

# Monitoring International Trends

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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:

- At the XXXII International Congress of the World Federation of Hemophilia 2016 Congress in Orlando, Florida (Section 1):
  - i) CSL Behring presented positive Phase III data on Afstyla (antihaemophilic factor (recombinant), single chain) in haemophilia A patients aged less than 12 years of age.
  - ii) CSL Behring announced new data from its Phase III PROLONG-9FP clinical development program evaluating Idelvion [Coagulation Factor IX (Recombinant), Albumin Fusion Protein], a long-acting recombinant albumin fusion protein for treating haemophilia B.
  - iii) Long-term follow-up data were presented from a Phase I/II clinical trial assessing Roche's emicizumab in patients with severe haemophilia A.
  - iv) NovoNordisk presented posters relating to haemophilia A and B, factor VII and factor XIII.
  - v) Octapharma sponsored two symposia: *Simple solutions to complex issues: Addressing today's challenges in VWD and haemophilia A*, and *A focus on human cell-line derived rFVIII in haemophilia A: Update on clinical experience with Nuwiq in PUPs and PTP*. Posters related to Nuwiq, Wilate, Octanate and fibrinogen were presented during the congress.
  - vi) Sangamo BioSciences presented new preclinical data on its gene therapy to treat haemophilia A.
  - vii) Updated data from uniQure's ongoing Phase I/II clinical study of its gene therapy for haemophilia B patients was presented
  - viii) Alnylam Pharmaceuticals announced new positive results from its ongoing Phase I study with fitusiran, an RNAi therapeutic targeting antithrombin for the treatment of hemophilia A and B and rare bleeding disorders.
  - ix) Interim results were presented of a Phase I/II study of BioMarin Pharmaceutical's BMN 270, an AAV5-FVIII gene transfer in severe haemophilia.
- Ingrid Pabinger reported on a phase I to phase III study of rVIII-SingleChain (CSL Behring) for the treatment of haemophilic bleeding episodes and as routine and surgical prophylaxis. (Section 1)
- Pharming announced positive results from a Phase II clinical study of Ruconest ( ) for prophylaxis in patients with hereditary angioedema. (Section 1)
- Shire announced the launch of a paediatric indication for HyQvia (Human Normal Immunoglobulin (10%), Recombinant Human Hyaluronidase) across Europe. (Section 1)

- A study pointed to another strategy for alleviating hereditary haemoglobin deficiencies using CRISPR/Cas9 genome editing. (Section 1)
- A Phase III trial showed that treatment with romiplostim induced a high rate of platelet response in children with chronic immune thrombocytopenia.
- Spark Therapeutics and Pfizer announced that the FDA had granted breakthrough therapy designation to SPK-9001, its candidate for the treatment of haemophilia B. (Section 2)
- Researchers in Quebec City were the first in Canada to be authorized by Health Canada and the US Food and Drug Administration (FDA) to test a Zika vaccine in humans. (Section 2)
- Emmaus Life Sciences announced that it would submit a new drug application (NDA) to the FDA for its sickle cell treatment. (Section 2)
- The FDA granted approval for Shire's CUVITRU [Immune Globulin Subcutaneous (Human), 20% Solution] in adult and paediatric patients two years of age and older, for patients with primary immunodeficiency. (Section 2)
- CSL flagged a possible share buyback of around \$A500 million after posting a 10 per cent fall in annual net profit, the result of its acquisition of the Novartis influenza vaccines business. (Section 3)
- Shire discontinued plans to further develop BAX 335, a haemophilia B gene therapy it acquired with its takeover of Baxalta. (Section 3)
- The US the National Hemophilia Foundation's Annual Meeting in received the announcement that a clinical practice guideline for care models for the management of people with haemophilia had been accepted for inclusion in the National Guideline Clearinghouse. The guideline, sponsored by NHF and McMaster University, recommends an integrated care model be used for people with haemophilia. (Section 4)
- Canadian Blood Services has changed its deferral policies and donor restrictions to broaden the pool of eligible donors. (Section 4)
- A Swedish study found no evidence that degenerative brain disorders can be transmitted via donated blood. (Section 5)
- An observational study found an increased risk of death for transfusion recipients receiving blood from either young or female donors; clinical trials are required to determine if indeed such donor characteristics actually do have an impact on recipient survival. (Section 5)
- The Zika virus was found to be locally transmitted in the continental US and the FDA issued a revised guidance recommending universal testing of donated whole blood and blood components for Zika virus in the US and its territories. (Section 6)
- It was confirmed that the Zika virus can be spread sexually even when a partner shows no signs of infection, and that men who had been infected with the Zika virus could return positive results for the Zika virus in their semen more than 180 days after the onset of their symptoms, and there was no suggestion that a limit had been reached. (Section 6)
- Confirmation continued that the Zika virus could be transmitted through blood and blood products. (Section 6)
- Development and testing of potential vaccines for Zika continued and scientists continued the search for potential treatments. (Section 6)
- Further evidence emerged of the range and severity of lasting damage the Zika virus could cause in its victims. (Section 6)
- SAB Biotherapeutics has started a Phase I clinical trial for its human antibody treatment for MERS-CoV. SAB's platform leverages genetically engineered cattle to produce large amounts of human antibodies. (Section 6)
- People infected with the Ebola virus were found to be more likely to survive if they were co-infected with malaria-causing *Plasmodium* parasites. (Section 6)
- The Ebola virus is now known to be able to last in semen for 565 days, showing the potential role of sex in sparking another outbreak. (Section 6)

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### 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.*

#### Haemophilia treatment

- a) At the XXXII International Congress of the World Federation of Hemophilia 2016 Congress in Orlando, Florida:
  - i) CSL Behring presented positive Phase III data on Afstyla (antihaemophilic factor (recombinant), single chain) in haemophilia A patients aged less than 12 years of age. The efficacy of Afstyla to treat bleeding events in patients on prophylaxis or

- on-demand regimens was rated as excellent or good by investigators<sup>1</sup> in over 96 per cent of all bleeding events. Afstyla, used prophylactically across different treatment intervals, including two to three times weekly, achieved low annualized spontaneous bleeding rates and low annualized bleeding rates in previously treated children and adolescents with haemophilia A. The study was part of the Phase I/III Affinity clinical program, which included two completed pivotal trials and one ongoing open-label, multicentre extension study evaluating the safety and efficacy of Afstyla in children, adolescents, and adults with haemophilia A.
- ii) CSL Behring announced new data from its Phase III PROLONG-9FP clinical development program<sup>2</sup> evaluating Idelvion [Coagulation Factor IX (Recombinant), Albumin Fusion Protein], a long-acting recombinant albumin fusion protein for treating haemophilia B<sup>3</sup>. The results showed that extended prophylaxis treatment regimens effectively prevented bleeds while also reducing overall use of Idelvion. An abstract reporting efficacy and safety results of Idelvion in haemophilia B patients undergoing surgery was also presented<sup>4</sup>.
  - iii) Long-term follow-up data were presented from a 16-subject Phase I/II clinical trial assessing the biologic emicizumab in patients with severe haemophilia A. Emicizumab binds to both factors IXa and X, replacing the function of the missing factor VIII. It was created by Chugai Pharmaceutical Co. and is being co-developed by Roche. Data showed good safety and prophylactic efficacy regardless of the presence of factor VIII inhibitors<sup>5</sup>. Future clinical trials will explore less frequent dosing schedules. Roche is expected to report phase III data for emicizumab early next year in patients who have developed inhibitors to factor VIII clotting factors, putting it on track for approval in 2018. With gene therapies moving quickly, Roche wants to establish itself in haemophilia in time to reap profits from a blockbuster drug.
  - iv) NovoNordisk shared data from 28 abstracts<sup>6</sup>. They included posters relating to haemophilia A<sup>7</sup> and B<sup>8</sup>, factor VII<sup>9</sup> and factor XIII<sup>10</sup>. So far, only about 1000

<sup>1</sup> Lead investigator, Ingrid Pabinger-Fasching, of the Medical University of Vienna

<sup>2</sup> Lead investigator of the PROLONG-9FP clinical development program, Elena Santagostino, Professor in the Medical School of Clinical and Experimental Hematology at the University of Milan/IRCCS Maggiore Hospital

<sup>3</sup> At the time of the Congress Idelvion was already approved in the US, EU and Canada and was under review by regulatory agencies in Australia, Switzerland and Japan.

<sup>4</sup> The relevant posters were *Long-term safety and efficacy of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with haemophilia B* (Poster #122); *Interim results of a Phase IIIb safety and efficacy extension study of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with haemophilia B* (Poster #113); and *Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin (rIX-FP) in haemophilia B patients undergoing surgery* (Poster #84).

<sup>5</sup> Patients given once-weekly subcutaneous injections of either 0.3, 1.0 or 3.0 mg/kg/week of emicizumab with median follow-up periods of 32.6 months, 27.0 months and 21.4 months, respectively, demonstrated a sustained decrease of 95 per cent in annualized bleeding rate (ABR), irrespective of their inhibitor status and prior treatment regimen. The ABRs for the three cohorts were 1.4, 0.2 and 0.0, respectively. The drug's safety profile was consistent with what was previously reported in the Phase 1 study. No thromboembolic adverse events or clinically significant laboratory abnormalities occurred.

<sup>6</sup> For a complete list of abstracts see: [www.wfh.org/congress/2016\\_Abstracts](http://www.wfh.org/congress/2016_Abstracts)

<sup>7</sup> *Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in patients with severe haemophilia A: results from the guardian(TM)2 trial* (P-T-97); and *First report of safety and efficacy of a glycoPEGylated FVIII (N8-GP) in previously treated paediatric patients with severe haemophilia A - results from the international phase 3 pathfinder(TM)5 trial* (P-T-103)

<sup>8</sup> *Psychosocial impact of mild to severe haemophilia B on affected adults and children: methods and demographics of the bridging haemophilia B experiences results and opportunities into solutions (B-HERO-S) study* (PO-T-26)

people in the world are known to have congenital FXIII A-subunit deficiency, characterised by a lifelong susceptibility towards bleeding, including spontaneous intracranial haemorrhage. Tretten was approved by the US Food and Drug Administration (FDA) in December 2013 after a trial in patients aged 7 to 60 years. In this abstract, Kearney et al report on a trial in 6 children aged between 1 and 4 years. They found there were no bleeding episodes requiring treatment with a FXIII-containing haemostatic agent during the trial (the annualized bleeding rate was zero).

- v) Octapharma sponsored two symposia. The first symposium, *Simple solutions to complex issues: Addressing today's challenges in VWD and haemophilia A*, was chaired by Professor Erik Berntorp (Lund University, Malmo, Sweden) and explored clinical issues in the management of patients with von Willebrand disease (VWD) and haemophilia A<sup>11</sup>. The second symposium, *A focus on human cell-line derived rFVIII in haemophilia A: Update on clinical experience with Nuwiq<sup>12</sup> in PUPs<sup>13</sup> and PTPs<sup>14</sup>* was chaired by Professor Craig Kessler (Georgetown University Medical Centre, Washington DC, USA). Discussion covered some complex issues in haemophilia A and the latest experience with Nuwiq<sup>15</sup>. A number of posters related to Nuwiq<sup>16</sup>, Wilate<sup>17</sup>, Octanate<sup>18</sup> and fibrinogen<sup>19</sup> were presented during the congress.

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<sup>9</sup> *Bleeding characteristics of patients with congenital haemophilia and inhibitors: data from a postmarketing study of recombinant activated factor VII (SMART-7) (P-W-79)*

<sup>10</sup> *Recombinant factor XIII is safe and effective for prophylaxis in young children with congenital FXIII A-subunit deficiency: results from an international phase 3 trial (MP-M-200).*

<sup>11</sup> Prophylactic therapy for VWD patients was discussed, including the management of bleeding in patients in the perioperative setting, and special issues related to VWD in women. Clinical experiences with Wilate, a double virus-inactivated VWF/FVIII concentrate containing both factors in a physiological 1:1 ratio, were presented including its use in immune tolerance induction in haemophilia A patients with FVIII inhibitors.

<sup>12</sup> Octapharma's human cell line recombinant FVIII Nuwiq(Human-cl rhFVIII), is a fourth generation rFVIII derived from a human cell line without chemical modification or fusion with any other protein and is devoid of antigenic non-human epitopes. The development aims of Nuwiq were to address the challenges of FVIII inhibitors and frequent infusions required during prophylaxis.

<sup>13</sup> Previously untreated patients

<sup>14</sup> Previously treated patients

<sup>15</sup> This included a review of the risk of inhibitor development throughout the life of haemophilia A patients, taking into account factors such as age and the need for intensive treatment during surgery. New interim data from a clinical study of Nuwiq in previously untreated patients (PUPs) was presented, as well as the importance of PK-guided personalised prophylaxis and its potential to reduce the number of infusions and bleeding rates.

<sup>16</sup> *Individualized prophylaxis with Nuwiq® (Human-cl rhFVIII) in previously treated adults with severe haemophilia A who had received regular routine prophylaxis in the past; PUPs with Severe Haemophilia A - A GCP Study Evaluating the Immunogenicity, Efficacy and Safety of Nuwiq® (NuProtect); Individual baseline thrombin generation and bleeding rate during personalized prophylaxis with Nuwiq® in previously treated patients with severe haemophilia A; Long-term Immunogenicity, Safety and Efficacy of Human-cl rhFVIII in Previously Treated Children with Severe Haemophilia A; and Experience with Nuwiq® in clinical trials with previously treated paediatric and adult patients*

<sup>17</sup> *Surveillance Study of Safety and Efficacy of a VWF/FVIII concentrate in patients with von Willebrand disease (VWD) - data report from an ongoing study (Wil-20)*

<sup>18</sup> *Immune tolerance induction in haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study (ObsITI) and Disease severity as a predictor of response to immune tolerance induction (ITI) in adult patients with haemophilia A and high titer inhibitors*

<sup>19</sup> *Pharmacokinetic (PK) Comparison of Two Fibrinogen Concentrates in Patients with Congenital Fibrinogen Deficiency: final analysis.*

- vi) Sangamo BioSciences presented new preclinical data on its gene therapy to treat haemophilia A. In mice and in monkeys, the gene therapy generated higher than normal levels of human factor VIII and was well tolerated. Sangamo now plans to file an investigational new drug application with the FDA and hopes to start a Phase I/II (human) clinical trial in 2017. The therapy uses an adeno-associated virus to carry complementary DNA encoding a synthetic version of factor VIII. The FDA has already approved Sangamo's zinc finger nuclease (ZFN) technology for testing in a Phase I/II clinical trial for haemophilia B. It is the first *in vivo* genome editing application to have been cleared by the FDA. Sangamo plans to begin that trial later this year. Sangamo's competitors include BioMarin in haemophilia A and Spark Therapeutics in haemophilia B.
  - vii) Updated data from uniQure's ongoing Phase I/II clinical study of its gene therapy AMT-060 for haemophilia B patients was presented by Dr Wolfgang Miesbach, Professor at the Universitäts Klinikum in Frankfurt, Germany.
  - viii) Alnylam Pharmaceuticals announced new positive results from its ongoing Phase I study with fitusiran, an investigational RNAi therapeutic targeting antithrombin for the treatment of hemophilia A and B and rare bleeding disorders. Fitusiran is designed to lower levels of antithrombin and thus promote sufficient thrombin generation to restore haemostasis and prevent bleeding in patients with hemophilia and rare bleeding disorders. New clinical data demonstrated that monthly subcutaneous administration of fitusiran achieved dose-dependent lowering of antithrombin and sufficient increases in thrombin generation to yield a median estimated annualized bleeding rate (ABR) of zero in seventeen patients with haemophilia A or B without inhibitors. Furthermore, data from an initial cohort of six haemophilia patients with inhibitors showed lowering of antothrombin, increased thrombin generation, and preliminary evidence for reduced bleeding. Fitusiran was found to be generally well tolerated to date in patients with and without inhibitors, and there were no thromboembolic events. Alnylam announced that it now plans to begin fitusiran pivotal studies in people with haemophilia with and without inhibitors in early 2017.
  - ix) John Pasi, Professor of Haemostasis and Thrombosis, Barts and the London School of Medicine, and Honorary Consultant Haematologist, The Royal London Hospital, presented interim results of an open-label, Phase I/II study of BioMarin Pharmaceutical's BMN 270, an AAV5-FVIII gene transfer in severe haemophilia. BMN 270 has received orphan drug designation from the European Commission and the US Food and Drug Administration (FDA). The data presented at the congress were updated since the Company reported preliminary data April 20, 2016.
- b) Ingrid Pabinger, professor at Medical University of Vienna, and colleagues conducted a phase I to phase III study of rVIII-SingleChain (CSL Behring)—a novel B-domain truncated rFVIII composed of covalently bonded FVIII heavy and light chains—for the treatment of haemophilic bleeding episodes and as routine and surgical prophylaxis<sup>20</sup>. The study included data from 173 adolescent and adult patients (aged at least 12 years) assigned to prophylaxis (n = 146) or on-demand therapy with rVIII-SingleChain (n = 27). The authors wrote: "This study, which was designed to reflect clinical practice, demonstrated with a robust dataset that rVIII-SingleChain is highly efficacious in the treatment of bleeding events, routine prophylaxis and in controlling hemostasis in a variety of surgical procedures in adolescents and adults with severe hemophilia A.....The study also demonstrated that rVIII-SingleChain has a favorable safety profile and is well tolerated. Very low annualized bleeding rates in patients on individualized prophylaxis hopefully has the potential to translate into prolonged freedom from debilitating joint disease."

<sup>20</sup> Mahlangu J, et al. "rVIII-SingleChain appears safe, effective for severe hemophilia A" *Blood*. 2016;doi:10.1182/blood-2016-01-687434.

## Other

- c) Pharming announced positive results from a Phase II clinical study of Ruconest (recombinant C1 esterase inhibitor, 50 IU/kg) for prophylaxis in patients with hereditary angioedema (HAE). The drug showed a clinically relevant and statistically significant reduction in attack frequency for both the twice-weekly and once-weekly treatment regimens as compared with placebo. Ruconest was generally well-tolerated. No patients withdrew from the study due to adverse events. No thrombotic or thromboembolic events were reported. There were no hypersensitivity or anaphylactic reactions. No neutralizing antibodies were detected.
- d) Shire announced the launch of a paediatric indication for HyQvia (Human Normal Immunoglobulin (10%), Recombinant Human Hyaluronidase) across Europe, following the marketing authorisation granted by the European Commission to Baxalta, in June 2016, just before its takeover by Shire. HyQvia is a replacement therapy to treat primary and certain secondary immunodeficiencies.
- e) A study led by scientists from St. Jude Children's Research Hospital<sup>21</sup> points to another strategy for alleviating hereditary haemoglobin deficiencies (beta-thalassemia and sickle cell disease) using CRISPR/Cas9 genome editing. First author Elizabeth Traxler and senior author Mitchell Weiss, both of St. Jude's, described in *Nature Medicine* how they mutated a 13 base pair stretch of promoters for subunits of foetal haemoglobin—hemoglobin subunit gamma 1 and 2 (HBG1 and HBG2). They edited patient-derived haematopoietic stem and progenitor cells. The edited cells produced levels of foetal haemoglobin that reduced sickle cell morphology when differentiated into red blood cells.
- f) Gamida Cell announced today that in a Phase I/II study the first patient with sickle cell disease had been transplanted with CordIn as the sole graft source. The transplant was performed at UCSF Benioff Children's Hospital Oakland, California. Mark Walters, Director of the Blood and Marrow Transplantation Program is the Principal Investigator. Gamida Cell CEO Dr. Yael Margolin said: "In the first Phase I/II study with sickle cell disease, the expanded graft was transplanted along with a non-manipulated umbilical cord blood unit in a double graft configuration. In the second Phase I/II study we updated the protocol from our first Phase 1/2 study so that patients would be transplanted with CordIn as a standalone graft, which is expanded from one full umbilical cord blood unit and enriched with stem cells using the company's proprietary NAM technology."
- g) A Phase III trial showed that treatment with romiplostim induced a high rate of platelet response in children with chronic immune thrombocytopenia<sup>22</sup>.

## 2. Regulatory

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

- a) The Swiss agency for therapeutic products, Swissmedic, approved Elocta (rFVIII Fc) for the treatment of haemophilia A. Swedish Orphan Biovitrum (Sobi) said Elocta is the only recombinant factor VIII Fc fusion protein with an extended half-life approved for haemophilia A treatment in Switzerland to offer prolonged protection against bleeding episodes with prophylactic injections every three to five days.
- b) Merck's investigational vaccine for Ebola Zaire, V920 (rVSV $\Delta$ G-ZEBOV-GP, live attenuated) was granted Breakthrough Therapy Status<sup>23</sup> by the US Food and Drug

<sup>21</sup> And including participants from the University of Pennsylvania, the Children's Hospital of Philadelphia, Pennsylvania State University, Oxford University, and Japan's University of Tsukuba.

<sup>22</sup> Chaturvedi S and McCrae KR. *Lancet*. 2016;doi:10.1016/S0140-6736(16)00589-4.  
Tarantino MD, et al. *Lancet*. 2016;doi:10.1016/S0140-6736(16)00279-8

Administration (FDA) while European Medicines Agency (EMA) accorded it PRIME (PRiority MEdicines) status<sup>24</sup>.

- c) Spark Therapeutics and Pfizer announced that the FDA had granted breakthrough therapy designation to SPK-9001, the lead investigational candidate in the companies' SPK-FIX program, in development for the treatment of haemophilia B. SPK-9001, a bio-engineered adeno-associated virus capsid expressing a codon-optimized, high-activity human factor IX variant, is being investigated in an ongoing Phase I/II trial as a potential one-time therapy.
- d) Researchers based at Universite Laval in Quebec City were the first in Canada to be authorized by Health Canada and the FDA to conduct clinical tests of a Zika vaccine in humans. The DNA-based vaccine had already been tested on cells and animals such as mice, guinea pigs and primates. The first phase of study involved administering the vaccine to 40 volunteers in Quebec City, Miami and Philadelphia, and was concerned with safety and immunogenicity, or the building of immune protection. The second phase, which will test for protective effects in a larger group of volunteers in an endemic region such the Caribbean or Latin America, could begin by the end of 2016 or early in 2017. The vaccine is being manufactured by Inovio Pharmaceuticals of Pennsylvania.
- e) Emmaus Life Sciences announced that it would submit a new drug application (NDA) to the FDA in September for its sickle cell treatment, orally administered pharmaceutical-grade L-glutamine. The therapy already has orphan drug and fast track designations from the FDA.
- f) On 1 August Shire announced that the FDA had approved the BAXJECT III reconstitution system for ADYNOVATE [Antihemophilic Factor, (Recombinant), PEGylated]. The new system reduces the number of steps in the reconstitution process. ADYNOVATE and the diluent will be pre-packaged in the BAXJECT III reconstitution system. ADYNOVATE, an extended circulating half-life recombinant Factor VIII (rFVIII) treatment built on the protein of ADVATE [Antihemophilic Factor (Recombinant)], was approved by the FDA in November 2015 for use in haemophilia A patients 12 years and older for on-demand treatment and control of bleeding and for prophylaxis to reduce the frequency of bleeding episodes. In early 2016, Baxalta, now part of Shire, filed for use in pediatric and surgical settings in the US.
- g) Shire announced on 14 September that the US Food and Drug Administration (FDA) had granted approval for CUVITRU [Immune Globulin Subcutaneous (Human), 20% Solution] in adult and paediatric patients two years of age and older. CUVITRU is a treatment for patients with primary immunodeficiency (PI), a group of more than 300 genetic disorders in which part of the body's immune system is missing or functions improperly. Globally up to six million people are thought to be affected. Shire now has the broadest portfolio of intravenous and subcutaneous immunoglobulin products, including the only once-a-month subcutaneous treatment option. "In the clinical study, primary immunodeficiency patients tolerated CUVITRU favorably despite the use of higher infusion site volumes and more rapid infusion rates than have been routine in the past," said Richard L. Wasserman, Medical Director of Pediatric Allergy and Immunology at Medical City Children's Hospital, Dallas, Texas. "The availability of CUVITRU as a high concentration, subcutaneous IG provides

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<sup>23</sup> The FDA's Breakthrough Therapy Designation expedites the development and review of a candidate that is planned for use, alone or in combination, to treat a serious or life-threatening disease. The candidate can be used when preliminary clinical evidence indicates that the drug might demonstrate substantial enhancement from existing therapies on one or more clinically significant endpoints.

<sup>24</sup> PRIME is an approach from the EMA to improve support for the development of medicines which focus on an unmet medical requirement. PRIME maximizes development plans and speeds up assessment of the medicine's application so they reach patients earlier. To be accepted for PRIME, a drug has to demonstrate its potential to benefit patients with unmet medical requirements based on early clinical data. <sup>24</sup>

primary immunodeficiency patients with the dosing flexibility that allows them to customize their therapy to best fit their individual needs." The approval follows the recent publication of a Phase II/III study of CUVITRU among North American patients in the *Journal of Clinical Immunology*. CUVITRU was approved in 17 European countries in June of 2016. The company expects to initiate additional global regulatory submissions for CUVITRU in late 2016 and 2017.

- h) The FDA wrote to Portola Pharmaceuticals rejecting AndexXa, or andexanet alfa, as an anticoagulant reversal drug for uncontrolled or life-threatening bleeding in patients receiving direct or indirect Factor Xa inhibitor. The FDA says it needs further manufacturing information and additional data to support including Factor Xa inhibitors enoxaparin and edoxaban on the label. AndexXa is an FDA-designated Breakthrough Therapy.
- i) Portola is seeking conditional approval in the EU for its anti-coagulant's use when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding and for patients requiring urgent or emergency surgery. Its submission is based on data from two Phase III ANNEXA studies that evaluated the safety and efficacy of IndexXa (andexanet alfa) in reversing the anticoagulant activity of the Factor Xa inhibitors rivaroxaban (Bayer's Xarelto) and apixaban (Pfizer/Bristol-Myers Squibb's Eliquis), showing in some cases reversal of the anticoagulant effect by 93.5 percent.

### 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.*

#### Company results

- a) Grifols increased its net revenues by 2.7 per cent to EUR 1,951.6 million in the first half of 2016. Overall revenues in Europe fell by 5.7 per cent to EUR 323.1 million. Sales in Spain showed positive growth. Revenues in the rest of the world increased by 6.9 per cent rising in North America by 5.9 per cent. Revenues of the Bioscience Division increased by 7.0 per cent with significant growth in sales volumes of IVIG<sup>25</sup>, alpha-1 antitrypsin<sup>26</sup> and albumin<sup>27</sup>. The growth in sales of factor VIII remained stable and the initial reactions to the SIPPET study (Survey of Inhibitors in Plasma Products Exposed Toddlers) data indicated increasing consideration of plasma derived FVIII in markets that have previously been more inclined to use recombinant factor VIII<sup>28</sup>.
- b) CSL booked net profit of \$US1.24 billion (\$A1.61 billion) for the year to June 30, down from \$US1.38 billion a year earlier. The company flagged a possible share

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<sup>25</sup> Demand remains strong, supported by growth in the US and Canada. IVIG use continues to grow in neurology, including the treatment of neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), neuromuscular diseases such as myasthenia gravis and various myopathies, particularly in countries with higher per capita consumption. Grifols continues to promote the use of IVIG in the treatment of primary immunodeficiencies, a significant source of growth in specific countries of Latin America and the Asia-Pacific region where health services are expanding.

<sup>26</sup> Growth in sales of albumin is supported by demand in China and the US.

<sup>27</sup> Grifols continues to promote the diagnosis of deficiency in the protein alpha-1 antitrypsin (DAAT) in the US and Europe and more recently in Latin America. Grifols is also strengthening the implementation of various disease management programs for patients with this genetic disorder, whose symptoms are similar to those of chronic obstructive pulmonary disease (COPD).

<sup>28</sup> The principal investigators of the SIPPET study were Flora Peyvandi and Pier Mannuccio Mannucci, of the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre in Milan.

buyback of around \$A500 million after posting this 10 per cent fall in annual net profit, the result of its acquisition of the Novartis influenza vaccines business. Excluding the impact of the Novartis unit, annual underlying after-tax profit rose 5.2 per cent to \$US1.47 billion, thanks to an 8.6 per cent rise in underlying revenue.

## Agreements

- c) In the US, the CDC Foundation announced in 2015 a partnership with the CDC's Division of Blood Disorders (within the National Center on Birth Defects and Developmental Disabilities) and other partners to support the development and operation of a longitudinal data collection system for Americans with sickle cell disease. Biogen is now joining this partnership. Coleen Boyle, director of CDC's National Center on Birth Defects and Developmental Disabilities said: "Understanding the clinical history of individuals living with sickle cell disease continues to be of great importance. The recent partnership fostered between Biogen and the CDC Foundation will further enable critical support for the collection and study of information leading to advances in sickle cell disease treatment."
- d) Chinese company Yabao Pharmaceuticals and LFB Biomedicaments (a fully-owned subsidiary of LFB SA, the French state-owned company) announced a strategic partnership to supply LFB's human albumin product Vialebex to China, which is the world's largest human albumin market with annual growth of 29 per cent from 2010 to 2014. Rockwell Medical signed an exclusive license and manufacturing supply agreement with Saudi-based ARAM Medical for the rights to commercialize Rockwell's Triferic<sup>29</sup> and Calcitriol<sup>30</sup> in the Middle East.

## Market forecasts

- e) Credence Research forecast that the global apheresis equipment market will reach \$USD 3 billion by 2023, with market growth driven by reimbursement policies and demand for plasma products.
- f) GlobalData forecast that the therapeutics market for venous thromboembolism<sup>31</sup> (VTE) will rise from \$US 2.8 billion in 2015 to \$US 3.7 billion by 2025, representing a compound annual growth rate of 2.89 per cent. This steady growth will occur across the seven major markets of the US, France, Germany, Italy, Spain, the UK, and Japan, and will be driven primarily by VTE primary prophylaxis, which is projected to increase from \$US 2.4 billion in 2015 to \$US 3.5 billion by 2025, at a compound annual growth rate of 4.01 per cent. Novel oral anticoagulants (NOACs)<sup>32</sup> will drive the market, and represent advances over warfarin. NOACs do not require routine blood monitoring or dose adjustments, have fewer drug-drug interactions, and do not have major dietary impacts. In terms of efficacy and safety, they appear to be non-inferior, if not superior, compared with warfarin. Reversing their effect in cases of trauma or emergency surgery has been a challenge, but reversal agents are becoming available.
- g) Globally the top three therapy areas accounted for 68 per cent of the overall pharmaceutical industry pipeline as of Q1 2016, according to GBI Research. Oncology is by far the largest therapy area, with close to 7,000 products in active development, almost matching the combined size of the next two therapy areas, infectious diseases and central nervous system disorders. Immunology, metabolic

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<sup>29</sup> Triferic is an iron replacement and haemoglobin maintenance drug for treating anaemia in haemodialysis patients.

<sup>30</sup> Calcitriol is a generic (active vitamin D) injection for treatment of secondary hyperparathyroidism in dialysis patients.

<sup>31</sup> deep vein thrombosis and pulmonary embolism

<sup>32</sup> Pradaxa, Xarelto, and Eliquis, are all currently available. The recent launch of a fourth NOAC, Savaysa, in the US and Japan will give physicians further treatment options when deciding on which anticoagulant is most suitable for their patients.

disorders and cardiovascular diseases each have pipelines consisting of over 1,000 products. The overall pharmaceutical industry pipeline increased by 5 per cent in Q1 2016. Only central nervous system disorders and immunology marginally decreased in size.

## Other

- h) At the World Federation of Hemophilia 2016 World Congress in Florida Bayer announced that six US haemophilia clinicians and researchers<sup>33</sup> were among 16 grant recipients under the company's Hemophilia Awards Program for 2016. A total of about \$US 2 million in grants were awarded to physicians and researchers in 11 countries.
- i) Also at the Congress CSL Behring announced five recipients<sup>34</sup> of the 2016 CSL Behring Professor Heimburger Award for coagulation research. These amounted to \$US 110,000 in total.
- j) Shire discontinued plans to further develop BAX 335, a haemophilia B gene therapy it acquired with its \$US 32 billion takeover of Baxalta. Shire will concentrate its attention on a preclinical gene therapy program. UniQure and Spark have both delivered some clinical data on their gene therapies, while Dimension Therapeutics and Sangamo Biosciences are approaching that point. The share price of the Dutch biotech UniQure rose 8.5 per cent on the day Shire announced its decision.
- k) BioMarin plans to start a Phase IIb trial in mid-2017 for its haemophilia A gene therapy candidate, which it hopes could be sufficient to support a submission for an accelerated approval by the FDA.
- l) Grifols said a Phase I study of its Alzheimer's vaccine showed a good safety profile and tolerability. products. The blind Phase I study did not evaluate the effectiveness of the treatment.
- m) Biotest opened a new plasma collection centre in Clemson, South Carolina.
- n) Global Health Investment Fund, backed by Microsoft founder Bill Gates<sup>35</sup>, has taken an \$A 3.3million (8.4 per cent) stake in an Australian biotech start-up, Atomo Diagnostics, which has invented quick, cheap and accurate tests for HIV, malaria and Ebola. An Atomo spokesman said: "The focus for the next 12 months is to launch a rapid home blood test for HIV in South Africa".

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<sup>33</sup> Dr Moanaro Biswas, University of Florida Cancer & Genetics, Research Center; Dr James Dahlman, Georgia Institute of Technology; Dr Gary Gilbert, Boston VA Research Institute; Dr Rahul Khanna, University of Mississippi; Dr Michael Milone, University of Pennsylvania; and Dr Maurizio Tomaiuolo, University of Pennsylvania .

<sup>34</sup> Antonino Cannavò, Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Italy). *Proposal: The role of non-neutralizing antibodies directed against factor VIII in hemophilia A patients enrolled in the SIPPET study.*

Christopher Ng, University of Colorado Denver, Hemophilia and Thrombosis Center (US) *Proposal: Multi-system evaluation of von Willebrand factor, function in Type 1 von Willebrand disease mutations.*

Alessandro Casini, University Hospitals of Geneva, Unit of Angiology and Haemostasis (Switzerland). *Proposal: Fibrin clot structure to assess phenotype in patients with congenital dysfibrinogenemia.*

Johan Boender, Erasmus University Medical Center Rotterdam (Netherlands). *Proposal: WUB-Kids: a prospective study of children with moderate and severe von Willebrand disease.*

Michiel Coppens, Academisch Medisch Centrum (Netherlands). *Proposal: Biomarkers to detect subclinical arthropathy and predict long-term clinical arthropathy in patients with hemophilia.*

<sup>35</sup> The fund is a joint venture between the Gates Foundation and JPMorgan,. It finances initiatives that benefit global health. It concentrates on infectious diseases that include malaria, pre-eclampsia, cholera and river blindness.

## 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) The US the National Hemophilia Foundation's (NHF) 68<sup>th</sup> Annual Meeting in Orlando received the announcement that a clinical practice guideline for care models for the management of people with haemophilia had been accepted for inclusion in the National Guideline Clearinghouse<sup>TM</sup>. The guideline, sponsored by NHF and McMaster University, recommends an integrated care model be used for people with haemophilia<sup>36</sup>. The integrated care team includes a haematologist, a haemophilia nurse, physical therapist, social worker, and 24-hour access to a specialized coagulation laboratory. The guideline recommends expanding the evidence base with further studies in: geriatric populations; populations with poor access to care; and patients who access care outside haemophilia treatment centres.
- b) Canadian Blood Services has changed its deferral policies and donor restrictions broaden the pool of eligible donors<sup>37</sup>:
  - i) The upper age limit for donating has been eliminated. Donors over the age of 71 no longer need to have their physician fill out an assessment form before donating blood.
  - ii) Donors who have a history of cancers such as breast cancer, thyroid cancer, and prostate cancer will now be eligible to donate if they have been cancer free for five years. This does not apply to those with a history of haematological cancers (such as lymphomas, leukemia or melanoma).
  - iii) Donors who have recently received most vaccines, such as fluvaccine, will no longer need to wait two days before donating blood.
  - iv) Donors who were born in or lived in some African countries (Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, and Nigeria) are now eligible to donate blood, as HIV testing performed on blood donors can now detect HIV strains found in these countries.
  - v) Geographic deferrals affecting Western Europe have been revised based on scientific evidence that indicates the risk of variant Creutzfeldt-Jakob Disease (vCJD), or mad cow disease, has decreased since January 2008. Donors who spent five years or more in Western Europe since 1980 are deferred from donating blood, but the end date is now 2007. Donors who reached the five year limit in Western Europe after 2007 will now be eligible to donate blood.
- c) Victims of Canada's hepatitis C tainted blood scandal of the 1990s will be compensated further from a surplus of more than \$C 200 million remaining in the trust fund, following a decision from Judge Paul Perell of Ontario Superior Court.

## 5. Safety and patient blood management

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

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<sup>36</sup> The NHF-McMaster Guideline on Models of Care for Hemophilia has been endorsed by the World Federation of Hemophilia, the American Society of Hematology, and the International Society for Thrombosis and Haemostasis, and was published in the July issue of *Haemophilia*, the official journal of the World Federation of Hemophilia. The guideline may be accessed online at <http://onlinelibrary.wiley.com/doi/10.1111/hae.2016.22.issue-S3/issuetoc>.

<sup>37</sup> The complete policy changes are available at [www.blood.ca/en/blood/recent-changes-donation-criteria](http://www.blood.ca/en/blood/recent-changes-donation-criteria)

## Appropriate Transfusion

- a) A Swedish study of nearly 1.5 million patients found no evidence that degenerative brain disorders such as Alzheimer's or Parkinson's disease can be transmitted via donated blood<sup>38</sup>. Dr. Irving Gomolin chief of geriatric medicine at Winthrop-University Hospital in Mineola, N.Y. said that the study "demonstrates that the transmission of these diseases via blood either is not biologically possible or, at worst, must be exceedingly rare."
- b) An observational study<sup>39</sup> has found an increased risk of death for transfusion recipients receiving blood from either young or female donors<sup>40</sup>; since this was an observational study, clinical trials are required to determine if indeed such donor characteristics have an impact on recipient survival.

## Other

- c) A study<sup>41</sup> has found that patients assigned to generic phosphate-buffered tirofiban were more likely to experience thrombocytopenia compared with patients assigned to citrate-buffered tirofiban or unfractionated heparin, according to post hoc results from the PRISM clinical trial<sup>42</sup>.
- d) Haematology researchers from The Children's Hospital of Philadelphia (CHOP) and the Perelman School of Medicine at the University of Pennsylvania have genetically engineered a clotting factor that can control bleeding in animal models<sup>43</sup>. If it is found to be effective in humans, it may provide a fast-acting antidote for surgery and trauma patients vulnerable to serious bleeding as a result of new anti-coagulants. "This molecule holds the potential to fill an important unmet clinical need," said study leader Rodney A. Camire, of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics at CHOP. "There are limited treatment options to stop uncontrolled bleeding in patients who are using the newer anticoagulant medications." Camire's team developed the molecule by modifying coagulation FXa,

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<sup>38</sup> A team led by Dr. Gustaf Edgren, of the Karolinska Institute in Stockholm followed more than 40,000 patients in Denmark and Sweden. All of the patients had received blood transfusions between 1968 and 2012 from people who were later diagnosed with any form of dementia or Parkinson's disease. These patients were compared with over 1.4 million patients who did not receive blood from donors later diagnosed with these illnesses. Patients in both groups were found to have had exactly the same chance of developing a neurodegenerative disorder. The study was published online in the journal *Annals of Internal Medicine*, 27 June.

<sup>39</sup> Chasse M, Tinmouth A, English SW, Acker JP, Wilson K, Knoll G, Shehata N, van Walraven C, Forster AJ, Ramsay T, McIntyre LA, Fergusson DA. "Association of Blood Donor Age and Sex With Recipient Survival After Red Blood Cell Transfusion". *JAMA internal medicine*. 2016. doi: 10.1001/jamainternmed.2016.3324. PubMed PMID: 27398639; Klein HG. "Blood Donor Demographics and Transfusion Recipient Survival-No Country for Old Men?" *JAMA internal medicine*. 2016. doi: 10.1001/jamainternmed.2016.3355. PubMed PMID: 27400131

<sup>40</sup> The study covered seven years. 30,503 red blood cells (RBC) transfusion recipients who received almost 188,000 RBC units from 80,755 donors were included. Researchers analyzed the effect of donor age and sex on the survival of the recipients. Recipients who received blood from a female donor appeared to have had an 8 per cent increase in mortality compared with those who received blood from a male donor. Recipients who received blood from r donors aged 17 to 29.9 years had a 6 per cent to 8 per cent higher risk of mortality compared with those receiving blood from donors aged 40 to 49.9 years.

<sup>41</sup> Adamo M, Ariotti S, Costa F, et al. "Phosphate- or citrate-buffered tirofiban vs unfractionated heparin and its impact on thrombocytopenia and clinical outcomes in patients with acute coronary syndrome". *JACC Cardiovasc Interv*. 2016;9:1667-1676. doi:10.1016/j.jcin.2016.05.031.

<sup>42</sup> PRISM (Platelet Receptor Inhibitor in Ischemic Syndrome Management) was a randomized, controlled, multicenter, double-blind involving patients with non-ST-segment elevation acute coronary syndrome.

<sup>43</sup> Nabil K. Thalji et al, "A rapid pro-hemostatic approach to overcome direct oral anticoagulants," *Nature Medicine*, published online July 25, 2016. <http://doi.org/10.1038/nm.4149>

a naturally occurring protein active in blood clotting. Using bioengineering techniques, they changed the shape of FXa into a novel variant that is more potent, longer-lasting and safer than wild-type (naturally occurring) FXa. This variant safely restored blood-clotting ability in injured mice that had previously received FXa inhibitors. Infusing the variant either before or during an active bleed significantly reduced bleeding. "Our next steps will be to test this approach in large animals to help determine whether this variant is effective and safe, and may progress to clinical trials," said Camire.

## 6. Infectious diseases

*The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).*

### Zika Virus

#### Its spread and testing

- a) At the end of July, US health officials were beginning to believe that mosquitoes in the continental US were spreading the Zika virus, at least in Florida. Initially, the FDA restricted blood collection in areas where Zika was then thought to be endemic, as it had in Puerto Rico. Then on 26 August, the FDA issued a revised guidance recommending universal testing of donated whole blood and blood components for Zika virus in the US and its territories.
- b) Also on 26 August US health officials confirmed that the Zika virus can be spread sexually even when a partner shows no signs of infection<sup>44</sup>.
- c) By early August there were reports that two men who had been infected with the Zika virus were continuing to return positive results for the Zika virus in their semen more than 180 days after the onset of their symptoms, and there was no suggestion that a limit had been reached.
- d) Brazilian clinicians on 17 August reported in a letter to the *New England Journal of Medicine* on two cases of likely Zika transmission related to a person who donated platelets while asymptomatic. In March, Brazilian officials reported two blood transfusion-related Zika infections, and in Puerto Rico in June, Zika detected in blood centre screening marked a rapid rise in disease activity.
- e) OraSure Technologies has been awarded a six-year, multi phased contract from the US Biomedical Advanced Research and Development Authority to develop its oral test kits for the Zika virus. The contract includes \$US 7 million initially with options of up to \$US 9.6 million further, and will support the company's clinical and regulatory services and assessment of additional product enhancements.

#### Vaccine development

- f) The National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health, launched a clinical trial of a vaccine candidate intended to prevent Zika virus infection. The Phase I study in at least 80 healthy volunteers

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<sup>44</sup> 26 August, 2016, US.Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report*

ages 18-35 years was to evaluate the experimental vaccine's safety and ability to generate an immune system response in participants. Scientists at NIAID's Vaccine Research Center (VRC) developed the vaccine. The NIAID Zika virus investigational DNA vaccine approach is similar to that used for a vaccine developed by NIAID for West Nile virus. That vaccine candidate was found to be safe and induced an immune response when tested in a Phase 1 clinical trial. The investigational Zika vaccine includes a small, circular piece of DNA—called a plasmid—that scientists engineered to contain genes that code for proteins of the Zika virus. When the vaccine is injected into the arm muscle, cells read the genes and make Zika virus proteins, which self-assemble into virus-like particles. The body mounts an immune response to these particles, including neutralizing antibodies and T cells. DNA vaccines do not contain infectious material—so they cannot cause a vaccinated individual to become infected with Zika. John Mascola, director of NIAID's VRC, said: "DNA or gene-based vaccines induce antibodies, but they also can activate the cell-mediated immune response, which ultimately could yield strong and durable protection against disease." Phase II trials are expected to begin early in 2017.

- g) Researchers from the Walter Reed Army Institute of Research (WRAIR), Harvard Medical School and Beth Israel Deaconess Medical Center successfully tested two Zika virus vaccine candidates on mice. The Harvard-developed DNA vaccine is based on an isolated strain of the virus in Brazil. The other is a purified inactivated virus (PIV) vaccine isolated in Puerto Rico, which was developed at WRAIR. The team hopes to begin human clinical trials before the end of the year.
- h) The US Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) announced on 7 September a \$US 8.2 million contract with Moderna Therapeutics of Cambridge, Massachusetts, to help speed the development of a Zika vaccine. ASPR's Biomedical Advanced Research and Development Authority (BARDA) will also contribute technical assistance. Over four years, BARDA will support a Phase 1 clinical trial, toxicology studies, vaccine formulation, and manufacturing. The agreement could be extended up to a total of five years and a total of \$US 125.5 million to support Phase II and III trials and commercial scale manufacturing. Moderna's vaccine uses messenger RNA, or mRNA, vaccine technology. Messenger RNA carries specific genetic codes to parts of the cell, in this case the genetic sequence of the Zika virus to generate an immune response. Producing vaccine from this type of technology is rapid compared with technologies that require the growth and purification of an attenuated (weakened) or inactivated (killed) virus.
- i) Takeda Pharmaceutical Co of Japan also has a contract with BARDA. It calls for funding of up to \$US 312 million if the agency deems Takeda's Zika vaccine worthy of moving through late stage testing and filing for approval. The initial payment for pre-clinical research is \$US 20 million.
- j) Inovio Pharmaceuticals is developing its Zika vaccine, GLS-5700, with GeneOne Life Science, Inc and academic collaborators from the US and Canada who are also working to advance Inovio's Ebola and MERS vaccines through clinical development. In June, Inovio began a human Zika trial, with sites in the US and Canada. All 40 subjects for the first clinical study have been fully enrolled and dosed. Inovio expects to report results before the end of this year. Now Inovio has initiated a clinical study of GLS-5700 in 160 subjects in Puerto Rico, where the Zika virus outbreak has been declared a public health emergency. The CDC estimates Zika will infect more than 25 per cent of the Puerto Rican population by the end of 2016<sup>45</sup>.

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<sup>45</sup> Inovio's second clinical study is a placebo-controlled, double-blind trial involving 160 healthy adult volunteers (80 subjects will receive vaccine and 80 subjects will receive placebo) to evaluate the safety, tolerability and immunogenicity of GLS-5700 administered with Inovio's CELLECTRA-3P device. This proprietary intradermal DNA vaccine delivery device has been shown to maximize antigen expression and immune responses in multiple human studies. Inovio will also assess

- k) Prokarium announced on 13 September the start of its program to develop an oral Zika vaccine. It said the new vaccine will be active against both modes of Zika transmission—insect-borne (antibody-mediated) and sexually transmitted (mucosal and cell-mediated) infections. Ted Fjällman, Prokarium’s CEO, said: “We use a safe bacterium, which is swallowed and then enters into the immune cells of the gut lining to produce vaccine there. The oral delivery means that we kick-start mucosal immunity, the body’s first defence against infection in e.g. the gut, nose or the vaginal tract. The production of vaccine from within immune cells means that our approach causes few or zero side effects, while crucially initiating cellular immunity, which is very important for combatting viruses like Zika”. The company has a Small Business Research Initiative innovation procurement contract from the UK Department of Health and the UK Vaccine Network, administered by Innovate UK. Prokarium’s partner is Public Health England.
- l) On 18 August Xenetic Biosciences of Lexington, Massachusetts, announced that it has commenced a collaboration with Excivion Ltd. of the UK to develop a vaccine against Zika and dengue viruses. Xenetic’s proprietary IMUXEN technology will be used to develop the vaccine. Excivion is a private company that has developed a proprietary antigen design platform for viral vaccines which it is applying to flavivirus infections. Xenetic’s IMUXEN vaccine delivery platform enhances the potency of vaccine antigens and provides for cold-chain-free distribution and stockpiling of vaccines for pandemic emergencies.

### Potential treatments

- m) Scientists at the University of Texas Medical Branch at Galveston began in January to try to find a cure for the Zika virus using medications that are already on the market. Of 774 tested, 20 were found to inhibit Zika activity<sup>46</sup>.
- n) A large-scale collaboration<sup>47</sup> has identified three compounds which may offer pregnant women and their developing foetuses protection against the damaging effects of Zika. They are: Niclosamide, which is already on the market as a treatment for tapeworm but appears to have antiviral properties that inhibit Zika from replicating; PHA-690509, an antiviral currently in development that works by interfering with gene expression; and Emricasan, which inhibits a natural process that causes programmed cell death. A report was published 29 August in *Nature Medicine*.
- o) Seattle-based biotech Kineta has received funding from the National Institute of Allergy and Infectious Disease (NIAID). Kineta CEO Shawn Iadonato said: “We are eager to expand testing of our broad spectrum antivirals in Zika virus as they have shown compelling efficacy across other flaviviruses such as dengue and West Nile and have the potential for long term development as a pan-flavivirus therapy.” Kineta’s *Innate Immune Antiviral program*, which will be researched as a treatment for Zika, hinges on a protein called IRF-3, “a critical first responder that is essential for inhibiting viral replication and clearing infection.” Kineta has raised over \$US 40 million since they were founded in 2008, including a \$US 7.2 million award to develop

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differences in Zika infection rates in participants given either placebo or vaccine as part of an exploratory endpoint. In preclinical testing, this synthetic vaccine induced robust antibody and T cell responses - the immune responses necessary to fight viral infections - in small and large animal models.

<sup>46</sup> The team isolated viral genes from *Aedes aegypti* mosquitoes in Tapachulas, Chiapa, Mexico and tested the drugs on the genes in-vitro. They used multiple cell types, including neural stem cells and amnion cells, which make up the amniotic sac, to monitor the effectiveness of the drugs on the cells. In some cases, the drug would eliminate just the virus, but not kill the cell, or vice-versa. Researchers plan to test how the drugs work in a living human body during clinical studies, where there are more complex and various types of cells acting at once.

<sup>47</sup> the National Institutes of Health, Johns Hopkins University in Baltimore, Florida State University, the Icahn School of Medicine at Mount Sinai in New York City, Emory University in Atlanta, and Zhejiang University in China

a treatment for Lassa Fever in May, and \$US 4 million last year to develop therapies for viral diseases like Ebola.

### Impact of the virus

- p) Researchers led by Vanessa van der Linden, from the Association for Assistance of Disabled Children, Reclife, Brazil, evaluated data from seven children with presumed congenital Zika virus infection<sup>48</sup> who had microcephaly and arthrogryposis<sup>49</sup>. They included infants in whom other infectious causes of microcephaly were excluded; two of the children had positive serology results for Zika infection in their cerebrospinal fluid. All children underwent neurologic and orthopaedic evaluations, advanced neuroimaging, joint ultrasound, nerve conduction studies, and electromyography. Six children had arthrogryposis in both the arms and legs, and all seven had bilateral hip dislocation. Other abnormalities included club foot in six children, knee flexion contracture in five children, and hyperextension with subluxation of the knee in three children. There were also joint deformities in the arms. Sensory nerve testing was normal, but motor action potentials were generally of low amplitude. All patients showed cortical calcification, reduced brain volume, and hypoplasia of the brainstem and cerebellum. The scientists noted that the presence of cortical malformations suggests infection probably occurred within the first five months of pregnancy.
- q) Researchers at Yale University investigated how the Zika virus passes through the placenta of an infected pregnant women to her foetus. They found<sup>50</sup> that two of the three types of placental cells they studied—fibroblasts and Hofbauer cells—were susceptible to infection in lab culture experiments.
- r) A study in monkeys, published online on 12 September in the journal *Nature Medicine*, found that the Zika virus starts to cause damage to brain development in the foetus shortly after mother's infection. Dr. Kristina Adams Waldorf, a professor of obstetrics and gynecology at the University of Washington in Seattle, said: "Our results remove any lingering doubt that the Zika virus is incredibly dangerous to the developing fetus, and provides details as to how the brain injury develops".
- s) Scientists at Rockefeller University and La Jolla Institute of Allergy and Immunology experimented with Zika virus in mice<sup>51</sup>. They focussed on neural stems cells, which are thought during gestation to be vulnerable to Zika virus and a probable factor in the damage that leads to microcephaly in newborns. Neural stem cells are found in limited parts of adult brains. Three days after the scientists injected the virus into the mice's bloodstreams, they harvested the brains and used antibodies to identify presence of Zika virus. They found viral particles surrounding the neural stem cells, with evidence of cell death and a drop in replication. Sujan Shresta, study coauthor, said that adult neurogenesis is involved with learning and memory: "We don't know what this would mean in terms of human diseases, or if cognitive behaviors of an individual could be impacted after infection". The scientists said the next step is to look at changes in neural stem cell populations in the infected adult mice over time and to see if patterns vary according to the strain of Zika virus.
- t) A study published in the journal *Radiology* reported on brain scans of 45 babies and foetuses in Brazil who were infected with Zika. While microcephaly is one of the well-known complications associated with the virus, this study also observed several other brain abnormalities like grey- and white-matter loss, issues with the brain stem and fluid buildup. "It's not just the small brain, it's that there's a lot more damage," said study author Dr. Deborah Levine, a professor of radiology at Harvard Medical School.

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<sup>48</sup> Vanessa van der Linden et al, "Congenital Zika syndrome with arthrogryposis: retrospective case series study", *BMJ* 2016; 354 doi: <http://dx.doi.org/10.1136/bmj.i3899> (Published 09 August 2016)

<sup>49</sup> Arthrogryposis is characterized by joint contractures at birth

<sup>50</sup> Findings were published in the *Journal of Clinical Investigation (JCI) Insight*

<sup>51</sup> Results were published in *Cell Stem Cell*

- u) Mariana Leal<sup>52</sup>, and colleagues tested the hearing of 70 infants in Brazil who had been diagnosed with Zika-linked microcephaly. Almost 6 per cent had hearing loss.
- v) Researchers from the World Federation of Neurology (WFN) based in Honduras and the US have found zika virus can be associated with another neurological disorder, besides meningoencephalitis and acute myelitis. In this case, its acute sensory polyneuropathy. The auto-immune disorder Guillian Barre Syndrome is also associated with Zika.
- w) A study from Brazil raised concerns about the potential of the Zika virus to continue inflicting damage to an infant's brain even after birth. It found the virus may linger in the blood of an infected baby for more than two months. The study also showed that Zika can cause serious harm to babies even if their mothers are infected relatively late in pregnancy<sup>53</sup>.

### Influenza: strains, spread, prevention and treatment

- a) From 2013 up to 14 August, 775 human cases of avian influenza A(H7N9) had been reported by the Chinese Mainland health authorities; 118 of those had been since October 2015.
- b) Researchers have used genetic sequencing to show that the 2009 global H1N1 influenza pandemic began in central Mexico, originating in pigs and spreading to humans<sup>54</sup>.
- c) FluGen of Madison, Wisconsin, has begun a Phase I trial of RedeeFlu, hoping to overcome the challenge of drifted flu strains<sup>55</sup>. Nearly 100 people aged 18 to 49 will participate in the study of an intranasal vaccine containing mutations in the M2 gene of the flu virus. The virus infects cells and expresses the "entire spectrum of influenza RNA and proteins," FluGen said, but doesn't cause an infection. The placebo-controlled trial will focus primarily on safety while also looking at antibody and T-cell responses for three dose levels. Others working on a universal flu vaccine include Sanofi, BiondVax and the US National Institute for Allergy and Infectious Diseases (NIAID)<sup>56</sup>. Sanofi unveiled last November a program named Cobra from a genetic sequencing collaboration with the University of Georgia<sup>57</sup>.

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

- a) By 11 September there had been in Saudi Arabia a total of 1451 laboratory-confirmed cases of MERS-CoV infection, including 610 deaths.
- b) A study in *Emerging Infectious Diseases*<sup>58</sup> explored the use of convalescent plasma from recovered MERS patients as passive immunotherapy and found the evidence to be lacking<sup>59</sup>. The authors suggested that their disappointing results could be explained by short-lasting antibody response to the virus, and they recommended

<sup>52</sup> of the Hospital Agamenon Magalhaes and the Federal University of Pernambuco in Brazil

<sup>53</sup> See *The New England Journal of Medicine*, 24 August 2016

<sup>54</sup> I Mena, M Nelson, F Quezada-Monroy *et al.* "Origins of the 2009 H1N1 influenza pandemic in swine in Mexico". *eLIFE* DOI: 10.7554/eLife.16777 (2016).

<sup>55</sup> Recently in the US, strain mismatches between flu vaccines and circulating strains caused low efficacy, notably 19 per cent in the 2014-2015 season.

<sup>56</sup> In September, BiondVax partnered with NIAID to launch a Phase II test of its candidate M-001 in the US.

<sup>57</sup> Sanofi Pasteur Senior Vice President of R&D John Shiver commented that while a universal flu vaccine is the "ultimate goal," it's more likely that a broader vaccine against multiple strains will be available before a vaccine that can protect against all strains.

<sup>58</sup> 20 July

<sup>59</sup> The plasma should contain MERS-CoV-specific antibodies and in theory could prevent death or otherwise lessen symptoms in patients. Researchers collected plasma from three sources: 96 patients with suspected or laboratory-confirmed MERS-CoV infection, 230 healthcare workers, and 17 household contacts exposed to the virus. Using ELISA (enzyme-linked immunosorbent assay), the researchers found only 12 of the 443 samples had adequately high antibody titers.

further ELISA testing with serum samples obtained from recently diagnosed or very ill patients.

- c) SAB Biotherapeutics has started a Phase I clinical trial for its human antibody treatment for MERS-CoV. This uses SAB's DiversitAb platform, which leverages genetically engineered cattle to produce large amounts of human antibodies<sup>60</sup>. The clinical report is expected by the end of March 2017. This is said to be the first time human antibodies derived from cattle have been transferred to humans. The study is being sponsored, funded and conducted by the US National Institutes of Health (NIH). SAB recently received a contract for up to \$US 5.3 million from the US Biomedical Advancement Research and Development Authority (BARDA). The contract is in part to produce the material that will be used in Phase II clinical trials which will probably be conducted in Saudi Arabia.
- d) A study in *Clinical Infectious Diseases* identified five pregnant MERS patients reported to the WHO from Saudi Arabia between November 2012 and February 2016. All five were in their second or third trimester when they acquired MERS. Two women died. A third suffered a stillbirth at 34 weeks gestation, and a fourth had an emergency caesarian section at 24 weeks' gestation, the baby dying soon after birth. The fifth patient recovered from the disease and delivered a healthy baby at term.

### **Ebola virus disease**

- a) A research team led by Professor Dave Stuart of Oxford University said the painkiller ibuprofen and the chemotherapy drug toremifene can "disable" the Ebola virus. Researchers, however, warn that this is just a starting point and more effective drugs would need to be created as both ibuprofen and toremifene have a relatively weak effect. The study was published in the journal *Nature*.
- b) Scientists from the National Institute of Allergy and Infectious Diseases, part of the US National Institutes of Health (NIH), led a project exploring the connection between Ebola survival and co-infection with malaria parasites<sup>61</sup>. People infected with Ebola virus were 20 per cent more likely to survive if they were co-infected with malaria-causing *Plasmodium* parasites, according to data collected at an Ebola diagnostic laboratory in Liberia in 2014-15. Moreover, greater numbers of *Plasmodium* parasites correlated with increased rates of Ebola survival, according to a dozen collaborating research groups in the new study. The survival difference was evident even after controlling for Ebola viral load and age.
- c) A new compound can block the protein Ebola virus uses to break out of cells and infect new cells, according to researchers from the University of Pennsylvania and Fox Chase Chemical Diversity Center, Inc<sup>62</sup>.
- d) The Ebola virus is now known to be able to last in semen for 565 days, showing the potential role of sex in sparking another outbreak.

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

- a) Researchers from McGovern Medical School at The University of Texas Health Science Center at Houston have been awarded \$US 11 million from the US National Institute of Allergy and Infectious Diseases to study the pathogenesis, transmission and detection of prion diseases – such as chronic wasting disease in deer – that can potentially spread to humans.

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<sup>60</sup> SAB is also planning clinical trials for a human antibody treatment for influenza. A Small Business Innovation Research, or SBIR grant, of up to \$US 1.42 million from NIH will help fund testing to file a new drug application with the FDA to undertake the trials.

<sup>61</sup> K Rosenke *et al.* "Plasmodium parasitemia associated with increased survival in Ebola virus-infected patients". *Clinical Infectious Diseases* DOI: 10.1093/cid/ciw452 (2016).

<sup>62</sup> H. Marie Loughran *et al.* 2016. "Quinoxaline-based inhibitors of Ebola and Marburg VP40 egress". *Bioorganic & Medicinal Chemistry Letters* 26 (15): 3429-3435; doi: 10.1016/j.bmcl.2016.06.053

- b) Chagas disease, a protozoal infection mainly affecting people and dogs in Mexico, South America, and Central America, although spreading worldwide through human migration, has been detected in a horse in Texas. Although canine cases of Chagas disease had previously been reported in southern Texas, this is the first known case of clinical infection in an American horse<sup>63</sup>.
- c) Leishmaniasis, Chagas disease and sleeping sickness are transfusion-transmitted diseases. Each infection is acquired from a type of kinetoplastid parasite. Researchers at the Genomics Institute of the Novartis Research Foundation screened over 3 million compounds in proliferation assays using all three parasites. They identified and refined GNF6702, which selectively inhibits all three kinetoplastid proteasomes but does not affect the growth of mammalian cell<sup>64</sup>s. The compound is well tolerated in mice and is now subject to further evaluation including toxicity testing.
- d) The head of pandemic and epidemic diseases at the World Health Organisation (WHO) said on 13 September that a yellow fever outbreak in Angola and Congo had been brought under control by a major vaccination campaign. However, although the level of vaccinations in Angola, as well as in Kinshasa and border regions, meant that there was no risk of a major outbreak there, there were still 32 endemic countries in Africa, so further outbreaks could not be ruled out.

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<sup>63</sup> Bryan LK, Hamer SA, Shaw S, et al: "Chagas disease in a Texan horse with neurologic deficits". *Vet Parasitol.* 2016; 216: 13-7. Epub 2015 Dec 2; available at <http://www.sciencedirect.com/science/article/pii/S0304401715300832>.

<sup>64</sup> Khare S, Nagle AS, Biggart A, Lai YH, Liang F, Davis LC, Barnes SW, Mathison CJ, Myburgh E, Gao MY, Gillespie JR, Liu X, Tan JL, Stinson M, Rivera IC, Ballard J, Yeh V, Groessl T, Federe G, Koh HX, Venable JD, Bursulaya B, Shapiro M, Mishra PK, Spraggon G, Brock A, Mottram JC, Buckner FS, Rao SP, Wen BG, Walker JR, Tuntland T, Molteni V, Glynne RJ, Supek F. "Proteasome inhibition for treatment of leishmaniasis, Chagas disease and sleeping sickness". *Nature* 2016.