Monitoring International Trends

posted October 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:

- ❖ Swab Tech's automated Surgical Swab-Washer recovers blood from swabs used in the hospital operating theatre. This blood can then be processed and transfused back into the patient. (Section 1)
- ❖ Australia's Therapeutic Goods Administration (TGA) approved CSL Behring's IDELVION [albutrepenonacog alfa] for patients with haemophilia B (congenital factor IX deficiency). (Section 2)
- ❖ The European Medicines Agency (EMA) granted Bluebird bio access to its Priority Medicines (PRIME) scheme for LentiGlobin investigational gene therapy in the treatment of patients with transfusion-dependent beta-thalassemia (TDT). The PRIME scheme speeds regulatory evaluations to bring innovative medicines to patients more quickly. (Section 2)
- ❖ The US Patent and Trademark Office (USPTO) granted Abbott Laboratories a patent for a method for determining volume and haemoglobin content of individual red blood cells. Together with the microscopic evaluation of the distribution of sizes, shapes and colour of red cells and other biochemical tests this method will provide insight into the condition of a patient with blood disorders such as microcytic anaemias. (Section 2)
- ❖ Siemens has received FDA approval for its handheld portable coagulation analyzer. (Section 2)
- ❖ The US Food and Drug Administration (FDA) received several adverse event reports associated with Baxter's Vascu-Guard Peripheral Vascular Patch during carotid endarterectomy (CEA). (Section 2)
- ❖ The FDA granted Sangamo BioSciences orphan drug designation for SB-FIX, the company's zinc finger nuclease (ZFN)-mediated genome editing product candidate for the treatment of haemophilia B. (Section 2)
- ❖ The FDA has approved two of Stryker's clot retrieval devices as a first-line therapy for ischemic strokes to be given together with a clot-dissolving drug. The devices were initially approved in 2012 to remove blood clots in stroke patients who could not take the drug or in whom the drug did not work. (Section 2)
- ❖ Emmaus Life Sciences submitted to the FDA a New Drug Application for an orally administered pharmaceutical grade L-glutamine (PGLG) for the treatment of sickle cell disease in adults and paediatric patients. (Section 2)
- ❖ Terumo and CytoSorbents will commercialize the latter's blood purification absorber for critically ill and cardiac surgery patients. (Section 3)

- Transparency Market Research (TMR) expects the global market for plasma protein therapeutics to rise at a compound annual growth rate of 7.0 per cent between 2016 and 2024. (Section 3)
- GlaxoSmithKline has named its next CEO, Emma Walmsley, who heads the company's consumer health business. (Section 3)
- CEO of NovoNordisk, Lars Sorensen, is stepping down from the beginning of 2017. (Section 3)
- GigaGen has received a grant to facilitate development of natural repertoire recombinant intravenous immunoglobulin (rIVIG) "hyperimmunes" against common pathogens for patients with primary immune deficiency (PID). (Section 3)
- SAB Biotherapeutics announced that its DiversitAb human antibody production platform, leveraging transchromosomic cattle, was identified as of one of the six most meritorious proposals emerging from the World Health Organisation (WHO) public consultation on platform technologies for priority infectious diseases with epidemic potential. (Section 3)
- Alexion Pharmaceuticals' drug, eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria costs more than $US 500,000 per patient per year. Ra Pharmaceuticals has been raising funds to start Phase II trials of an alternative, RA101495, early in 2017. (Section 3)
- HemoSonics announced the publication of four journal articles describing the first clinical experiences with the company's QuantraTM Hemostasis Analyzer, designed to improve the management of critical bleeding. (Section 5)
- Jeffrey L. Carson has been awarded more than $US 16.1 million by the US National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) to lead a nation-wide clinical trial to evaluate whether a restrictive or a liberal blood transfusion is most beneficial to patients who have had a heart attack, in terms of improving their survival rates and reducing the risk of recurrence. (Section 5)
- AABB's new guidelines on thresholds for red blood cell transfusions were published online in the *Journal of the American Medical Association*. The two-tier recommendation lowers the haemoglobin threshold from 10 g/dL to 7 g/dL for haemodynamically stable adults and 8 g/dL for patients who either have cardiovascular disease or are undergoing cardiac or orthopaedic surgery. The guidance also says red blood cells stored for any length of time within their licensed dating period are as safe as blood stored 10 days or less for most stable patients, even newborns. (Section 5)
- A retrospective study found that amongst almost 3,000 patients who underwent total joint arthroplasty and received aspirin for venous thromboembolism prophylaxis, the use of tranexamic acid led to decreased bleeding and transfusion rates without an increased incidence of subsequent venous thromboembolism. (Section 5)
- A recent review in *The International Journal of Clinical Transfusion Medicine* presented an overview of the indications, use and evidence for cryoprecipitate transfusion in haemorrhage, how it may promote haemostasis, and recent developments in extended thaw cryoprecipitate. (Section 5)
- A study has found that intravenous iron postoperatively may reduce infections, transfusions and length of hospital stay. (Section 5)
- Researchers have identified a potential genetic link between platelet activity and cardiovascular disease. (Section 6)
- Scientists say they have discovered a new treatment for sepsis, a drug which prevents bacteria from sticking to the inner-most side of blood vessels. (Section 6)
- University of Utah scientists say that a factor found in umbilical cord blood could be used to fight inflammation and sepsis in adults. (Section 6)
- There is growing evidence that platelets aid the dissemination of cancer cells. (Section 6)
- Novuson Surgical has been awarded a grant by the US National Institute of Health's National Heart, Lung, and Blood Institute (NHLBI) to further develop a novel

approach to mitigate the effects of perioperative bleeding in surgically reconstructed great vessels in neonates using a therapeutic modality of ultrasound. (Section 6)

- The European Medicines Agency (EMA) announced that patients receiving drugs derived from blood plasma or urine are not at increased risk of catching Zika, even if the body fluids come from countries where the virus is prevalent. (Section 7)
- Researchers found that the Zika virus remains in some macaques' organs and fluids, even after the immune system has removed it from the blood stream. (Section 7)
- The US government is funding the development of several Zika vaccine candidates. (Section 7)
- For the Southern Hemisphere's 2017 flu season, the World Health Organisation (WHO) recommended that trivalent vaccines contain an A/Michigan/45/2015 (H1N1) pdm09-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus; and a B/Brisbane/60/2008-like virus. WHO recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus. (Section 7)
- A GlaxoSmithKline-led team reported that a two-dose adjuvanted H7N9 vaccine showed promise in a clinical trial, triggering a robust antibody response and being well tolerated. (Section 7)
- Viable avian flu virus is readily detectable in the air of live-poultry markets, and researchers based at Hong Kong University isolated three subtypes during recent sampling: H5N6, H7N9, and H9N2. (Section 7)
- By 29 September there had been in Saudi Arabia 1457 laboratory-confirmed cases of MERS-CoV infection, including 611 deaths. (Section 7)
- Work continues on vaccines against the Ebola virus. (Section 7)
- Researchers have discovered it may be possible to test patients for Creutzfeldt-Jakob disease using urine samples. (Section 7)

Table of Contents

1. 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.

Sickle Cell Disease

a) Mast Therapeutics reported top-line results from EPIC, a Phase III clinical study of its investigational new drug vepoloxamer (MST-188) for the treatment of patients with sickle cell disease experiencing vaso-occlusive crisis (VOC). The study did not meet its primary efficacy endpoint of demonstrating a statistically significant reduction in the mean duration of VOC (82 hours in the vepoloxamer group compared with 78 hours in the placebo group). There were no statistically significant differences between treatment groups across the two secondary efficacy endpoints, rate of re-hospitalization for VOC and the occurrence of acute chest syndrome. Brian M. Culley, the company's CEO, said: "We are exceedingly disappointed with these top-line results. While clearly not the outcome we wanted, we believe the insights and data from the largest placebo-controlled clinical trial ever completed in sickle cell disease will substantially advance the understanding of vaso-occlusive crisis and the still maturing clinical science necessary to support the development of new therapeutics for this debilitating disease…in the coming weeks the Company intends to review the full data set from EPIC. In addition, we plan to perform an interim analysis of the ongoing heart failure trial of vepoloxamer. However, based on the data we've seen to date, we expect we will terminate all clinical development of vepoloxamer".

b) Global Blood Therapeutics gave an encore presentation of the GBT440-001 study data supporting the durability, safety and mechanism of action of GBT440 in sickle cell disease (SCD) in an oral session at the Academy for Sickle Cell and Thalassemia (ASCAT) 10th Anniversary Conference in London. Dr Jo Howard, consultant haematologist and head of the red cell/ sickle cell service at Guy's and St Thomas' NHS Foundation Trust in London, said: "Haemoglobin oxygen affinity modulation is a very promising approach for modifying disease in SCD because it intervenes on the fundamental pathologic process- HbS polymerization. GBT440 is an exciting haemoglobin modifier in development because of excellent specificity and pharmaceutical properties resulting in both increased potency and an improved safety profile. Over three months of dosing, GBT440 has shown profound and durable reductions in haemolysis and sickling, which provides further support that this novel haemoglobin modifier has the potential to be a once-daily treatment for

patients with sickle cell disease….Further, given that all 34 SCD patients dosed with GBT440 for 28 to 90 days have shown a positive haematologic response, I believe that GBT440 could potentially transform the treatment of this devastating disease."

c) A Phase II clinical trial is assessing the effects of hydroxyurea-based therapy at the maximum tolerated dose to prevent stroke in children with sickle cell anemia (SCA)[1].

Other

d) UK company Swab Tech is developing and commercialising its automated Surgical Swab-Washer. This recovers blood from swabs used in the hospital operating theatre. This blood can then be processed and transfused back into the patient. New capital raised will enable SwabTech to finalise the product design, secure a CE mark and hold UK and international product launches.

e) Kamada announced positive top-line results, meeting the primary endpoint of its US Phase II clinical trial of its proprietary inhaled Alpha-1 Antitrypsin (AAT) therapy for the treatment of Alpha-1 Antitrypsin Deficiency (AATD). AATD is an orphan disease currently treated by intravenous AAT augmentation therapy.

2. Regulatory

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

a) Australia's Therapeutic Goods Administration (TGA) approved CSL Behring's IDELVION [albutrepenonacog alfa] for patients with haemophilia B (congenital factor IX deficiency). Japan's Ministry of Health, Labour and Welfare (MHLW) also approved IDELVION for patients with factor IX deficiency. It was recently approved in the US, EU, Switzerland and Canada. The therapy has dosing intervals of up to 14 days.

b) Bluebird bio announced on 21 September that the European Medicines Agency (EMA) had granted access to its Priority Medicines (PRIME) scheme for LentiGlobin investigational gene therapy in the treatment of patients with transfusion-dependent beta-thalassemia (TDT). The PRIME scheme provides extra support and increased interaction to companies, to optimize development plans and speed regulatory evaluations to bring innovative medicines to patients more quickly. To be accepted for the scheme, a therapy must demonstrate potential benefit for unmet medical needs through early data. Bluebird has ongoing participation in the EMA's Adaptive Pathways Pilot program, which also expedites patient access using the existing EU regulatory framework for medicines, including conditional approval. David Davidson, chief medical officer of Bluebird bio, said: "Earlier this year we completed enrollment in the Northstar (HGB-204) global clinical study of LentiGlobin drug product in patients with TDT, which along with the supporting HGB-205 study, will form the basis of our eventual application for conditional approval in the EU under the Adaptive Pathways Pilot program."

c) The US Patent and Trademark Office (USPTO) granted Abbott Laboratories a patent for a method for determining volume and haemoglobin content of individual red blood cells. Together with the microscopic evaluation of the distribution of sizes, shapes and colour of red cells and other biochemical tests this method will provide added

[1]Angela E Rankine-Mullings et al., "EXpanding Treatment for Existing Neurological Disease (EXTEND): An Open-Label Phase II Clinical Trial of Hydroxyurea Treatment in Sickle Cell Anemia", *JMIR Research Protocols*. 2016 | vol. 5 | iss. 3 | e185.

insight into the condition of a patient with blood disorders such as microcytic anaemias[2].

d) China Biologic Products announced that Shandong Taibang Biological Products Co. Ltd., its majority-owned subsidiary, had approval from the China Food and Drug Administration (CFDA) to begin human clinical trials on its human antithrombin III. No Chinese manufacturer currently offers plasma-derived ATIII. China Biologic expects to commence clinical trials for the ATIII product in 2017 and to take around two years. ATIII is designed to treat hereditary and acquired ATIII deficiency in surgical or obstetric procedures, and to treat thromboembolism.
e) Siemens has received FDA approval for its handheld portable coagulation analyzer. The Xprecia Stride Coagulation Analyzer looks at Prothrombin Time International Normalized Ratio (PT/INR). It screens fingerstick blood samples to deliver results in minutes.
f) Swedish Orphan Biovitrum (Sobi) announced on 3 October that the European Commission (EC) had approved the transfer of the marketing authorisation for Alprolix (eftrenonacog alfa), a recombinant clotting factor for treating haemophilia B, from Biogen to Sobi[3].
g) The FDA has received several adverse event reports associated with Baxter's Vascu-Guard Peripheral Vascular Patch during carotid endarterectomy (CEA), including three potentially related patient deaths. Reports in 2016 are said to include intraoperative or postoperative bleeding and haematomas, some of which required additional clinical intervention. The Vascu-Guard patch is typically used for peripheral vascular reconstruction, including carotid, renal, iliac, femoral, profunda, and tibial blood vessels, as well as arteriovenous access revisions. In June 2016, Baxter recalled specific lots of the patch due to difficulty distinguishing surface textures. On August 12, 2016, the FDA categorized the recall as a Class II recall, which indicated that the product may pose a slight threat of serious health problems or death. By late September, the FDA was concerned that the Vascu-Guard patch may not be performing as intended and that patients treated with the product may be at risk for serious adverse health consequences. The FDA was reported to be investigating deaths (potentially linked to the patch) after CEA surgery, in particular arterial bleeding in the neck which could rapidly lead to airway obstruction, hypoxia, diminished brain perfusion, stroke, and/or cardiac arrest.
h) The FDA has granted True North Therapeutics orphan drug designation[4] TNT009 for the treatment of autoimmune haemolytic anaemia, including cold agglutinin disease (CAD)[5]. TNT009 is currently in a phase Ib clinical study in patients with CAD, and positive interim results from the study were announced in June 2016. True North received orphan drug designation for TNT009 from the European Medicines Agency (EMA) in February 2016.
i) The FDA granted Sangamo BioSciences orphan drug designation for SB-FIX, the company's zinc finger nuclease (ZFN)-mediated genome editing product candidate

[2] Microcytic anaemia is amongst the types of anaemia characterized by red blood cells (erythrocytes) of smaller size (microcytes) which are less intense in colour (hypochromic). Causes include chronic conditions of iron deficiency and thalassemia.

[3] The EC approved Alprolix in May 2016, based on results from two global phase III clinical trials that demonstrated the efficacy, safety and pharmacokinetics of Alprolix for the treatment of haemophilia B: the pivotal B-LONG study for previously treated adults and adolescents, and the Kids B-LONG study for previously treated children under age 12.

[4] The FDA grants orphan drug designation to drugs and biologics for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US. The designation provides incentives such as tax credits towards the cost of clinical trials. If a product with the designation subsequently receives the first FDA approval for the disease, the product receives exclusivity.

[5] CAD is an autoimmune haemolytic anaemia in which autoantibodies target and destroy red blood cells, causing anaemia, fatigue and potentially fatal thrombosis.

for the treatment of haemophilia B. Sangamo will initiate a Phase I/II clinical study in adult subjects with the disease.

j) The FDA has approved two of Stryker's clot retrieval devices as a first-line therapy for ischemic strokes to be given together with a clot-dissolving drug. The devices were initially approved in 2012 to remove blood clots in stroke patients who could not take the drug or in whom the drug did not work.

k) Emmaus Life Sciences announced its submission, with request for priority review, to the FDA of a New Drug Application for an orally administered pharmaceutical grade L-glutamine (PGLG) for the treatment of sickle cell disease in adults and paediatric patients. The submission was supported by data from the Phase III trial of PGLG, which demonstrated a reduction in the frequency of sickle cell crises and hospitalizations. A reduction in cumulative days hospitalized and a lower incidence of life-threatening acute chest syndrome was also found in patients treated with PGLG. The FDA had previously granted Orphan Drug and Fast Track designations to the Company's orally administered pharmaceutical grade L-glutamine.

3. 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.

Agreements

a) Terumo and CytoSorbents have teamed up to commercialize the latter's blood purification absorber for critically ill and cardiac surgery patients[6]. CytoSorbents' device CytoSorb is an extracorporeal cytokine absorber[7] approved in the EU. Blood is pumped out of the body and through the CytoSorb cartridge, which contains porous polymer beads that absorb cytokines. The "purified" blood is then recirculated back to the patient. Arik Anderson, president of Terumo's Perfusion and Surgical Devices division, said: "CytoSorb integrates with the heart-lung machine platform, giving surgical teams, for the first time, the ability to safely reduce dangerous inflammatory mediators in real-time as they are being generated during cardiac surgery." CytoSorbents has previously joined forces with Fresenius Medical Care to commercialize the CytoSorb.

Market forecasts

b) Transparency Market Research (TMR) expects the global market for plasma protein therapeutics to rise at a compound annual growth rate of 7.0 per cent between 2016 and 2024. The market stood at $US 18.5 billion in 2015 and is expected to reach $US 31.84 billion by the end of 2024. North America held the dominant share in the global market in 2015, followed by Europe. Plasma protein therapeutics are increasingly used in the treatment of primary immunodeficiency disorder (PID). The PID segment is likely to exhibit a compound annual growth rate of 7.6 per cent between 2015 and 2024.

[6] Under the agreement, Terumo has exclusive rights to distribute the CytoSorb cardiopulmonary bypass procedure pack for use during cardiac surgery in France, Sweden, Denmark, Norway, Finland and Iceland.

[7] The immune system releases cytokines in response to life-threatening conditions, so clinical situations where a patient's cytokine levels are elevated can include trauma, serious burns, severe lung injury and sepsis and infection. An excess of cytokines can cause cell damage, organ failure and death.

i) New indications, the increasing geriatric population, and investments in research are boosting prospects for the market in North America. TMR expects the North American plasma protein therapeutics market to reach $US 13.8 billion by the end of 2024 from $US 7.5 billion in 2015. This represents a compound annual growth rate of 7.9 per cent.
ii) TMR says that in Europe, demand for protein therapeutics is increasing because of the rise in the number of clinical indications for immunoglobulin across haematology, neurology, dermatology, nephrology, immunology, ophthalmology, and rheumatology.
iii) TMR expects the Asia Pacific to emerge as the most lucrative market for plasma protein therapeutics. There is rising demand for albumin and immunoglobulin and the region imports these from North America and Europe.
iv) In Latin America the plasma protein therapeutics market is restrained by low rate of diagnosis and treatment and high pricing.

Personnel

c) GlaxoSmithKline has named its next CEO, Emma Walmsley, who heads company's consumer health business. Current CEO Andrew Witty retires in March, but will join the GSK board from 1 January.
d) CEO of NovoNordisk, Lars Sorensen, is stepping down after sixteen years in the position. He will be replaced from the beginning of 2017 by Lars Fruergaard Jorgensen, currently the company's executive vice president and head of corporate development.

Other

e) GigaGen has received a $US 1.5 million grant from the US National Institutes of Health (NIH) through the Small Business Innovation Research (SBIR) program in the National Institute of Allergy and Infectious Diseases (NIAID). The grant is to facilitate development of natural repertoire recombinant intravenous immunoglobulin (rIVIG) "hyperimmunes"[8] against common pathogens for patients with primary immune deficiency (PID)[9]. Dave Johnson, CEO of GigaGen said: "We are pleased that the NIH has recognized the power of our drug discovery technology to create new recombinant drugs that previously have only been available by harvesting plasma from humans. Recombinant IVIG hyperimmunes hold great potential for improving the quality of life for not only PID patients, but also other types of immunocompromised patients such as transplant recipients, and ultimately can be used to combat emerging pathogens such as Zika." The US Patent and Trademark Office has issued US Patent No. 9,422,547 to GigaGen, covering protein expression methods for producing polyclonal antibodies from natural immune repertoires.
f) SAB Biotherapeutics announced that its DiversitAb human antibody production platform, leveraging transchromosomic cattle, was identified as of one of the six most meritorious proposals emerging from the World Health Organisation (WHO) public

[8] Hyperimmunes are a specialised subset of plasma-derived intravenous immunoglobulin (IVIG) enriched with antibodies against a particular pathogen, such as rabies, tetanus, cytomegalovirus or herpes zoster.
[9] PID includes a range of congenital disorders such as common variable immune deficiency (CVID) and X-linked agammaglobulinemia (XLA), where the body is unable to make antibodies adequately. People with PID are subject to common infections that other people can overcome or prevent through vaccination. The standard treatment for PID is regular doses of intravenous immunoglobulin (IVIG), created by pooling antibodies from the plasma of multiple donors. Many PID patients suffer recurrent infections such as pneumonia and receive prophylactic antibiotics. Currently available and approved hyperimmunes do not necessarily address the bacterial and viral pathogens usually responsible for morbidity and mortality in PID patients. The NIH grant will support the the development of recombinant hyperimmunes against these.

consultation on platform technologies for priority infectious diseases with epidemic potential[10].

g) Alexion Pharmaceuticals earns over $US 2 billion a year through its drug, eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria[11]. Soliris costs more than $US 500,000 per patient for a year of treatment. Amongst companies hoping to develop an alternative is Ra Pharmaceuticals, of Cambridge, Massachusetts, which has been raising funds to start Phase II trials of RA101495 early in 2017. RA101495 is subcutaneous injection.

4. 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.

a) China Biologic Products announced that its majority-owned subsidiary, Shandong Taibang Biological Products Co. Ltd., had approval from the China Food and Drug Administration (the "CFDA") to begin human clinical trials on its Human Coagulation Factor IX ("FIX") product. China Biologic plans to commence clinical trials for the FIX product in 2017 and expects to complete these trials by 2018[12].

b) The Scottish National Blood Transfusion Service (SNBTS) will relocate to its new headquarters in phases between January and May 2017[13]. The purpose-built facility in the Heriot-Watt Research Park, Riccarton, Edinburgh will deal with the manufacturing, testing and distribution of blood, tissue and cell products for all of Scotland. SNBTS currently operate across Scotland, with manufacturing operations divided between different sites.

c) In India, data released by the National AIDS Control Organisation (NACO) suggests that 2,234 people contracted the human immunodeficiency virus (HIV) after receiving blood transfusions in hospitals between October 2014 and March 2016.

5. Safety and patient blood management

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

[10] SAB's October 2015 proposal, "Targeted Human Immunoglobulin to WHO Priority Pathogens Using Transchromosomic (Tc) Bovine," outlined a two-year project, leveraging a dedicated herd of human antibody producing cattle, to be readily available should an outbreak occur. When needed, the Tc Bovine could be used to develop quickly, test, and manufacture product to submit to regulators. Targeted human polyclonal immunoglobulins produced in the platform would be quickly scalable to be an effective global response.

[11] a condition in which the complement system—a part of the immune system—destroys red blood cells, causing blood clots and organ failure.

[12] Mr. David (Xiaoying) Gao, Chairman and Chief Executive Officer of China Biologic, said: "We are proud to become the first domestic Chinese plasma company to introduce the effective treatment of FIX deficiency to patients who are routinely treated with fresh frozen plasma when other treatments are unavailable or unaffordable. Once we commercially launch the FIX product, we expect that our prothrombin complex concentrate product, which is used to treat haemophilia B when affordable FIX product is unavailable, will play a more critical role in the under-served market for general blood clotting treatments in China, including liver disease and surgical bleeding. Our FIX product represents the fourth coagulation factor product from China Biologic".

[13] Office, warehouse and laboratory functions will transfer before the end of January 2017, and blood processing and tissue services will be transported in stages after that.

Appropriate Transfusion

a) HemoSonics announced the publication of four journal articles[14] describing the first clinical experiences with the company's QuantraTM Hemostasis Analyzer, designed to improve the management of critical bleeding. The articles discuss the results of multi-centre clinical studies of 150 cardiac and spine surgery patients. Dr. Bruce Spiess[15], lead author of one of the papers, said: "The Quantra is a major leap forward in viscoelastic testing, as current hemostasis testing is limited by long result times and incomplete parameter measures. These studies demonstrate that the Quantra provides clot time and clot stiffness results that correlate with existing technologies. In addition, the device delivers extremely important information through its Fibrinogen Contribution and Platelet Contribution measures that are not currently available in a rapid time frame. With the Quantra, we have a tool to help rapidly and accurately determine the cause of critical bleeding, enabling precise treatment and reducing unnecessary blood transfusions."

b) Jeffrey L. Carson[16], has been awarded more than $US 16.1 million by the US National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) to lead a nation-wide clinical trial to evaluate whether a restrictive or a liberal blood transfusion is most beneficial to patients who have had a heart attack, in terms of improving their survival rates and reducing the risk of recurrence. Carson said: "Outcomes appear to be different for patients who have been treated with a transfusion following a heart attack or significant coronary event." Several small studies, including a pilot study overseen by Carson, indicated that patients who have had a heart attack and have anaemia may have an increased risk of mortality with a restrictive transfusion approach. The Myocardial Ischemia and Transfusion (MINT) clinical trial will be conducted in up to 80 centres in the US and Canada[17]. It will include 3,500 patients who will be randomly allocated to be treated with either a liberal or restrictive transfusion strategy.

c) AABB's new guidelines on thresholds for red blood cell transfusions were published online in the *Journal of the American Medical Association*. The two-tier recommendation lowers the haemoglobin threshold from 10 g/dL to 7 g/dL for haemodynamically stable adults and 8 g/dL for patients who either have cardiovascular disease or are undergoing cardiac or orthopaedic surgery. The guidance also says red blood cells stored for any length of time within their licensed dating period are as safe as blood stored 10 days or less for most stable patients, even newborns.

d) A retrospective study[18] found that amongst almost 3,000 patients who underwent total joint arthroplasty and received aspirin for venous thromboembolism prophylaxis, the use of tranexamic acid led to decreased bleeding and transfusion rates without an increased incidence of subsequent venous thromboembolism.

e) A recent review[19] in *The International Journal of Clinical Transfusion Medicine* presented an overview of the indications, use and evidence for cryoprecipitate

---

[14] On 20 September in *Anesthesia & Analgesia*

[15] Professor and Associate Chief for Research within the Department of Anesthesiology at the University of Florida

[16] the Richard C. Reynolds Professor of Medicine at Rutgers Robert Wood Johnson Medical School and provost at Rutgers Biomedical Health Sciences in New Brunswick.

[17] Participating clinical sites include the University of Toronto Medical School, Centre Hospitalier de l'Universite de Montreal, Duke Clinical Research Institute, Saint Louis University, University of Pittsburgh Medical Center, Rhode Island Hospital, Westchester Medical Center, and Ottawa Hospital Research Institute.

[18] Heller S, et al. "Decreased bleeding, transfusion rate seen with use of tranexamic acid and aspirin during TJA", *J Arthroplasty*. 2016;doi:10.1016/j.arth.2015.12.042.

[19] Wong H, Curry N, "Cryoprecipitate transfusion: current perspectives**",** *International Journal of Clinical Transfusion Medicine,* Volume 2016:4 Pages 89—97
https://dx.doi.org/10.2147/IJCTM.S99042

transfusion in haemorrhage, how it may promote haemostasis, and recent developments in extended thaw cryoprecipitate.

f) A recent US study[20] suggests that in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), blood transfusion is linked to acute kidney injury, even when used in patients with preprocedural anemia who later experience a postprocedural bleeding event. The retrospective cohort study evaluated 1,756,864 patients enrolled in the National Cardiovascular Data Registry CathPCI Registry and admitted to the hospital for ACS and undergoing PCI between July 1, 2009, and June 30, 2014.

Treating anaemia

g) A study[21] has found that intravenous iron postoperatively may reduce infections, transfusions and length of hospital stay.

Other

h) A retrospective cohort study[22] has found that co-treatment with proton pump inhibitors (PPIs) in patients initiating warfarin was associated with reduced risk of warfarin-related upper gastrointestinal (GI) bleeding.

6. Research (not elsewhere included)

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

a) Researchers have identified a potential genetic link between platelet activity and cardiovascular disease[23]

b) Scientists from the Royal College of Surgeons in Ireland, Dublin City University and the University of Leuven in Belgium have discovered a new treatment for sepsis[24]. They say the new drug prevents bacteria from sticking to the inner-most side of blood vessels[25]. Lead researcher Dr Steve Kerrigan, of the RCSI, said a patent application has been filed and he is now seeking to progress to commercialisation, with a view to moving rapidly towards human clinical trials.

c) University of Utah scientists say[26] that a factor found in umbilical cord blood can be used to fight inflammation and sepsis in adults. When the factor was given to mice, it

---

[20] Karrowni W, et al. "Blood Transfusion and the Risk of Acute Kidney Injury Among Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention", *Circ Cardiovasc Interv.* 2016;doi:10.1161/CIRCINTERVENTIONS.115.003279.

[21] Khalafallah, Alhossain A et al. "Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial", *The Lancet Haematology* , Volume 3 , Issue 9 , e415 – e425

[22] Ray WA, et al. "PPIs linked to lower risk for warfarin-related upper GI bleeding", *Gastroenterol***ogy,** 2016;doi:10.1053/j.gastro.2016.08.054

[23] Montenont E, et al. "Platelet WDR1 suppresses platelet activity and associates with cardiovascular disease". *Blood* 2016;Epub ahead of print.

[24] The research was reported in the *Journal of Thrombosis and Haemostasis*.

[25] Sepsis, or septicaemia or blood poisoning, is a life-threatening complication of an infection or injury. Bacteria present in the blood interact with blood vessels and this impairs the regulation by the cells that line the inside of the blood vessel. These cells die, causing the blood vessel to leak. This leads to the spread of the condition and the collapse of the circulatory system. Failure of the body's vital organs is rapid.

[26] They reported their work in *The Journal of Clinical Investigation*

reversed fever, altered respiratory rates and death. But the factor can be found only in newborns less than two weeks old.

d) Metastasis of cancer cells to sites away from the primary tumour is the leading cause of cancer-related death, and there is growing evidence that platelets aid the dissemination of cancer cells. Pierre Henri Mangin and colleagues at the Etablissement Français du Sang-Alsace have shown that a molecule expressed on platelets, known as α6β1 integrin, participates in tumour metastasis by promoting interactions between tumour cells and platelets[27].
e) Novuson Surgical (a Bothell WA based spinout from the University of Washington's Applied Physics Laboratory's Center for Industrial and Medical Ultrasound) has been awarded a $US 1.47 million grant by the National Institute of Health's (NIH) National Heart, Lung, and Blood Institute (NHLBI) to further develop a novel approach to mitigate the effects of perioperative bleeding in surgically reconstructed great vessels in neonates using a therapeutic modality of ultrasound.

7. 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

Its spread and testing

a) A lab study[28] has shown that control programs that focus only on adult mosquitoes may not halt Zika's spread. Female mosquitoes can transmit the Zika virus to their eggs and offspring. "The implications for viral control are clear," said study co-author Dr. Robert Tesh, of the University of Texas Medical Branch in Galveston. The study authors say larvicide should become an integral part of efforts to stop the spread of the virus.
b) On 21 September he European Medicines Agency announced that patients receiving drugs derived from blood plasma or urine are not at increased risk of catching Zika, even if the body fluids come from countries where the virus is prevalent. It said its experts had assessed the risks and concluded that manufacturing processes used for such products (including solvents or detergents, pasteurisation and filtration) would inactivate or remove the Zika virus.
c) North American researchers have found that the Zika virus remains in some macaques' organs and fluids, even after the immune system has removed it from the blood stream[29].

[27] "Platelet integrin α6β1 controls lung metastasis through direct binding to cancer cell-derived ADAM9", in *JCI Insight.*
[28] published online 29 August in the *American Journal of Tropical Medicine and Hygiene*.
[29] Christa E Osuna et al. "Zika viral dynamics and shedding in rhesus and cynomolgus macaques", *Nature Medicine* (2016). DOI: 10.1038/nm.4206

Vaccine development

d) In the US, The Biomedical Advanced Research and Development Authority (BARDA) is providing $US 43 million to Sanofi Pasteur to fund Phase II development of the candidate Zika vaccine known as Zika purified inactivated virus (ZPIV). If the Phase II testing is successful, BARDA could provide another $US130 million for follow-up studies. BARDA, along with the Walter Reed Army Institute of Research and the National Institutes of Health, started working on the candidate in March, with Sanofi signing on in July to contribute its vaccine development experience.
e) The US National Institute of Allergy and Infectious Diseases has developed an experimental DNA-based vaccine that recently entered human safety trials.
f) Both vaccines above are expected to be ready for field testing in January 2017 in the South American summer.
g) BARDA is providing financial support for the development of Takeda's Zika vaccine.
h) Moderna Therapeutics said in September it planned to file an investigational new drug application with the FDA by the end of 2016, which would allow it to begin Phase 1 trials on the vaccine. .It too has received US government funding.

Other mosquito-borne diseases

i) Takeda of Japan and Indian drugmaker Zydus Cadila are planning to develop a vaccine against chikungunya. Others with chikungunya candidates already in clinical testing include Austria's Themis Bioscience[30], the US National Institute for Allergy and Infectious Diseases (NIAID) and India's Bharat Biotech. Themis Bioscience started a Phase II trial for its vaccine in August. Takeda is already working on vaccines against dengue[31] and Zika. Chikungunya is spread by *Aedes aegypti* and *Aedes albopictus* mosquitoes, the same insects that carry Zika and dengue fever.
j) Sun Pharma, India's biggest pharmaceutical company, has signed a deal with the Delhi unit of the International Centre for Genetic Engineering and Biotechnology (ICGEB) to develop a dengue vaccine.
k) A study by John Hopkins researchers[32] of mosquitoes' sense of smell concluded that altering the taste of human blood could curb the spread of malaria.
l) Liberian malaria cases declined following mass drug administration during the Ebola outbreak[33]..

Influenza: strains, spread, prevention and treatment

m) For the Southern Hemisphere's 2017 flu season, the World Health Organisation (WHO) recommended that trivalent vaccines contain an A/Michigan/45/2015 (H1N1) pdm09-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus; and a B/Brisbane/60/2008-like virus. WHO recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus.
n) A collaboration involving the universities of Lancaster, Aston and Complutense in Madrid has designed two "universal" flu vaccines: a US -specific vaccine with coverage of 95 per cent of known US influenza strains and a universal vaccine with

[30] Austrian biotech Themis Bioscience has begun a Phase II for its Chikungunya virus vaccine, what it calls "the most advanced" candidate of its kind.
[31] Takeda Pharmaceutical Company announced in September that it had vaccinated the first subject in the Tetravalent Immunization against Dengue Efficacy Study (TIDES), a Phase III double-blind, randomized and placebo-controlled trial of its live-attenuated tetravalent dengue vaccine candidate (TAK-003).
[32] Published online 3 October in *Nature Communications*
[33] Kuehne A, et al. 'Impact and Lessons Learned from Mass Drug Administrations of Malaria Chemoprevention during the Ebola Outbreak in Monrovia, Liberia, 2014'. PLoS ONE 11(8): e0161311. doi:10.1371/journal.pone.0161311

coverage of 88 per cent of known flu strains globally[34]. Pharmaceutical industry partners are being sought to synthesize the computer-designed vaccines for laboratory proof-of-principle tests.

o) Dr. Anne De Groot[35] and her team will use the NIH's Small Business Innovation Research grant to EpiVax to work on developing a more effective vaccine for the H7N9 influenza. The program aims to re-engineer H7N9 viral proteins so they can be more easily detected by the immune system, resulting in a more potent vaccine product.

p) A GlaxoSmithKline-led team reported[36] that a two-dose adjuvanted H7N9 vaccine showed promise in a clinical trial, triggering a robust antibody response and being well tolerated.

q) Viable avian flu virus is readily detectable in the air of live-poultry markets, so anyone visiting the markets can become infected. Researchers based at Hong Kong University isolated three subtypes during recent sampling: H5N6, H7N9, and H9N2[37].

MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

r) By 29 September there had been in Saudi Arabia 1457 laboratory-confirmed cases of MERS-CoV infection, including 611 deaths.

Ebola virus disease

s) Merck and NewLink Genetics have won a $US 24.8 million contract to support the development of their Ebola vaccine. The candidate has a breakthrough designation from the FDA and priority medicine status from the EMA. This grant brings to more than $US100 million the total invested into the Ebola vaccine candidate, rVSVΔG-ZEBOV GP (V920), by the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services. The award also includes another optional $US 51 million. Dr. Thomas Monath, of the NewLink Infectious Disease Division, said: "This new contract issued by BARDA will enable accelerated full-scale production of V920, once it is approved, and is a critical step in helping to make this vaccine available to the health care community as they work to control epidemics and protect medical workers and others at high risk". Merck in-

---

[34] Qamar M. Sheikh et al., "Towards the knowledge-based design of universal influenza epitope ensemble vaccines", *Bioinformatics* (2016) doi: 10.1093/bioinformatics/btw399. Dr. Derek Gatherer of Lancaster University said: "Every year we have a round of flu vaccination, where we choose a recent strain of flu as the vaccine, hoping that it will protect against next year's strains. We know this method is safe, and that it works reasonably well most of the time. However, sometimes it doesn't work—as in the H3N2 vaccine failure in (the northern hemisphere) winter 2014-2015—and even when it does it is immensely expensive and labor-intensive. Also, these yearly vaccines give us no protection at all against potential future pandemic flu. It doesn't have to be this way. Based on our knowledge of the flu virus and the human immune system, we can use computers to design the components of a vaccine that gives much broader and longer-lasting protection." Dr Pedro Reche of Complutense University said: "A universal flu vaccine is potentially within reach. The components of this vaccine would be short flu virus fragments—called epitopes—that are already known to be recognized by the immune system. Our collaboration has found a way to select epitopes reaching full population coverage." Dr. Darren Flower of Aston University said: "Epitope-based vaccines aren't new, but most reports have no experimental validation. We have turned the problem on its head and only use previously-tested epitopes. This allows us to get the best of both worlds, designing a vaccine with a very high likelihood of success."

[35] A University of Rhode Island research professor and co-founder, chief executive and chief scientific officer at EpiVax.

[36] Anuradha Madan, et al, "Immunogenicity and safety of an AS03-adjuvanted H7N9 pandemic influenza vaccine in a randomized trial in healthy adults", *J Infect Dis*. (2016) doi: 10.1093/infdis/jiw414

[37] They reported their findings in *Eurosurveillance*.

licensed the vaccine candidate from NewLink in late 2014, gaining exclusive worldwide rights to develop and market it. Merck paid a $US 30 million upfront in October 2014 followed by $US 20 million in February 2015 for the start of the pivotal clinical trial. NewLink stands to receive escalating royalties on sales of the Ebola vaccine. NewLink originally in-licensed the vaccine from the Public Health Agency of Canada (PHAC).

t) Johnson & Johnson announced that Janssen Vaccines & Prevention B.V. completed its submission to the World Health Organisation (WHO) for Emergency Use Assessment and Listing (EUAL) for its investigational preventive Ebola prime-boost vaccine regimen. The EUAL can be activated when there is an outbreak of a disease with high morbidity or mortality and an absence of approved treatment or prevention options[38].

u) BioCryst Pharmaceuticals declared positive results from a proof-of-concept study of its broad spectrum antiviral, BCX4430, for the delayed treatment of Ebola virus infection in rhesus macaques.

v) Scientists[39] have described a strategy to target a vulnerability shared by all known types of Ebola virus. Two antibodies developed with this strategy blocked the invasion of human cells by all five ebolaviruses, and one of them protected mice exposed to lethal doses of Ebola Zaire and Sudan, the two most dangerous.

Other diseases: occurrence, diagnosis, prevention and treatment

w) Currently, patients are screened for Creutzfeldt-Jakob disease (CJD) by using MRI scans, brain biopsies, or taking samples of cerebrospinal fluid. Now UK researchers have discovered it may be possible to test patients for Creutzfeldt-Jakob disease using urine samples[40].

x) Briotech announced that a study[41] shows that the company's formulation of patent-pending pure hypochlorous acid (HOCl) inactivates infectious proteins (prions) that cause chronic brain diseases in humans and animals. (Section 7)

---

[38] The decision to grant EUAL to the investigational preventative vaccine regimen would follow an appraisal of available data including quality, safety, and immunogenicity, as well as a risk/benefit analysis. Although EUAL potentially allows for use of a vaccine in an emergency, the vaccine remains investigational pending standard regulatory agency review and approval. The first clinical data for the investigational Janssen vaccine regimen among healthy volunteers were published in *The Journal of the American Medical Association* in April 2016. The Phase 1 results from a UK study suggested that the regimen was well-tolerated and produced an immune response. 100 per cent of study participants achieved an initial antibody response to Ebola, and this was sustained eight months following vaccination among all volunteers. This was the first of 10 clinical studies across the US, Europe and Africa. The first study of the vaccine regimen in a country affected by the Ebola epidemic began in Sierra Leone in October 2015. Janssen is also initiating a first-in-human Phase I clinical study of a second-generation, multivalent version of the AdVac/MVA-BN vaccine regimen intended to protect against multiple filoviruses.

[39] The team included scientists from Albert Einstein College of Medicine, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Integrated Biotherapeutics, Vanderbilt University Medical Center, and The Scripps Research Institute. They published their views in *Science.* The paper is titled "A 'Trojan Horse' Bispecific Antibody Strategy for Broad Protection Against Ebolaviruses." This work was supported by three grants from the National Institutes of Health, U19 AI109762, R01 AI088027, and 1R41 AI122403; by Joint Science and Technology Office-Defense Threat Reduction Agency (DTRA) award CB04088; and DTRA award HDTRA1-13-C-0015.

[40] Connie Luk et al., "Diagnosing Sporadic Creutzfeldt-Jakob Disease by the Detection of Abnormal Prion Protein in Patient Urine", *JAMA Neurol.* Published online October 3, 2016. doi:10.1001/jamaneurol.2016.3733

[41] Published in *PLOS Pathogens*. Investigators were from the US National Institute of Allergy and Infectious Diseases (NIAID) Rocky Mountain Laboratories, the University of Washington (UW) Bothell, UW Seattle, the University of Verona (Italy), and Briotech.