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ibpn international blood/plasma news

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COMPANIES IN THIS ISSUE

AABB
ALEXION PHARMACEUTICALS
AMERICA'S BLOOD CENTERS
AMERICAN RED CROSS
ASAHI KASEI PHARMA AMERICA
AUSTRALIAN RED CROSS
BAXALTA
BAXALTA GmbH
BAYER
BioMarin Pharmaceutical
BIOVERATIV THERAPEUTICS
bluebird bio
CANADIAN PLASMA RESOURCES
CSL BEHRING
ERYTECH Pharma
ETHICON
FRESENIUS KABI
GENENTECH
GigaGen
GLOBAL BLOOD THERAPEUTICS
GRIFOLS
IMMUCOR GTI DIAGNOSTICS
IPFA
JAPAN BLOOD PRODUCTS ORG
JEFFREY MODELL FOUNDATION
KM BIOLOGICS
NIHON PHARMA
NOVO NORDISK
PFIZER
PPTA
ProMetic Life Sciences
PROMETIC PLASMA RESOURCES
ROCHE
SANOFI
SPARK THERAPEUTICS
SWEDISH ORPHAN BIOVITRUM
TAKEDA
VERSITI

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BUSINESS BRIEFS

* **GRIFOLS announced that, in a first-time broad global relationship with ETHICON to provide plasma protein-based solutions to manage surgical bleeding, it will introduce a new fibrin sealant product to be brand named *VISTASEAL* in the U.S. and *VERASEAL* in other select markets**. The Grifols-developed product, which combines human plasma-derived fibrinogen and thrombin, will be commercially launched in the second half of 2019. It is administered with Ethicon's airless spray device technology.

The alliance also anticipates pairing Grifols' lyophilized human thrombin with Ethicon's currently available *SURGIFLO Hemostatic Matrix* to provide surgeons with more advanced options to facilitate and induce clotting during surgery. "Grifols is committed to applying its plasma leadership to its collaboration with Ethicon, whose strengths in device technology and market success in reaching millions of patients worldwide enable us to make important advances in biosurgery and the control of surgical bleeding," said **Eduardo Herrero**, president of Grifols Bioscience Industrial Group.

* **The U.S. non-profit blood and related blood services provider VERSITI announced that it is transitioning its four Midwest blood centers to a single unified Versiti brand this year**:

Previous name	*New name*
Indiana Blood Center	Versiti Blood Center of Indiana
Heartland Blood Centers	Versiti Blood Center of Illinois
Michigan Blood	Versiti Blood Center of Michigan
BloodCenter of Wisconsin	Versiti Blood Center of Wisconsin

In addition, Versiti is establishing a fifth blood center – Versiti Blood Center of Ohio – to serve the Ohio State Wexner Medical Center; this new Columbus, Ohio-based blood center is set to open on July 1, replacing blood and specialty laboratory services previously provided by the **AMERICAN RED CROSS**.

* Responding to a joint letter and formal request from **AABB**, the **AMERICAN RED CROSS** and **AMERICA'S BLOOD CENTERS**, **the U.S. Centers for Medicare and Medicaid Services (CMS) has issued a preliminary recommendation to establish a new "not otherwise classified" (NOC) HCPCS Level II billing code that U.S. hospitals can use to bill insurers and secure reimbursement for new types of transfused blood products prior to the creation of a permanent HCPCS billing code**.

In its letter, the three co-signing entities argued that a miscellaneous/NOC code for blood products "is instrumental to facilitating the timely adoption of new products that may have the potential to result in improved clinical outcomes." This new "not otherwise classified" code is expected to become effective on January 1, 2020.

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* **Japan's Ministry of Health, Labour and Welfare (MHLW) has recently published its 2019 plan for the domestic production and import of plasma-derived and recombinant medicinal products**. This plan includes, among others:

	Domestic Demand (a)	Domestic Production (b)	Imports (Plasma) (c)	Recombinant (d)	Total (b)+(c)+(d)
Albumin (Kg)	31,508	18,221	12,360	-	30,581
Factor VIII (000 IU)	794,800	68,400	0	774,400	842,800
Factor IX (000 IU)	166,900	34,800	0	104,800	139,600
IVIG/SCIG (Kg)	6,085	5,884	406	-	6,290

According to this published plan, 1,120,000 liters of plasma for fractionation will be made available to the country's three fractionators in 2019 (**KM BIOLOGICS**, **NIHON SEIYAKU** and **JAPAN BLOOD PRODUCTS ORGANIZATION**), representing a 13% increase over 2018 plasma volume directed to domestic fractionation.

* **In Germany, 2019 blood and blood component prices below have been reported by the Blood Transfusion Service of three Red Cross Regions**. These prices are only indicative and may be negotiated with customers:

	Region 1		Region 2		Region 3	
	Euros	Dollars	Euros	Dollars	Euros	Dollars
Red cell concentrates	€92	$103.16	€89.50	$100.36	€89	$99.80
Additional fee for:						
Group A Rh Negative	€15	$16.82	-	-	-	-
Group B Rh Negative	€15	$16.82	-	-	-	-
Group O	€21	$23.55	€10	$11.21	-	-
Group O Rh Negative	€28	$31.40	-	-	-	-
Pooled Platelets	€328	$367.79	€299	$335.27	€299	$334.15
Apheresis Platelets	€537	$602.14	€498	$558.41	€560	$627.93
Fresh frozen Plasma (ml)	€0.20	$0.22	€0.20	$0.22	€0.20	$0.22

€1.00 = $1.1213

* **The timeframe for ROCHE'S pending $4.3 billion acquisition of SPARK THERAPEUTICS has been pushed back again, as U.S. regulators continue to scrutinize the deal for possible anti-competitive effects**. Roche reported that both companies have received a request from the Federal Trade Commission (FTC) for additional information and documentary material in connection with its review of the proposed deal, while the UK Competition and Markets Authority has separately opened its own investigation.

Roche has extended the offering period of its previously announced tender offer to purchase all of the outstanding shares of Spark common stock for $114.50 per share.

* **In the first quarter of 2019, an estimated 8% of all U.S. hemophilia A patients on treatment, and significantly more of those specifically on prophylaxis, used GENENTECH/ROCHE'S *HEMLIBRA*,** according to The Marketing Research Bureau's newly released report titled *Hemophilia Care & Price Monitoring, Wave #26*. This and other report findings were based on surveys of 20 Hemophilia Treatment Centers (HTCs) collectively managing more than 6,700 patients with hemophilia A, hemophilia B and von Willebrand disease.

TAKEDA'S *ADVATE* maintained its leadership position with 41% of all hemophilia A patients in the survey sample. **SANOFI'S** *ELOCTATE* and **BAYER'S** *KOGENATE FS* also held respectable market positions, while the aggregate share of all the plasma-derived factor VIII products used for on-demand treatment and prophylaxis accounted for less than 5% all hemophilia A patients.

In the hemophilia B therapeutics arena, **PFIZER'S** *BeneFIX* maintained its market leadership, as well over half of the patients in the patients' sample used this product. However, its share slipped slightly as patients continued to switch to extended half-life (EHL) recombinant products, in particular Sanofi's *ALPROLIX* and **CSL BEHRING'S** *IDELVION*. This product switching activity was more moderate than two to three years ago, when these EHL recombinant factor IX products were first introduced.

Genentech/Roche's *HEMLIBRA* dominated the inhibitor market, capturing the majority of hemophilia A patients with inhibitors, with a corresponding reduction in the patient market shares of Takeda's *FEIBA*, **NOVO NORDISK'S** *NovoSeven* and immune tolerance induction (ITI) treatments.

Distribution of Hemophilia A Treatments by Category - 2013 to 2019
(percentage of hemophilia A patients in each product category)

Product	*Feb 2013*	*Feb 2019*
Non-Factor Therapy	0.0%	7.8%
EHL Recombinant	0.0%	18.9%
Standard Recombinant	89.3%	68.5%
Plasma-derived FVIII	10.7%	4.8%
Total	100.0%	100.0%

* **FRESENIUS KABI USA has received U.S. FDA 510(k) clearance to market its *ALYX Component Collection System* for use in the collection of multiple blood components, including but not limited to:**

- Two units of leukocyte-reduced red blood cells (2RBC);
- Concurrent single unit of leukocyte-reduced RBCs and plasma as fresh frozen plasma (FFP), source plasma, plasma frozen within 24 hours after phlebotomy (PF24) and held at room temperature up to 24 hours after phlebotomy (PF24RT24); and
- FFP, source plasma, PF24 and PF24RT24 in isolation.

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* **In France, the following 2019 blood component prices were published in the *Journal Officiel* of December 26, 2018. These prices supersede the 2018 prices previously published in December 2017** (see *IB/PN*, Vol. 36, Issue 5, page 65):

	Euros (€)	USD ($)
Whole blood, unit	121.67	136.43
Red cells, unit, leukocyte-depleted	201.23	225.64
Random donor platelet concentrate unit (> 1 x 10^{11} cells)	82.11	92.07
Each additional unit (0.5 x 10^{11})	41.06	46.04
Apheresis platelet dose (> 2 x 10^{11})	238.13	267.02
Amotosalen-treated platelet concentrate (> 1 x 10^{11}) from whole blood unit	82.11	- 92.07
Amotosalen-treated platelet dose (> 2 x 10^{11}), each additional unit (0.5 x 10^{11})	238.13 59.52	267.02 66.74
Apheresis plasma for fractionation, Category #1 * per liter:	105	117.74
Recovered plasma for fractionation, Category #1* per liter:	75.9	85.11
Apheresis plasma for fractionation, Category #2 ** per liter:	46.6	52.25

* Frozen within 24 hours after collection
** Frozen within 72 hours after collection

€1.00 = $1.1213

* **ProMetic Life Sciences completed of a previously announced equity rights offering, raising aggregate gross proceeds of C$37,998,000 (US$28,357,000)**. Following the rights offering, 23.2 million common shares have been issued and are outstanding.

BLOOD & BIOTECHNOLOGY

* **The French clinical-stage biopharmaceutical firm ERYTECH Pharma announced that the U.S. FDA has accepted its Investigational New Drug (IND) application for *eryaspace* – the enzyme L-asparaginase encapsulated inside donor-derived red blood cells – which will enable the company to initiate enrollment of U.S. patients in its ongoing Phase 3 TRYbeCA trial evaluating *eryaspace* as a second-line treatment for pancreatic cancer**. TRYbeCA1 is projected to enroll approximately 500 patients with metastatic pancreatic cancer at more than 120 clinical trial sites in **Europe** and the **U.S.** Enrollment of U.S. patients is expected to begin in the third quarter of 2019.

Eligible patients are randomized 1:1 to receive *eryaspase* in combination with standard chemotherapy or chemotherapy alone. The primary endpoint of TRYbeCVA1 is overall survival. The trial started enrolling patients in **Spain** in September 2018, and is now actively enrolling patients in several **European** countries.

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Announcement

The Marketing Research Bureau is pleased to announce the completion of its latest U.S. hemophilia care market report:

HEMOPHILIA CARE & PRICE MONITORING

WAVE #26, 2019 (United States)

This study, based on in-depth telephone interviews with hemophilia treatment centers and other hemophilia stakeholders, updates the hemophilia care market situation in the United States, with particular focus on:

- Analysis of coagulation factor brands, including the adoption and perception of new recombinant factors VIII and IX, as well as *Hemlibra*;
- Market shares of coagulation factor products;
- Trends in immune tolerance and prophylaxis;
- Awareness of new products and technologies in development, including gene therapy;
- Impact of the 340 B program and patients' issues; and
- Coagulation factor prices.

To obtain more information, please contact The Marketing Research Bureau at:

(203) 799-0298 Email: mrb_ibpn@marketingresearchbureau.com

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* **Japan's Ministry of Health, Labour and Welfare (MHLW) has approved ALEXION PHARMACEUTICALS' novel long-acting C5 complement inhibitor *ULTOMIRIS* (ravulizumab) for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)**. Administered intravenously every eight weeks, *ULTOMIRIS* was first approved in the **U.S.** for the PNH indication in December 2018. PNH is an ultra-rare blood disorder characterized by hemolysis mediated by an uncontrolled activation of the complement system. *ULTOMIRIS* works by inhibiting the C5 protein in the terminal complement cascade.

The MHLW approval was based on comprehensive results from two Phase 3 studies which enrolled a total of 441 patients who had either never been treated with a complement inhibitor before, or who had been stable on Alexion's *SOLIRIS* (eculizumab), which also binds and inhibits C5.

The efficacy of *ULTOMIRIS* administered every eight weeks was non-inferior to the efficacy of *SOLIRIS* administered every two weeks with respect to all 11 clinical endpoints; the safety profile of the two drugs was also found to be comparable. Additional data showed that *ULTOMIRIS* provided immediate and complete C5 inhibition that was sustained for eight weeks and eliminated breakthrough hemolysis associated with incomplete C5 inhibition.

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"Based on the totality of our compelling data from the largest Phase 3 program ever conducted in PNH, we believe *ULTOMIRIS* has the potential to become the new standard of care for patients with PNH in **Japan**, said executive vice president and head of R & D **John Orloff, MD**.

Alexion has submitted a supplemental Biologics License Application (sBLA) to the U.S. FDA for approval of *ULTOMIRIS* as a treatment for adult patients with atypical hemolytic uremic syndrome (aHUS) and plans to submit similar applications in Japan and the European Union later in 2019. The product is also currently being evaluated in a Phase 3 clinical study in children and adolescents with aHUS, administered intravenously every eight weeks.

Additional Phase 3 studies have been initiated to evaluate *ULTOMIRIS* as a potential treatment for patients with generalized myasthenia gravis (gMG).

* In a three-year update to results of its investigational gene therapy treatment for adults with severe hemophilia A, **BioMarin Pharmaceutical reported that bleed rate control with valocotogene roxaparvovec 6e13 vg/kg dose was maintained for a third year with a median annualized bleed rate (ABR) of zero and mean ABR of 0.7 for that year**. In the year prior to study entry, the mean ABR was 16.5 and the median was 16.3.

This represents a 96% reduction in mean ABR over three years, with continued absence of target joints and target joint bleeds during the three years of observation. A substantial and sustained reductions in bleeding requiring factor VIII were also observed in the 4e13 vg/kg cohort, with a mean ABR of 1.2 and a median of zero after two years.

In addition, factor VIII levels in the 6e13 vg/kg dose appeared to be approaching a plateau in year three, with mean 32.7 IU/dL and 36.4 IU/dL factor VIII levels (measured with the chromogenic substrate assay) at the end of year 3 and year 2, respectively; the respective median end of year 3 and year 2 factor VIII levels were 19.9 IU/dL and 26.2 IU/dL.

"With three years of data, it's clear that valoctocogene roxaparvovec has the potential to change the way we treat this debilitating disease, which can improve the quality of life for people with severe hemophilia A," said principal investigator **John Pasi, MB, ChB, PhD**. "For people who have had to inject themselves with factor VIII every other day to prevent bleeding, this treatment has the potential to be transformational."

The company announced that, **as of the end of May 2019, eight adult patients in the 20-patient cohort of the Phase 3 GENEr8-1 study achieved factor VIII levels of 40 IU/dL or more, at 23 to 26 weeks following valoctocogene roxaparvovec administration, which met pre-specified clinical criteria for regulatory review in the U.S. and Europe**. For all 16 patients who had reached week 26 by the April 30 cutoff since administration, the estimated median ABR was zero and the estimated mean ABR was 1.5, representing a reduction of 85% from baseline levels where all patients were on standard of care prophylaxis.

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* **Despite its multiple anticoagulant, anti-inflammatory and cytoprotective effects that could theoretically be beneficial, treatment with ASAHI KASEI PHARMA AMERICA'S recombinant soluble human thrombomodulin (ART-123) did not significantly reduce 28-day all-cause mortality in a pivotal clinical trial of critically ill patients with sepsis-associated coagulopathy**. Known as the SCARLET trial, this randomized, double-blind, placebo-controlled, multinational, multicenter Phase 3 study was conducted in intensive care units at 159 sites in 26 countries.

The 28-day all-cause mortality rate was 106 of 395 patients (26.8%) in the ART-123 group versus 119 of 405 (29.4%) in the placebo group (P = 0.32, Cochran-Mantel-Haenszel test), a difference of 2.55% (95% confidence interval, -3.68% to 8.77%). In a post-hoc sensitivity analysis for the primary outcome that accounted for pooled site as a random effect, the adjusted 28-day all-cause mortality rate was 24.8% in the ART-123 group versus 27.5% in the placebo group (P =0.31). Complete findings of this 800-patient study are published in the May 19 issue of *JAMA*.

* **The European Commission has granted conditional marketing authorization for bluebird bio's *ZYNTEGLO* (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-global gene), a gene therapy for patients aged 12 years and older with transfusion-dependent β-thalassemia who do not have a β^0/β^0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available**. The product was reviewed as part of the European Medicine Agency's (EMA's) Priority Medicines (PRIME) and Adaptive Pathways programs, which support medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options.

ZYNTEGLO is a single-administration gene therapy that addresses the underlying genetic cause of transfusion-dependent β-thalassemia, and offers patients who do not have a β^0/β^0 genotype the potential to become transfusion independent, which once achieved is expected to be life-long.

"As one of the investigators in the clinical studies of *ZYNTEGLO,* I have witnessed firsthand the hope this gene therapy can provide to patients and their families who have often been managing this disease and transfusions for yours, often for decades," said **Professor Franco Locatelli, MD, PhD**, who serves as director, Department of Pediatric Hematology/Oncology and Cell and Gene Therapy, IRCCS Ospedale Pediatrico Bambino Gesù in Rome, **Italy**.

bluebird bio said it intends to continue the country-by-country reimbursement authorization process to help ensure access to *ZYNTEGLO* for appropriate patients.

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RESEARCH AND DEVELOPMENT

* **Oral administration of GLOBAL BLOOD THERAPEUTICS' deoxygenated sickle hemoglobin (HbS) polymerization inhibitor, voxelotor, significantly increased hemoglobin levels and reduced markers of hemolysis in patients with sickle cell disease**, according to findings from the Phase 3, multicenter, double-blind, randomized, placebo-controlled HOPE trial published in the June 14 online issue of the *New England Journal of Medicine*.

A total of 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. Most participants had sickle cell anemia (homozygous hemoglobin S or hemoglobin Sβ^0-thalassemia) and approximately two-thirds were receiving hydroxyurea at baseline**. In the intention-to-treat analysis, a significantly higher percentage of participants had a hemoglobin response in the 1500 mg voxelotor group (51%, 95% confidence interval [CI], 41 to 61) than in the placebo group (7%, 95% CI, 1 to 12)**.

At week 24, the primary endpoint of proportion of patients with a greater than 1.0 g/dL increase in hemoglobin from baseline was met, with 59% in the 1500 mg voxelotor group, 38% in the 900 mg voxelotor group, and just 9.2% in the placebo group. Anemia worsened between baseline and week 24 in fewer participants in each voxelotor dose group than in those receiving placebo. At week 24, the 1500 mg voxelotor group also had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. Adverse event rates were similar across all three trial groups.

"The results show that voxelotor has the potential to modify the morbidity of chronic organ damage associated with sickle cell disease by improving anemia and hemolysis," said senior investigator **Jo Howard, MD**, consultant hematologist at Guy's and St. Thomas' NHS Foundation Trust at King's College, London. "This represents a potential paradigm shift for sickle cell disease treatment toward addressing hemolytic anemia and organ damage," she added.

* **The ratio between circulating factor VIII and von Willebrand factor (VWF) may serve as a reliable biomarker of recovery and relapse in patients with acquired hemophilia A (AHA)**, according to findings of a retrospective cohort study published in the May 25 issue of the journal *Haemophilia*. The FVIII:C/WVF:Ag ratio was examined for its ability to predict relapse in 64 consecutive patients with AHA. In this cohort, all patients had a very low FVIII:C/VWF:Ag ratio at the time of diagnosis.

This value progressively increased over the first weeks of immunosuppressive treatment. Twenty-seven patients were followed long enough (longer than one year) to show that in the 22 patients who did not relapse, the FVIII:C/VWF:Ag ratio remained durably normalized. By contrast, in the five patients who relapsed during follow-up, the investigators noted either no normalization of this ratio, or a secondary decrease to an abnormal value of <0.7 after normalization.

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The French study authors concluded that the FVIII:C/VWF:Ag ratio could be considered a sensitive biological marker to predict recovery and/or relapse in acquired hemophilia A.

* **A systematic review and meta-analysis of the available clinical literature found no significant differences in the Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores between Alzheimer's patients treated with intravenous immunoglobulin (IVIG) and those receiving placebo**, according to **Chinese** investigators reporting in the June 2019 issue of *Expert Review of Neurotherapeutics*.

With the aim to determine the efficacy and safety of IVIG for Alzheimer's disease (AD) and mild cognitive impairment (MCI) due to AD, the investigators searched PubMed, EMBASE, CINAHL, Cochrane Library and China National Knowledge Infrastructure through March 2019. Five eligible studies were found that randomized a total of 772 patients with AD and MCI due to AD to IVIG or placebo treatment. Results from these studies were pooled via a random-effects model.

While no significant differences were found in either MMSE or ADAS-Cog scores, IVIG was well tolerated, even with long-term therapy for 18 months. The study authors suggested that "well-designed randomized controlled trials with large sample sizes are required in the future" to assess whether IVIG treatment can improve cognition of modify disease in patients with AD and MCI due to AD.

* **A separate systematic review and meta-analysis by Greek, UK and U.S. investigators similarly concluded that "albeit safe, intravenous immunoglobulin is inefficacious for treatment of patients with Alzheimer's disease."** Examination of five placebo-controlled trials included in the meta-analysis found that, compared to placebo, IVIG at dosage of 0.2 and 0.4 g/kg once every two weeks did not significantly change the ADAS-Cog score.

In their report published in the April 15, 2019 issue of the *American Journal of Alzheimer's Disease and Other Dementias*, the authors suggested that future trials targeting earlier stages of disease or application of different dosing regimens may be warranted to clarify the therapeutic potential of IVIG for treatment of Alzheimer's disease.

Erratum

In a feature in the May 2019 issue of *IB/PN* covering **FRESENIUS KABI'S** announced CE Mark approval for the *Amicus Extracorporeal Photopheresis (ECP) System* for the palliative treatment of skin manifestations of cutaneous T-cell lymphoma, we erroneously identified **Christian Hauer** as an employee of Mallincrodt. Mr. Hauer is the Transfusion and Cell Technologies division president at **FRESENIUS KABI**. We regret this error.

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PLASMA COLLECTION AND FRACTIONATION NOTES

* **Starting in July, CANADIAN PLASMA RESOURCES (CPR) will be able to increase its plasma collections at its two centers in Saskatoon, Saskatchewan and Moncton, New Brunswick, following Health Canada's recent authorization of twice-weekly collection from plasma donors – 104 donations annually with at least one full day between donations**. The collection volume per donation will remain unchanged, ranging from 690 to 880 milliliters depending on donor weight, the same as in the **U.S.** To ensure donor safety, and in accordance with current regulations, CPR will continue to monitor the donor's health (total proteins before each donation and protein composition every 16 weeks).

The allowable plasma donation frequency in **Canada** became more flexible at the end of 2014 when Health Canada issued a new set of regulations that were less complicated and detailed than the previous ones (18 to 23 donations over a rolling six-month period, with a volume cap dependent on the donor's weight, with many variations). **PROMETIC PLASMA RESOURCES** took advantage of these new regulations in 2015 when it acquired **EMERGENT BIOSOLUTIONS'** plasma center in Winnipeg, Manitoba.

* **The number of source plasma collection centers continues to climb in the U.S., reaching 737 centers in 2018**, according to a presentation by **PLASMA PROTEIN THERAPEUTICS ASSOCIATION (PPTA)** president and CEO **Amy Efantis** at PPTA's Plasma Protein Forum this month in Reston, Virginia. A total of 66 new collection centers were added in 2018, close to the 70 centers added annually between 2015 and 2016, and again between 2016 and 2017. The pace of plasma collection center growth remains dramatically slower in the **European Union**, with an average of about five new centers added annually between 2014 and 2018.

* **China now has 263 plasma collection centers drawing some 2.9 million qualified plasma donors across 650 counties**, according to a presentation at PPTA's Plasma Protein Forum by **Zhang Rui,** deputy director, Bureau of Medical Administration at **China's** National Health Commission. A total of 8,623 kilograms of plasma for fractionation were collected in 2018, an increase of nearly 12% over the 7,717 kilograms collected in 2017 and nearly 50% over the 5,820 kilograms collected in 2015. In **China**, **s**ource plasma is collected from healthy donors aged 18 to 55 years.

The needs for transfused blood and blood components in both urban and rural areas across China are met by a network of 452 blood centers, including 32 provincial blood centers, 321 regional blood centers and 99 hospital-based blood banks. Altogether, non-remunerated blood donors are able to access more than 3,000 blood collection sites. Nucleic acid testing (NAT) to screen blood and plasma collections for HIV and hepatitis viruses was fully implemented by the end of 2015.

PRODUCT SAFETY UPDATE

* At last month's 11th Plasma Product Biotechnology (PPB) Meeting in his presentation titled *Current Situation on the Quality and Safety of the Supply of Plasma for Manufacturing in Asia*, **INTERNATIONAL PLASMA AND FRACTIONATION ASSOCIATION (IPFA) executive director Dr. Paul Strengers reported on progress made in plasma collection in selected countries in the Asia & Pacific region, in particular Australia** and **Thailand**:

- **Thailand**: 28,334 liters of recovered plasma for fractionation in 2015 and 108,193 liters in 2018,
- **Australia**: In 2018/19, for the first time, the **AUSTRALIAN RED CROSS** collected more units of plasma than whole blood, approximately 61,000 vs. 60,000 units, respectively. This contrasts with over 100,000 whole blood donations and ca. 25,000 plasma donations 10 years previously.

With regard to **Asia and Pacific countries**, Dr. Strengers also noted that:

- Levels of quality and safety of the supply of plasma for manufacturing differ widely across **Asian** countries;
- In general, the quality and safety of plasma for manufacturing still need significant improvement,
- Some countries have achieved GMP compliance and are involved in (contract) manufacturing (**Japan, Australia, New Zealand, Singapore, Malaysia, Hong Kong, Taiwan, South Korea**),
- While some countries are improving their blood transfusion organizations with the aim of conforming with GMP standards and optimizing the quality of plasma (e.g. **Indonesia, Thailand, Vietnam, Sri Lanka**), other countries (in particular **India**) have a long way to go.

PEOPLE

* **SWEDISH ORPHAN BIOVITRUM (Sobi)** has appointed **Amy Pott** as its new head of **Sobi North America**, replacing **Rami Levin**, who is leaving Sobi. Ms. Pott was most recently group vice president and U.S. franchise head for Internal Medicine & Oncology at Shire. Additional roles at Shire including group vice president for U.S. Commercial Operations and vice president of Strategy, Planning & Analytics at Baxalta.

Prior to her U.S. roles for Shire and Baxalta, Ms. Potts served for 10 years at Baxter, where she held UK and international roles working with both rare diseases and medical devices. She has also held positions at the UK National Institute for Health & Clinical Excellence (NICE) and the NHS Confederation.

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SPECIAL ANNOUNCEMENT

* **The JEFFREY MODELL FOUNDATION** (El Dorado Hills, CA) **has released a 75-minute documentary film titled "Do Something: The Jeffrey Modell Story."** It recounts the experience of a boy diagnosed with a severe primary immunodeficiency disorder and his impassioned plea for his parents and physicians to "do something" about the disease that frequently sickened him.

In 1987, a year after Jeffrey succumbed to the disease in 1986, his parents, Fred and Vicki, committed themselves to turn their pain into purpose and established the Jeffrey Modell Foundation to help millions of others fight back against the disease that took their son's life. "Do Something: The Jeffrey Modell Story" is now available through iTunes, Amazon, Google Play, Vimeo, Vudu and DVD. For more information, visit https://dosomethingdoc.com.

RECENT U. S. PATENTS

* **Purification Method for Vitamin K Dependent Proteins By Anion Exchange Chromatography. #10,202,417.** Assigned to **Baxalta Inc.** (Bannockburn, IL) and **Baxalta GmbH** (Zug, Switzerland). A method for the purification of an active vitamin K-dependent protein comprising the steps of:

(a) loading a first anion exchange resin material with the Vitamin K-dependent protein in a loading buffer in the absence or low concentration of divalent cations;

(b) performing at least three washing steps with washing buffers that are absent of said divalent cations but that contain counter anions,

wherein the first washing buffer has a pH between 6.8 and 7.5, the second washing buffer has a pH between 5.5 and 6.5, and the third washing buffer has a pH between 7.0 and 8.2,

(c) eluting the Vitamin K-dependent protein with an eluant comprising 1-3 mM calcium and a counter-anion to form an eluate containing the active vitamin K dependent protein, wherein the eluant has a conductivity between 15 and 22 mS/cm (25° C.), and a pH of between 7.0 and 9.0;

(d) diluting the obtained eluate pool, and increasing the concentration of the calcium,

(e) loading a second anion exchange resin material with the diluted eluate pool as obtained after step (c); and

(f) collecting the flow-through containing the active Vitamin K-dependent protein.

* **Chimeric Clotting Factors. #10,202,595.** Assigned to **Bioverativ Therapeutics, Inc.** Waltham, MA). A chimeric protein comprising two polypeptides, wherein (A) the first polypeptide comprises (i) an activatable Factor VII (Ac) and (ii) a first Fc domain (Het1), wherein the activatable Factor VII comprises a Factor VII (FVII) zymogen comprising a heavy chain

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(HC), a light chain (LC), and a protease-cleavage site that is not naturally occurring in the FVII zymogen inserted between the HC and the LC;

wherein (B) the second polypeptide comprises (i) a soluble Tissue Factor (Em) and (ii) a second Fc domain (Het2); and

wherein the chimeric protein has a higher thrombin activity compared to a reference FVII protein comprising an activated FVII (FVIIa) alone or an FVIIaFc fusion protein, as measured by a thrombin generation assay.

* **Polypeptide Substrate for the Detection of von Willebrand Factor Cleaving Protease ADAMTS13. #10,202,633.** Assigned to **Immucor GTI Diagnostics, Inc.** (Waukesha, WI). An isolated polypeptide substrate for a disintegrin-like and metallopeptidase with thrombospondin type-1 motif, 13 (ADAMTS13), wherein said polypeptide substrate is from 45 to 70 amino acids in length and comprises (a) the amino acid sequence set forth in SEQ ID NO:7; or (b) an amino acid sequence substantially similar to SEQ ID NO:7 (ID7), wherein:

(i) the amino acid corresponding to position 4 of ID7 is lysine (K); and

(ii) the amino acid corresponding to position 15 of ID7 is cysteine (C).

* **Method for Treating Vascular Stenosis or Occlusive Disease Due to Thrombi by Administering a Saxatilin-Fc Fusion Protein. #10,208,097.** Assigned to Industry-Academic-Cooperation Foundation, Yonsei University (Seoul, South Korea). A method for treating vascular stenosis or occlusive disease due to thrombi, comprising:

administering to a subject in need thereof a pharmaceutically effective amount of a saxatilin derivative comprising saxatilin, which consists of the amino acid sequence of SEQ ID NO: 2, conjugated to an immunoglobulin Fc region.

* **Recombinant Fibrinogen High-Production Line and Method for Producing Same. #10,208,101.** Assigned to **Japan Blood Products Organization** (Tokyo, Japan). A recombinant animal cell comprising genes encoding the Aα chain, Bβ chain, and γ chain of fibrinogen and gene(s) encoding α2 plasmin inhibitor (α2PI) and/or plasminogen activator inhibitor-2 (PAI-2), wherein functional fibrinogen is produced by co-expressing said fibrinogen genes with α2PI and/or PAI-2 in said animal cell, and wherein said cell suppresses degradation of fibrinogen during cell culture and/or increases the production amount of fibrinogen independent of the suppressive effect, compared to the same animal cell expressing fibrinogen but which does not co-express α2PI and/or PAI-2.

* **Albumin Variants and Uses Thereof. 10,208,102.** Assigned to University of Oslo (Oslo, Norway). A variant human serum albumin (HSA) polypeptide that binds to FcRn with increased affinity relative to wild type HSA, wherein said polypeptide comprises substituted amino acids, wherein said substitutions are selected from a group specified in the patent.

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* **Removal of Serine Proteases By Treatment With Finely Divided Silicon Dioxide. #10,208,106.** Assigned to **Baxalta Inc.** (Bannockburn, IL) and **Baxalta GmbH** (Zug, Switzerland). A method for preparing an IgG composition having a reduced amount of a serine protease or a serine protease zymogen, the method comprising the steps of:

(a) precipitating a cryo-poor plasma fraction, in a first precipitation step, with from about 6% to about 10% alcohol at a pH of from about 7.0 to 7.5 to obtain a first precipitate and a first supernatant;

(b) precipitating IgG from the first supernatant, in a second precipitation step, with from about 23% to about 27% alcohol at a pH of from about 6.7 to about 7.3 to form a second precipitate;

(c) suspending the second precipitate to form a first suspension;

(d) contacting the first suspension with from about 0.02 grams fumed silica per gram precipitate formed in step (b) to about 0.06 grams fumed silica per gram precipitate formed in step (b) under a solution condition suitable to bind a serine protease or serine protease zymogen; and

(e) separating the fumed silica from the first suspension to form a newly clarified suspension by:

(i) filtering the suspension through a filter press to form a clarified suspension;

(ii) washing the filter press with at least 3 filter press dead volumes of a wash buffer, thereby forming a wash solution; and

(iii) combining the clarified suspension formed in sub-step (i) with the wash solution formed in sub-step (ii), thereby forming an enriched IgG composition.

* **Artificially Produced Polyclonal Immunoglobulin Preparation. #10,208,131.** Assigned to National University Corporation Chiba University (Chiba, Japan). An artificial polyclonal immunoglobulin composition, comprising, as active ingredients, polypeptides represented by amino acid sequences set forth in SEQ ID NOS: 1 to 204 of the sequence listing.

* **Platelet-Rich Plasma Compositions and Methods of Preparation. #10,214,727.** Allan Mishra (Menlo Park, CA). A method of preparing a platelet-rich plasma (PRP) composition comprising:

isolating platelets at a concentration of 151,000/microliter to 7,000,000 per microliter to obtain PRP, and

adding CD34+ cells at a concentration of 1-3$\times 10^9$ per liter to 100$\times 10^9$ per liter to the PRP to obtain the PRP composition.

* **Recombinant Fusion Proteins and Libraries From Immune Cell Repertoires. #10,214,740.** Assigned to **GigaGen, Inc.** (South San Francisco, CA). A method of generating a recombinant immunoglobulin library, whose individual steps are characterized in the patent.

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MEETINGS

October 18-20, 2019
European Hemophilia Consortium (EHC) Conference
Carlton Shearwater Hotel
Ballinasloe, Galway, Ireland
Phone: +32 2 893 2470
Email: office@ehc.eu
Website: https://www.ehc.eu/

October 19-22, 2019
AABB Annual meeting
Henry B. Gonzalez Convention Center
San Antonio, TX
Phone: 301-907-6977
Website: www.aabb.org

November 6-8, 2019
International Primary Immunodeficiencies Congress (IPIC)
Madrid Marriott Auditorium Hotel & Conference Centre
Madrid, Spain
Phone: +351 21 324 50 54
Email: ipic2019@aimgroup.eu
Website: www.ipic2019.com

November 13-14, 2019
11th WFH Global Forum
Westin Hotel
Montréal, Canada
Phone: 514-875-7944
Email: gf@wfh.org
Website: www.wfh.org

December 7-10, 2019
61st American Society of Hematology Annual Meeting & Exposition
Orange County Convention Center
Orlando, FL
Phone: 202-776-0544
Website: www.hematology.org

December 8-12, 2019
American Society of Health-System Pharmacists Mid-Year Meeting
Mandalay Bay
Las Vegas, NV
Phone: 866-279-0681
Website: www.ashp.org

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