnote-ref-23)
24. The investigators found that sepsis in mice bred to be deficient in SHARPIN resulted in enhanced levels of interleukins 1β and 18 and active caspase 1, as well as shortened survival. Treatment with a caspase 1 inhibitor reversed these effects by reducing levels of interleukins 1β and 18, decreasing cell death in the spleen, and prolonging survival. [↑](#footnote-ref-24)
25. Rasmussen said the CDC concluded that Zika causes microcephaly based on a checklist of specific criteria that included:

    * Women who deliver babies with microcephaly were infected with Zika during the first and second trimester of gestation.
    * A consistent pattern has developed where pregnant women infected with Zika have given birth to children with microcephaly and other brain-related defects.
    * The link makes sense biologically, with autopsies revealing the presence of Zika in the brains of babies with severe microcephaly who died.

    [↑](#footnote-ref-25)
26. Rolland M, Li X, Sellier Y, Martin H, Perez-Berezo T, Rauwel B, et al. “PPARg Is Activated during Cogenital Cytomegalovirus Infection and Inhabits Neurogenesis from Human Neural Stem Cells”, PLOS One. 2016. [↑](#footnote-ref-26)
27. ADEM is caused by the immune system attacking the myelin sheaths around nerves of the brain and spinal cord—a hallmark of multiple sclerosis (MS). Unlike MS, which flares up repeatedly, ADEM usually happens only once, and patients generally recover within several months. In severe cases, ADEM can lead to coma, vision loss, or paralysis. [↑](#footnote-ref-27)
28. a disorder that affects the peripheral nerves and can cause (usually temporary) paralysis—an association seen in previous studies [↑](#footnote-ref-28)
29. The work was published March 28 in [*Nature Chemical Biology*](http://www.nature.com/nchembio/index.html). [Chaitan Khosla](https://profiles.stanford.edu/chaitan-khosla), a professor of chemistry and of chemical engineering, was one of the senior authors on the paper. [↑](#footnote-ref-29)
30. [Selasi Dankwa](http://www.nature.com/ncomms/2016/160404/ncomms11187/full/ncomms11187.html#auth-1) et al., “Ancient human sialic acid variant restricts an emerging zoonotic malaria parasite”, *Nature Communications,* Volume 7, Article number 11187. doi:10.1038/ncomms11187 [↑](#footnote-ref-30)
31. The paper, “Rapid and long-term immunity elicited by DNA encoded antibody prophylaxis and DNA vaccination against Chikungunya virus,” was prepared by Inovio authors and their academic collaborators, and was published in The Journal of Infectious Diseases. [↑](#footnote-ref-31)
32. # Beth D. Kirkpatrick, Stephen S. Whitehead et al., “The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model”, Science Translational Medicine ,16 Mar 2016:Vol. 8, Issue 330, pp. 330ra36 (DOI: 10.1126/scitranslmed.aaf1517)

    [↑](#footnote-ref-32)
33. Sanofi Pasteur and the University of Georgia published the preclinical results in *Journal of Virology*. [↑](#footnote-ref-33)
34. The Texas Chagas Disease task force will work with health care providers, doctors and residents to raise awareness about Chagas disease. The illness is spread by triatomine bugs, which are commonly called "kissing bugs" because they prefer to bite people on the lips. [↑](#footnote-ref-34)
35. John G. Gray et al., "Defining and Assessing Analytical Performance Criteria for a TSE-Detecting Amyloid Seeding Assay," The *Journal of Molecular Diagnostics*, Volume 18, Issue 3 (May 2016). (DOI: [dx.doi.org/10.1016/j.jmoldx.2016.01.005](http://dx.doi.org/10.1016/j.jmoldx.2016.01.005)). [↑](#footnote-ref-35)