THE SOURCE

MAGAZINE OF THE PLASMA PROTEIN THERAPEUTICS INDUSTRY

SPRING 2014

Global Healthcare Focus

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SPRING 2014

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In My View

BY JAN M. BULT, PRESIDENT AND CEO

One of the most important goals that we have as an industry is to provide sufficient supply of plasma derived medicinal therapies for all patients in the world. The starting material is human plasma that can be obtained as either recovered plasma from whole blood donations or as source plasma from plasma apheresis donations. Most recovered plasma comes from voluntary non-remunerated donors (VNRD) whereas most source plasma comes from voluntary compensated donations. Both source materials are safe and are needed to manufacture the lifesaving therapies. Plasma derived medicinal therapies from both sources are safe, efficacious and needed.

The availability of recovered plasma is an issue of concern. It is considered a "by-product" of whole blood donations where plasma can be obtained from blood donations that exceed their shelf life. This plasma is then provided to a domestic or foreign fractionator for the manufacture of therapies. This recovered plasma is by far not enough to manufacture sufficient therapies. The private industry plays a vital role in the collection of plasma and manufacture of plasma protein therapies. The situation with recovered plasma is not getting better.

Thanks to improved transfusion management, component therapy and changed surgical procedures the need for blood transfusions has been reduced during the last years. I have heard that many blood banks are facing a reduction of 6-8 % per year and have to review their financial operations. This means that it is predictable that it will become more and more difficult to operate economically.

It is with that in mind that I am surprised to read a newly published WHO document called "Towards Self-Sufficiency in Safe Blood and Blood Products based on Voluntary Non-Remunerated Donation." One of the fundamental problems is that there is a world of difference between Whole Blood and Plasma Derived Medicinal Products. I don't understand why the WHO is so persistent to bring these two different issues together.

In the accompanying "Rome Declaration" the participants of the meeting call on national authorities to:

- Introduce legislation to prohibit compensation for the donation of plasma
- Introduce additional labelling requirements
- Provide sufficient financial resources to move towards self sufficiency
- Phase out in a programmed manner the use of therapies made from compensated donors

There is so much more but that will take up too much space. Nowhere do I see an attempt to address what to do to increase the availability of these lifesaving therapies to patients that depend on them. I see a big effort to reduce the use of therapies to obtain a political goal at the expense of patient's wellbeing. One WHO official several years ago called them "rich countries therapies." Are you really kidding me? How can someone come up with such an argument?

We do everything we can to help patients in the world. I expect responsible national authorities to do the same. This will not be the last word on this topic. •

Jan M. Bult, President & CEO

The Affordable Care Act – The Good, The Bad and The Ugly

BY BILL SPEIR

The change is here. January 1, 2014 finally arrived, bringing with it the promise of a better American healthcare system from the Affordable Care Act (ACA)—a system where the uninsured do not exceed 40 million people; where a catastrophic health-event doesn't bankrupt a family; where premiums and out-of-pocket costs are affordable for all of us, not just the wealthy.

In this article, we explore the good, the bad and the ugly of the ACA's implementation. It is certainly too early to determine if the ACA has kept its promise, but it is not too early to see where we are in this historic month.

THE GOOD

You can't start reviewing "The Good" of the ACA implementation without remembering that the law eliminated life-time caps, annual benefit limits and underwriting pre-existing conditions. These provisions certainly benefit individuals that rely on plasma protein therapies.

Since October 1, 2013, the ACA's Health Insurance Marketplaces, also known as health exchanges, have been open for business. As of January 24, 2014, 3 million Americans had signed up for a Marketplace plan. The Obama Administration report on the implementation said 54 percent of customers for the Marketplace are women. About 60 percent of customers chose the second least expensive plan, or the silver plan, while 20 percent chose the cheapest option, the bronze plan, which also features the highest deductibles. Nearly 80 percent of the newly insured chose a plan that offered federal subsidies to help defray costs.

The report also mentioned that roughly 6.3 million have signed up for Medicaid since October. It is not known how many of these individuals are part of the new eligibility category under the ACA and how many are individuals who were otherwise eligible for traditional Medicaid categories. In the big scheme of things, this is not really important. What is important is that 6 million individuals will have a plan for their health care. Of course, as we learned, some of them had to change to new plans.

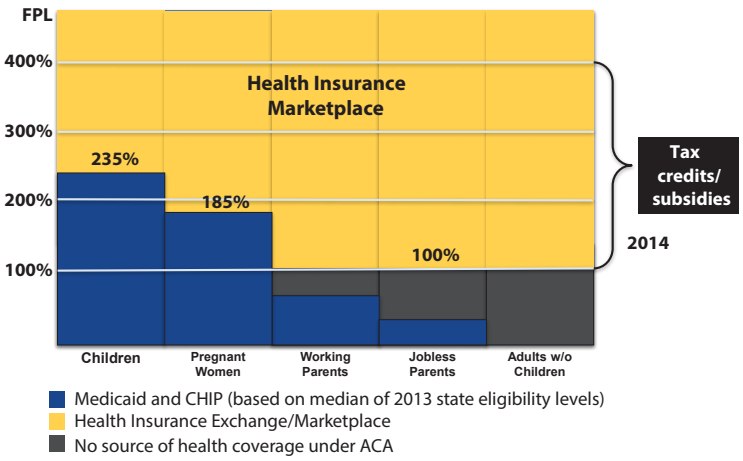
THE BAD

President Barack Obama said, "If you like your health care plan, you can keep it." However, it is estimated that 4 million individuals received cancellation notices from insurance companies that said otherwise. This was one of the many surprises administration received in the last few months of 2013, one that is small compared to the roll-out of the healthcare.gov website.

October 1, 2013, arrived with a lot of hope for the Administration's new Travelocity-styled website where individuals could select their ACA plan. It was a debacle; the system crashed, people were kicked out of the system after hours spent trying to get a health plan and for the lucky few that were able to sign-up for a plan, there were other problems.

A presentation to Congress in October showed that roughly 50 percent of the applicants for government subsidies were getting inaccurate information. For some, the system was creating duplicate records. There were also questions about the security of the information individuals entered. The Administration assured Congress that the security problems were theoretical and were fixed.

ACA Eligibility for Coverage in States That Did Not Expand Medicaid



A difficult roll out is expected whenever the government takes on a large task. Tasks don't get much larger than the one facing the Administration in implementing the ACA. And history shows that the bugs get worked out and the fixes are made.

THE UGLY

Of course one fix that will be difficult to make is the situation where the poorest of Americans aren't being helped under the ACA. The ACA was passed with the expectation that individuals with incomes below 100 percent of poverty level would be enrolled in Medicaid, the state and federal partnership that provides healthcare country's low-income families.

The Supreme Court found this to be unconstitutionally coercive and left it up to the states to decide if they would participate in Medicaid expansion. As of January 9, 2014, 25 states, and the District of Columbia, have decided to expand their Medicaid programs. This means in half the states, those with incomes below 100 percent of the federal poverty level ($11,490 for an individual), will not be able to get healthcare coverage under the ACA. The promise of affordable healthcare—the promise of the ACA—has not been kept for these individuals. •

BILL SPEIR, *Director, State Affairs*

Patient Protection and Affordable Care Act

The ACA includes numerous provisions that take effect between 2010 and 2020. Policies issued before 2010 are exempted by a grandfather clause from many of the changes to insurance standards, but they are affected by other provisions. Significant reforms, most of which took effect on January 1, 2014, include:

Guaranteed issue prohibits insurers from denying coverage to individuals due to pre-existing conditions.

Partial community rating - requires insurers to offer the same premium price to all applicants of the same age and geographical location without regard to gender or most pre-existing conditions (excluding tobacco use).

Minimum standards for health insurance policies are established.

An individual mandate requires all individuals not covered by an employer sponsored health plan, Medicaid, Medicare or other public insurance programs (E.g. Tricare) to secure an approved private insurance policy or pay a penalty, unless the applicable individual has a financial hardship or is a member of a recognized religious sect exempted by the Internal Revenue Service. The law includes subsidies to help people with low incomes comply with the mandate.

Health insurance exchanges will commence operation in every state. Each exchange will serve as an online marketplace where individuals and small businesses can compare policies and buy insurance (with a government subsidy if eligible). In the first year of operation, open enrollment on the exchanges runs from October 1, 2013 to March 31, 2014. The original enrollment deadline date to be covered for January 1, 2014 was December 15, 2013, but the deadline was delayed, first to December 23, 2013 and later to December 24, 2013. In subsequent years, open enrollment will start on October 15 and end on December 7.

Low-income individuals and families whose incomes are between 100% and 400% of the federal poverty level will receive federal subsidies on a sliding scale if they purchase insurance via an exchange. Those from 133% to 150% of the poverty level will be subsidized such that their premium costs will be 3% to 4% of income. In 2014, the subsidy would apply for incomes up to $45,960 for an individual or $94,200 for a family of four; consumers can choose to receive their tax credits in advance, and the exchange will send the money directly to the insurer every month. Small businesses will also be eligible for subsidies.

Medicaid eligibility expanded to include individuals and families with incomes up to 133% of the federal poverty level, including adults without disabilities and without dependent children. The law also provides for a 5% "income disregard", making the effective income eligibility limit for Medicaid 138% of the poverty level. Furthermore, the State Children's Health Insurance Program (CHIP) enrollment process is simplified. However, in National Federation of Independent Business v. Sebelius, the Supreme Court ruled that states may opt out of the Medicaid expansion, and several have done so.

Payment and delivery reforms such as accountable care organizations and patient-centered medical homes are being piloted as possible replacements for fee-for-service to promote value-based care.

Businesses which employ 50 or more people but do not offer health insurance to their full-time employees will pay a tax penalty if the government has subsidized a full-time employee's healthcare through tax deductions or other means. This is commonly known as the employer mandate. In February, 2014, however, this provision was delayed until 2016 for employers with 50-99 employees. Employers with 100 or greater employees will have to begin offering insurance beginning in 2015.

2014: New Congressional Session Kicks Off and Affordable Care Act Coverage Begins

BY CARRIE FIARMAN ZLATOS

On January 3, 2014 the second session of the 113th U.S. Congress commenced. As 2014 is a mid-term election year, Congress promptly began working to avoid another government shutdown and fund the government through the end of fiscal year (FY) 2014. On January 17, Congress passed, and the President signed, a 12-bill omnibus spending package providing $1.012 trillion in funding for federal discretionary spending accounts for the remainder of FY 2014. The omnibus appropriations law adheres to the discretionary spending caps established by the Bipartisan Budget Act of 2013 that provides partial sequester relief to government agencies for FY 2014 and FY 2015. Notably, the law reinstates the U.S. Food & Drug Administration's (FDA) access to previously sequestered user fees and provides an additional $1 billion to the National Institutes of Health (NIH) for basic research. As Congress gears up for upcoming debates on increasing the debt ceiling, PPTA continues its Capitol Hill advocacy to ensure any initiatives used as offsets do not adversely affect patient access to plasma protein therapies.

The beginning of the year also saw the initiation of insurance coverage for millions of people gaining access to insurance in the Patient Protection and Affordable Care Act's (ACA) Health Insurance Marketplaces (Marketplaces). While ensuring quality of coverage in the Marketplaces will remain a top priority for patients, industry and policymakers, all plans offered in the Marketplaces are required to provide coverage for an essential health benefits (EHB) package that encompasses 10 benefit categories. Importantly, among other required services, EHB packages must include coverage for prescription drugs, ambulatory patient services, laboratory services, preventive and wellness services and chronic disease management. In addition to these EHBs, consumers will no longer be denied insurance for pre-existing conditions or face rescissions of coverage. These protections, in addition to the other important reforms provided by the ACA, are vital protections for many patients who rely on life-sustaining plasma protein therapies.

The initiation of enrollment in the Marketplaces on October 1, 2013, marked an important step in the implementation of the ACA; however, the first two months of enrollment were challenged by persistent technical failures including regular website and enrollment portal crashes. The failures resulted in prolonged enrollment delays and propelled Congress to hold hearings focused on the Marketplace failures. After significant technical overhauls, the month of December saw a surge in sign-ups for coverage through Marketplace plans. As of January 24, 3 million people had signed up for private insurance through the Marketplaces since October 1. According to the Centers for Medicare and Medicaid Services (CMS), an additional 6.3 million people either enrolled or began enrollment for coverage through expanded Medicaid or Children's Health Insurance Program (CHIP) from October 1 to December 31 of 2013 through state agencies or state-based Marketplaces. Enrollment is expected to grow as open enrollment continues through March 31.

While the healthcare law's initial technical failures appear to be predominantly resolved, consumers continue to face significant challenges arising from a lack of transparency in plan offerings, and are reporting difficulty in reviewing plans and determining levels and quality of coverage. Despite important protections afforded by the ACA, opaque benefit designs which lack information on coverage of therapies and limited provider networks make it difficult to navigate plan offerings and determine the best possible plan given a particular health status. These challenges are especially acute for individuals living with rare or chronic conditions. Additionally, with the lack of a universal appeals process, consumers may face appeals processes that vary by plan or even by state, resulting in disparities in patient access.

While it is still too early to determine the specific impact of the ACA on patient access to plasma protein therapies, PPTA remains committed to helping shape the law's implementation to ensure patients have timely and appropriate access to the best possible treatment and care. •

CARRIE FIARMAN ZLATOS, *Manager, Federal Affairs*

Plasma Centers in the Community

BY JOSHUA PENROD

For a number of years now, PPTA and member companies have engaged in a long-term industry profile project, designed to improve understanding about source plasma and plasma collection for a variety of audiences. From people who are considering donation to patient stakeholders and their families, plasma and plasma products are too often poorly understood. At worst, failure to recognize the importance of plasma can harm others. As a result of this, the industry profile project seeks to educate a broad cross-section of people in the United States and Europe about the importance of plasma and the special nature of plasma donation.

By now, many thousands of people have seen the educational videos that the industry has produced, and many more have visited our websites, notably www.donatingplasma.org. The sites have easy-to-access and useful facts about plasma and plasma donation, as do the brochures and other materials that we've developed in multiple languages.

The action point for many plasma centers, however, is within the local community. With national and international campaigns, and even endorsements by members of Congress and state governors, the neighborhood in which a plasma center dwells is the world that is experienced. Individuals, neighboring businesses and community groups who know only about rumors and jaded pictures provided by the industry's detractors are willing to fight against a plasma center – be it a new operation, or an expanded operation already in existence. Oftentimes, detractors will use "facts" and "figures" from decades ago, alleging that such derogatory portrayals of the past are valid today. Plasma collection centers, whether in Germany, Austria, the Czech Republic, or the United States, can always benefit from presenting the best and most positive aspects of plasma collection to the community in which they are located.

It is time to replace fiction with fact! Locating a plasma collection center in a community gives a significant boost to the neighborhood and surrounding areas, and here are a few reasons why:

- Employment at a plasma center gives anywhere from 40-60 local people good jobs, with many full-time and part-time opportunities.
- Working at a plasma center can create a new pathway for a career in the industry or other allied health care fields.
- A plasma center which collects 60,000 donations a year can put millions of dollars per year back into the local economy. IQPP-certified plasma collection centers only accept donors who reside in the local area, essentially guaranteeing that the money distributed in donation fees gets recirculated back into the community benefiting local businesses, restaurants, banks and so on.
- Creation of a greater tax base within the community, developing real estate and attracting other businesses to the area. A plasma center creates a relationship with members of community, in which the center itself acts as an economic pump driving goods and services into the area.
- Plasma products developed from plasma collected at each and every plasma center are used to treat people not only in far-off places, away from the center, but many friends, neighbors and relatives of those in the community.

Just these points alone ought to be enough to convince any community group that a plasma collection center is a winning economic and social benefit. "Ought to be," however, isn't always the case; the myths and the difficulties of perception still endure. With the ongoing efforts of the industry, and events like International Plasma Awareness Week (IPAW), we are working to make sure that more people know about the great things that happen globally...and locally...with plasma collection. •

JOSHUA PENROD, *Vice President, Source*

Why Compensated Donation is ETHICALLY IMPERATIVE

BY JAMES STACEY TAYLOR, PH.D.

Recent moves to open commercial plasma collection centers in Ontario, Canada, have reinvigorated discussion of the ethics of offering compensation to plasma donors. But the question of whether or not persons should be compensated for donating their plasma is not new, having been around at least as long as Edwin Cohn's 1940 development of cold ethanol fractionation to break plasma down into its components. Considering its longevity, it is not surprising that this debate has by now acquired a familiar form: The opponents of compensated donation outline a series of objections to the practice, and then those who favor it show why these objections do not hold.

This way of proceeding is unfortunate, for it places the proponents of compensated donation on the defensive—a position that is ill-suited to participants in an industry whose products (whether developed from compensated or uncompensated donated plasma) save thousands of lives annually. A break away from this way of conducting the debate is thus long overdue. And such a break can readily be achieved, for compensating plasma donors is required by the moral requirement to secure persons' informed consent to the medical procedures that they participate in.

James Stacey Taylor, Ph. D., associate professor of philosphy at The College of New Jersey

CROWDING OUT, COMPENSATED DONATION AND INFORMED CONSENT

One common objection to compensating plasma donors is that such compensation would "crowd out" uncompensated donations and hence lead to less plasma being secured overall. This objection is clearly false—in fact, the opposite is true: With a few notable exceptions, such as Germany, Austria and the Czech Republic, the world supply of plasma derivatives (and hence the patients who depend on them) is strongly dependent on the U.S. source plasma industry and its compensated donors. But while this objection to donor compensation is misplaced, it is based on a grain of truth, for when compensation is offered *some* former donors will cease to donate. But this fact should provide only cold comfort to the opponents of compensated donation, for the lesson to be learned from it turns out to support the view that compensated donation is not only ethically acceptable, but is ethically required.

Some people who choose not to donate after compensation for plasma is introduced make this decision because the costs that they incur in donating—including the cost of giving up other activities that they could have been doing while they were donating—are higher than the level of compensation that is offered to them. When such a donor was donating she was doing so because she did not realize that the act of donation was economically inadvisable for her. Such a person would not have realized donating plasma was economically inadvisable for her because she did not have all of the information that she needed to make a properly informed decision as to whether or not she should donate. As it is ethically incumbent upon healthcare professionals to secure persons' informed consent to the medical procedures that they are subject to, they should provide all of the information that they could expect would be relevant to persons' decisions. Since we know that some people would stop donating once they realized the level of compensation that could be offered would not be enough to cover their costs—including the costs to them of giving up other activities that they could have done instead of donating—it is clear that for these people information concerning the amount of compensation that could be offered is crucial for them to be able to make a fully informed decision. As we cannot tell in advance which prospective donors would need this information in order to give their informed consent to donation, this information should be provided to all prospective donors. Since this information could only be provided in a system where donors were *actually compensated* for their plasma, offering compensation is required to ensure that donors have given their informed consent to donate. This does *not* mean that the ethical duty to secure a person's informed consent to the medical procedures that she is subject to requires that all plasma donations must be compensated. The requirement that persons should be informed of the level of compensation offered for their donation in order to give their informed consent to donate requires only that a system of donor compensation be available. This requirement thus does not preclude the possibility that uncompensated donors could give their informed consent to their donations. But it *does* require that such an uncompensated system operate in tandem with one in which donors are compensated, so that the information about the current level of compensation being offered is available even to persons who then chose to donate without receiving it.

CONCLUSION

Typically, a defense of compensated plasma donation will conclude with the observation that, since the objections that it has addressed that were leveled against offering plasma donors compensation fail, compensated donation is ethically acceptable. Bolder defenses of compensated donation might go further, noting, for example, that the world supplies of plasma—and hence the health and wellbeing of patients worldwide—are dependent upon compensated, or that compensating donors is ethically required to acknowledge their sacrifice. Yet these defenses of compensated donation do not go far enough. Even if plasma supplies could be met by uncompensated donation, and even if no donor wished to receive compensation for her sacrifice, compensation must at least be offered so that prospective donors can be fully informed about the level of value that is placed upon their donation. This information is essential for a prospective donor to be able to make an informed decision as to whether she believes that her time would be best spent donating, or doing something else. If we take the ethical requirement of informed consent seriously, then, offering compensation for plasma donation is not merely ethically acceptable, but is ethically required. •

JAMES STACEY TAYLOR, PH.D., *The College of New Jersey*

Fenwal Inc.
A TRUSTED PARTNER FOR PLASMA PROFESSIONALS

BY MATT KUHN

Fenwal has a long history as a pioneer and global leader in the development of products that improve the safety and availability of blood. The company's roots go back to 1949 with the founding of Fenwal Laboratories and the invention of the non-breakable blood pack plastic blood-collection container. The latest chapter in this history was written last year when Fenwal Inc. was acquired by Fresenius Kabi, a global health care company based in Germany that specializes in pharmaceuticals and technologies for infusion, transfusion and clinical nutrition.

The people, products and unique capabilities of Fenwal were all important reasons Fresenius Kabi decided to add Fenwal to its growing, global portfolio in health care. The company has since accelerated Fenwal investments in innovations that will help shape the future of transfusion medicine for years to come.

Being part of a global, diversified health care company is not new for Fenwal. While Fenwal operated as an independent company since 2007, prior to that, for more than 50 years, it was part of Baxter International, Inc.

"Regardless of our ownership structure, throughout our history Fenwal has worked continually with our customers to develop products and services that help improve the practice of transfusion medicine, making life-saving blood therapies available to the medical professionals and patients worldwide who rely on them. We remain dedicated to our plasma center customers and we will continue to focus and invest in those relationships for the long term," says Dean A. Gregory, President, Medical Devices, for Fresenius Kabi, North America.

Benefitting from more than 60 years of innovative leadership from Fenwal, the Aurora integrates advanced technology to deliver timely, insightful information about procedures.

A HISTORY OF INNOVATION AND SERVICE

In addition to introducing the first plastic blood pack, Fenwal launched the first multiple blood pack and sampling segments, the first integrated blood pack unit, the first five-day platelet storage container and the first integral soft housing filter in the United States.

More recently, Fenwal played a key role in developing automated systems to increase the safety and availability of innovative blood therapies. From the first fully automated blood-cell separator to the most advanced aphaeresis technology, Fenwal continues to be a world leader in the development of innovations that advance the practice of blood transfusion.

"While innovation is important and it is something we are proud of as a company, we know today's customers need more than that to meet their goals," says Lori Conway, Vice President, Global Plasma at Fenwal. "Fenwal focuses on our customers' needs and places high priority in becoming a trusted and valued partner."

Fenwal has a highly experienced plasma field team in the U.S. that offers donor programs and materials, training programs, clinical education and other business solutions. Fenwal technical service support has received Service Capability and Performance (SCP) certification, the global standard for service excellence. Fenwal is one of only 100 companies, and the only company in the blood technology field, to be certified as meeting these stringent global standards. The SCP Standards focus on optimizing performance in a wide range of business process areas necessary to deliver top quality customer service and support. By constantly enhancing performance in these areas, the Fenwal service team is setting the standard for exceptional service in health care.

In addition to the hands-on service and support provided directly by Fenwal plasma consultants, Fenwal has recently enhanced its customer portal, which can be accessed at www.fenwalinc.com. The customer portal is the single online resource for a wide range of information including technical information for operators and service technicians, training materials, product information, plasma center checklists and Fenwal contact information.

"Another big part of our commitment to customers can be found in our continuous improvement efforts," says Conway. "The Fenwal Production System is how we define our continuous improvement initiative within Fresenius Kabi. We regard continuous improvement as part of our day-to-day culture."

With a focus on quality products, customer partnerships, continuous improvement and plans for growth and investment, it's the goal of Fenwal to ensure that its future – and that of its customers - is as successful as its well-known past.

MATT KUHN, *Senior Director, Communications, Fresenius-Kabi Corporate Communications*

European Court of Justice Turns Focus to Plasma,

CLARIFIES SCOPE OF PHARMA CODE AND BLOOD DIRECTIVE

BY JOHN DELACOURT AND ALBERTO GIUMMARRA

Adding to its recent docket of cases addressing blood and plasma products, the European Court of Justice will soon offer an important clarification of two pieces of legislation critical to the plasma protein therapies industry:

Directive 2001/83 on medicinal products[1] (a.k.a. the Pharma Code) and Directive 2002/98 on human blood and blood components (a.k.a. the Blood Directive). The vehicle for addressing these issues is *Octapharma France SAS v. ANSM*, in which Octapharma challenged the French authorities' denial of a marketing authorization for its Octaplas product. Although the decision of the Court remains pending, the recently issued opinion of the Advocate General[2] strongly suggests the Court will conclude that the commercialization of "industrially prepared plasma" is governed exclusively by the Pharma Code. This is a welcomed development that should shield private sector producers of "industrially prepared plasma" and plasma protein therapies from protectionist regulation at that national level, both in France and throughout the European Union (EU).

THE FRENCH CASE

The underlying case in France arose out of a dispute regarding classification of Octapharma's Octaplas product. Octaplas is an industrially-prepared "plasma SD," used in transfusions, that is produced by freezing fresh plasma and attenuating viruses via a solvent detergent process.[3] In October 2010, the French health products authority – Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) – declared that Octaplas was a labile blood product.[4] This classification had important implications for the Octapharma's efforts to obtain a marketing authorization for the product due to the regulatory framework governing the blood sector in France. Under French law, the blood agency – L'Ésblissement française du sang (EFS) – has a monopoly on both the collection of blood and the preparation and distribution of labile blood products.[5] Consequently, the classification of plasma SD as a labile blood product meant that it could only lawfully be distributed in France by EFS.

Octapharma argued that ANSM's decision was inconsistent with the strong global consensus on this issue.

In response, Octapharma commenced a proceeding in the Conseil d'Etat to have the ANSM decision declaring plasma SD a labile blood product annulled. Octapharma argued that ANSM's decision was inconsistent with the strong global consensus on this issue, explaining that the company has been able to successfully market Octaplas as a medicinal product in 30 countries worldwide, including EU members Austria, Belgium, Germany and the United Kingdom. It further argued that ANSM's decision was in violation of a specific provision of EU law, Article 3(6) of the Pharma Code, which, as amended, exclusively governs plasma from whole blood prepared by an industrial process.[6]

ANSM, in turn, took the position that Octapharma had misread and misinterpreted the governing EU law. ANSM argued that the relevant law was not the Pharma Code, but the Blood Directive, which establishes standards for the collection, testing, processing, storage and distribution of human blood. ANSM further argued that, unlike the Pharma Code, which is classified as legislation in an area of "shared competency" under the Treaty on the Functioning of the European Union (TFEU)[7], the Blood Directive is legislation in an area of "national competency."[8] The legal significance of this distinction is that, in an area of shared competency, "complete harmonization" of national level requirements to bring them into compliance with the EU standard is required. In an area of national competency, in contrast, only "minimum harmonization" is required, meaning that as long at the Member State meets the minimum level of the EU standard, it is permitted to enact more stringent protective measures in its own territory. Because the distribution of plasma SD is governed by the Blood Directive, ANSM argued, France is permitted to enact even stricter national regulations in this area, regardless of what other European Member States may be doing.[9]

PROCEEDINGS AT THE EUROPEAN COURT OF JUSTICE

Faced with a case in which the outcome would largely be determined by the interpretation of EU directives, the Conseil d'Etat referred two questions to the European Court of Justice:

1. Is industrial plasma intended for transfusions governed by *both* the Pharma Code and the Blood Directive and, if so, should the Pharma Code be interpreted as being the exclusive legal basis for regulating a product only when the requirements of the overlapping EU legislation – here the Blood Directive – are less strict than those of the Pharma Code?
2. Should the Blood Directive, because it is legislation in an area of shared competency, be interpreted as permitting national regulation that imposes stricter requirements than the Pharma Code – specifically, national regulation that conflicts with the provisions of the Pharma Code stating that the sole limitation that may be placed on marketing of a medicinal product within the EU is the prior grant of a marketing authorization?

The Advocate General determined that industrially prepared plasma is governed by the Pharma Code only, even if intended for transfusions.

On November 7, 2013, Advocate General Niilo Jääskinen issued an opinion providing preliminary responses to these questions. The opinion of the Court remains pending.

The Advocate General answered Question 1 in the negative. According to his reading of the relevant legislation, industrial plasma, even if intended for transfusions, is *not* governed by both the Pharma Code and the Blood Directive, but by the Pharma Code only. To reach this conclusion, the Advocate General provided an exhaustive history of specific, detailed amendments to multiple provisions of both the Pharma Code and the Blood Directive.[10]

Ultimately, the Advocate General determined that two amendments were the most important. First, passage of the Blood Directive amended Article 109 of the Pharma Code, clarifying that the Blood Directive would apply to "collection and testing" of all blood and blood components, as well as to their "processing, storage and distribution" when those products were intended for transfusions.[11] Second, in recognition of subsequent "scientific and technological progress," the Pharma Code was later amended by Directive 2004/27, which modified Article 3(6) to read that the Pharma Code "shall not apply to . . . [w]hole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process."[12]

Taking these two provisions together, the Advocate General concluded that:

- Industrially prepared plasma – a category that encompasses plasma SD, and should be broad enough to encompass plasma derivatives, such as Ig, albumin and blood clotting factors – is governed by the Pharma Code only, even if intended for transfusions.
- The Blood Directive continues to govern the "collection and testing" of industrially prepared plasma, but not its "processing, storage and distribution" – a category broad enough to encompass commercialization activities.[13]
- Because the Pharma Code is legislation in an area of shared competency, where complete harmonization is required, national level authorities may *not* impose stricter regulatory requirements on commercialization activities relating to industrially prepared plasma.[14]

Because the answer to Question 1 fully resolved the dispute before the Court, the Advocate General did not address Question 2.

In the event of an unfavorable ruling, the French Government requested in advance that enforcement of the ruling be delayed, arguing that a new regulatory framework for overseeing these products would need to be developed in

France (e.g., the state monopoly, EFS, does not have the necessary authorizations to act as a pharmaceutical establishment), and that the resulting delay would put patient safety and the public health at risk. Surprisingly, the Advocate General refused. Although the refusal was based on technical legal reasons – the issue of implementation of the ruling was beyond the scope of the questions presented and the Court had taken no evidence on the burden of developing a new regulatory regime – it is also fair to view it as a comment on the weakness of the French Government's case. As the Advocate General observed, rather harshly, there was simply "no warrant for the French authorities, or indeed those of any other Member State, to maintain the view that the marketing authorization of [industrial plasma] intended for transfusion was not governed by [the Pharma Code]." [15]

IMPACT OF THE DECISION

Although it bears repeating that the recently issued opinion was that of the Advocate General, and not the final opinion of the European Court of Justice, it is nevertheless a strong indicator of how the case will ultimately be decided. The Court gives great weight to the views of its Advocate General, and significant deviations in approach are unusual. Consequently, barring an unexpected change of course by the Court, the decision will have a number of important implications for the plasma protein therapies industry.

- **Strengthens Differentiation Arguments –** Industry advocates have long argued that there is a fundamental difference between whole blood for transfusion and plasma for fractionation, and that regulatory policy should reflect that difference. The Advocate General's opinion makes that argument easier. Provided that the decision stands, the European Court of Justice will have drawn a clear line between "industrial plasma," which is a medicinal product covered by the Pharma Code, and other blood products, which are the primary focus of the Blood Directive.
- **Weakens Legal Basis for Protectionist Regulation -** As the Advocate General's opinion makes clear, one of the most important consequences of classification under the Pharma Code is the limitation this places on national level regulation of "industrial plasma." Because the Pharma Code is legislation requiring "complete harmonization," stricter national level requirements, regardless of intent, are not permitted. This is an important victory and future source of comfort for private sector manufacturers operating in European countries with a public sector monopoly on blood and plasma collection, a state-owned fractionator, or – as in the case of France – both, who are concerned that the close relationship between such entities and the national regulator might potentially give them a competitive advantage.
- **Clarifies Agendas for Blood Directive Revision –** As previously noted in The Source, DG Sanco has commissioned a study of the blood and plasma sector, which is widely regarded as a precursor to revision of the Blood Directive.[16] In light of this development, the opinion of the European Court of Justice is not likely to be the final word on either the scope of the Blood Directive or regulatory treatment of "industrial plasma." If it is not satisfied with the final disposition of the Octapharma case, it is reasonable to expect that the Government of France – and perhaps other like-minded EU Member States – will seek a more favorable outcome through the legislative process. It is therefore important for industry advocates to be equally vigilant in protecting these gains as the process of revising the Blood Directive moves forward. •

JOHN DELACOURT, *Vice President, Legal Affairs and*
ALBERTO GIUMMARRA, *Manager, European Health Policy*

[1] See, e.g., *Humanplasma GmbH v. Republik Österreich*, Case C-421/09 (Dec. 9, 2010) (Opinion of the Court), available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do? uri=CELEX:62009CJ0421:EN:HTML (holding that Austrian law banning importation of blood products not obtained from donations made "without any payment whatsoever" violated free trade principles of the TFEU).

[2] *Octapharma France SAS v. ANSM*, Case C-512/12 (Nov. 7, 2013) (Opinion of the Advocate General), available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX: 62012CC0512:EN:HTML ("AG Opinion").

[3] Id. at ¶ 2 n.4.

[4] Id. at ¶ 3.

[5] Id. at ¶ 4.

[6] Id. at ¶ 5.

[7] Article 114 – 114/3 TFEU.

[8] Article 168/4(a) TFEU.

[9] AG Opinion, supra note 2, at ¶ 6.

[10] Id. at ¶ 22.

[11] Id. at ¶¶ 14, 16,

[12] Id. at ¶¶ 19, 21.

[13] Id. at ¶¶ 25-28.

[14] Id. at ¶¶ 29-30.

[15] Id. at ¶ 39.

[16] See Laura Savini and Alberto Giummarra, *European Union Considers Revisions to Blood Directive*, The Source, Fall 2013, at 24.

A Question of Safety, Efficacy… and Money

BY PROFESSOR ALBERT FARRUGIA

The development of robust, expert authorities—which can assess a therapy developed for the market—is essential for any health care system.

Authorities such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA) are charged with evaluating the therapies for safety and efficacy before they enter the market, and with monitoring their performance to these criteria after approval has been granted. Their processes are geared to transparent standards and their practice is embedded in legislation controlled by elected representatives. I, myself, had the honor of serving in the Australian TGA for fifteen years, and my PPTA colleague Mary Gustafson was, similarly, a senior official of the FDA. In the PPTA, we are conscious of the need of regulatory agencies and their essential contribution to patient care.

A historically key feature of the work of regulatory agencies has been their detachment from issues pertaining to costs and reimbursement of therapies. The principle that approval to enter the market should be based solely on evidence of safety, quality and efficacy is also embedded in law in many countries, including, for example, Australia. It is felt, in my view justifiably, that the question as to whether a therapy is safe and efficacious is separate from whether it should be paid for. Entirely different paradigms are in play. If regulators had to include cost issues in their review, the primacy of safety and efficacy might be undermined. Entirely valid, but separate, systems are in place for assessing reimbursement issues. As a former regulator still committed to these principles, I am now increasingly anxious that they are in danger of being eroded. As a result of the crisis in the global economy and the continuing increase in health care costs, disturbing signs have been emerging that governments and other funders are increasing pressure on regulators to conform more closely to cost issues. Over the past years, this has manifested in, for example, the U.S. Senate urging the FDA to share its (confidential) clinical trial data with the Centers for Medicare & Medicaid Services[1] (CMS). We have seen insurers imposing their own clinical criteria for reimbursement[2], we observe the danger of comparative effectiveness research being obscured by cost-effectiveness[3] and we feel apprehension as to how this will affect the care of patients with rare, chronic disorders.

I was happy, therefore, to participate in a workshop convened by the EMA recently to review the ongoing collaboration between the Agency and the European Network of Health Technology Assessment bodies (EUNETHTA). I recommend perusal of the presentations of this event[4]. It may be observed that presentations by regulators, HTA bodies, industry and patients were followed by breakout sessions on various themes. I was intrigued that the main workshop theme was "Parallel Scientific Advice in Drug Development", but many speakers interpreted this as convergent or common pathways. For example, the breakout session I engaged in, "Principles and Policy," was managed by a group of participants who proposed "Consensus" and "Harmonization" in developing scientific advice for common use by regulators and HTA agencies[5]. However, as was pointed by some regulars during their workshop presentations[6], scientific principles for efficacy, which regulators are charged with, are different from those for effectiveness is what concerns HTA bodies. As we have

previously pointed out[7], HTA, for effectiveness, seeks to address population health benefits which risks overlooking small-population, expensive diseases. Regulators currently approve for the market based on legislated processes and are decision-makers, whereas HTA bodies simply generate a framework for advice for decision-makers, in a much more politicized process. In my view, this is how it should be. The decision on whether a medicine is safe and efficacious should continue to be based on science and evidence. It is then entirely appropriate for elected, accountable representatives to assess HTA advice as to whether it should be reimbursed. But incorporating such an HTA process in the initial approval represents, to me, a contamination and a conflict with the regulatory process.

The decision on whether a medicine is safe and efficacious should continue to be based on science and evidence.

Let me illustrate with an example drawn from the EMA workshop. The eminent HTA authority, Professor David Barnett, illustrated his talk with the example of the HTA of a medicine to treat macular degeneration, a serious eye condition threatening eyesight[8]. Over the course of their assessment, the HTA experts had cause to require evidence that bi-ocular vision leads to higher quality of life than mono-ocular vision, i.e. that two eyes are better than one! This had to be elicited from an additional survey from patients, who, you may not be surprised to hear, did confirm that two eyes ARE better than one! I will not comment on the basis of this process, but will simply suggest that any such exercise in the approval process for the drug to reenter the market is inherently flawed. Approval processes need to be based on scientific evidence, not assessments of the obvious.

I noted with interest the plea for harmonization between HTA and regulatory processes. We ex-veterans of the regulatory agencies are very familiar with the efforts for harmonization between such agencies worldwide. Some progress has been made, but much remains to be done before regulation ceases to be a potential threat to patient access. I would not like this to be preceded by an attempt to dilute regulatory standards with HTA criteria.

In the workshop, I was also struck with the views of the representative of a European Rare Disease patient organization[9]. Strong endorsement of the Regulatory-HTA convergence was offered, on the basis of efficiency and rapidity of access. I would suggest, respectfully, that the current level of bureaucratic inefficiency in some agencies, whether regulatory or HTA, is not likely to be addressed by convergence, but demands action to increase efficiency and accountability to performance targets. This is a very important, but separate issue and allowing it to influence this important debate may muddy the waters.

It is no coincidence that this debate is occurring during an era of financial stringency, when governments in Europe, in particular, are seeking to maximize their resources. It is clear to me that, compared to the established regulatory agencies, the emerging HTA sector lacks expertise, and that accessing the scientific minds of the regulatory agencies for HTA purposes is very much in the forefront of this exercise. Yet, the allocation of resources is a political decision which should be accountable and transparent. Regulators, whose roles demand that they have long memories, will remember how the inclusion of cost and so-called cost – benefit considerations led to fatal delays in the implementation of blood safety measures. The example of the FDA's BPAC voting to delay measures to decrease the spread of HIV, delays based on "evidence" and "cost-effectiveness" are, I am sure, still etched in the Administration's mind[10]. Perhaps the newly emerged bodies dealing with HTA, comparative effectiveness and all the other disciplines aiming to address costs do not have such a level of awareness.

Let elected officials make the decision on what gets funded. And if they ignore the most important people involved – the patients – let them bear the consequences. And leave the regulators to do their job unhindered – assess safety and efficacy based on scientific evidence, with both eyes open. •

PROFESSOR ALBERT FARRUGIA, *Vice President, Global Access*

[1] See http://thomas.loc.gov/cgi-bin/cpquery/?&sid=cp112jpCLS&r_n=sr073.112&dbname=cp112&&sel=TOC_252660&
[2] http://www.igliving.com/Assets/IGL/Articles/IGL_2007-04_AR_Medicare-Local-Coverage-Determinations-Limit-Access-to-IVIG.pdf
[3] http://www.academyhealth.org/files/publications/ResearchInsightsCER.pdf
[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000721.jsp&mid=WC0b01ac058004d5c3
[5] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155850.pdf
[6] See, for example http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155677.pdf
[7] https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&cad=rja&ved=0CFAQFjAE&url=http%3A%2F%2Fcdn.f1000.com%2Fposters%2Fdocs%2F253505542&ei=h7bWUvr6NJTmoATX5YDIAw&usg=AFQjCNFDao6lMftUDQ9AVYP97tI07mcJUA&sig2=VfCB1-9h9TH73zH8zd-S4w&bvm=bv.59378465,d.cGU
[8] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155669.pdf
[9] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500155668.pdf
[10] See HIV and the Blood Supply – An analysis of crisis decision – making (1995). On http://www.nap.edu/catalog.php?record_id=4989

The New EU PHARMACOVIGILANCE LEGISLATION

BY ILKA VON HOEGEN

Some years ago, there were high profile cases of withdrawals of medicinal products because of safety issues that were not highlighted in pre-market studies of the products. These post-market safety issues renewed the interest in pharmacovigilance (PhV).

PhV is a drug safety science that involves the monitoring of adverse events associated with the use of drug products with the goal to prevent or lessen adverse events. The European Union (EU) enacted a new PhV legislation in December 2010, which represents the biggest change to EU PhV requirements since the establishment of the European Medicines Agency (EMA), who is the responsible regulatory body in the EU.

The new legislation acknowledges that spontaneous reporting of Adverse Drug Reactions (ADR) is the most important contribution to the PhV data collection. While before, only physicians and pharmacists were allowed to report ADRs, now, in the spirit of transparency and patient empowerment, patients can also directly report their experiences into the new centralized Eudravigilance data base.

But it will not be only the regulators who have to deal with the increase of information, also the pharmaceutical manufacturers, i.e. the marketing authorization holders (MAH), will have to introduce a signal management system to regularly monitor Eudravigilance to assess the safety of their products and validate any signal.

If that was the only increased burden for MAHs, there would probably be sighs of relief. But there is much more for them to do. They need to establish an elaborate quality system for their pharmacovigilance activities associated with detailed documentation on every aspect, regular staff training, internal audits and external inspections. The good news though, is that the new legislation re-enforces the cooperation and harmonization of inspection activities in the EU. A PhV System Master File will now be a part of the Marketing Authorisation dossier, or even several dossiers for more than one product. Other good news is that now changes to the Master File will not have to be notifiable in every case. There is also the requirement for additional monitoring for all products with a new substance and biological medicinal products including biosimilars. Also, for some products, for example those for pediatric use, post-authorization safety studies additional monitoring activities have to be performed.

Periodic Safety Update Reports (PSURs) are now Periodic Benefit Risk Evaluation Reports (PBRER), as specified in the International Conference on Harmonisation (ICH) Guideline ICH E2C(R2)[1]. The submission frequency is determined by a drug's risk profile and can be between 6 months to 28 years.

Signal management requires that MAHs have a process in place that ensures all signals are detected via EudraVigilance, validated and notified to the Competent Authorities (CA) when a safety issue emerges or the benefit risk balance or public health are affected. It is certainly helpful that all the information can be found in the centralized EudraVigilance data base, but on the other hand, the amount of information will probably be abundant, particularly now that patients can also directly report their observations. These reports could pose a specific challenge, because patients cannot be expected to describe their experiences in accepted medical terms.

Finally, a newly defined Risk Management Plan (RMP) is required for all new applications. The EMA Pharmacovigilance Risk Assessment Committee (PRAC) plays a key role in the context of the RMP to ensure continuous regulatory oversight. In the interest of transparency, a summary of the RMP will be made public.

This integration of all these elements aim to ensure that the benefit-risk of medicinal products authorized in the EU is continuously monitored throughout its life cycle, with the aim to improve their risk - the benefit-risk. •

While before, only physicians and pharmacists were allowed to report ADRs, now, in the spirit of transparency and patient empowerment, patients can also directly report their experiences into the new centralized Eudravigilance data base.

ILKA VON HOEGEN, *Senior Director, Quality and Safety*

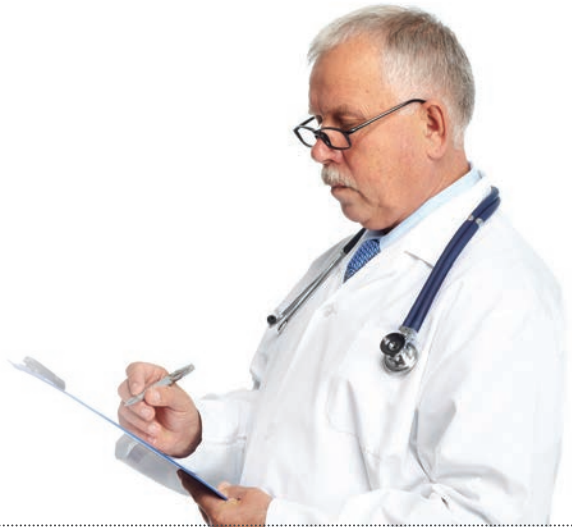
[1]1EMA/CHMP/ICH/544553/1998 January 2013

Potency Assignment to Clotting Factor Concentrates: AN EASY TASK?

BY ILKA VON HOEGEN

Determination of a biological parameter follows, in principle, the same paradigm: one needs an assay, a standard, possibly a reagent, then performs the test and the result in valid everywhere on this planet.

In reality, the situation is often much more complex as highlighted in the recent workshop on "Characterization of new clotting factor concentrates (FVIII, FIX) with respect to potency assays used for labelling and testing of post infusion samples." The workshop, sponsored by the European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and Health Care (EDQM) and the Council of Europe (COE), was held to share scientific information on the challenges of translating traditional potency testing outcomes to new product manufacturing technologies. The EDQM is increasingly concerned that the



The ultimate goal is to assist the clinician in managing his patients. It is generally known and accepted that the current testing technologies and measurements are crude. So when observed variability is the reality, what implications does it have for clinical decision making?

issues observed with existing recombinant clotting factor concentrates, when transferring labelled potency into the clinical laboratory, will be even more challenging with new recombinant and/or modified products that are currently under development. The Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH/SSC) "recommendations on the potency labelling of Factor VIII and IX concentrates"[1] were praised for their systematic and harmonized approach during the workshop and it was concluded that new products fall into the flow diagram of the ISTH/SSC recommendations. When linking assay results for recombinant products to clinical efficacy, the variability is acceptable when the available plasma derived standards are used, but there is more variability with new long-acting products. This increased variability leads to the question of whether actions should be taken to make the testing results more accurate and meaningful. There are several options:

- Could product specific standards overcome these limitations and what would be the implications of such an approach?
- Do we need a new set of requirement for these new products in the form of individual European Pharmacopoeia (Ph. Eur.) Monographs?
- Should regulatory guidance determine the assay that has to be used for potency labeling, or give more than one option or leave the choice entirely to the manufacturer?

Currently in the Ph. Eur., only the chromogenic assay is described for labelling of clotting factor concentrates, while in clinical laboratories and regulatory areas outside of Europe, e.g., in the U.S., the one stage assay is predominantly used. In view of the fact that each test system produces a different result, there is a need to correlate one assay with the other, for example, by applying a conversion factor. In conclusion, there is a lot of variability. Even within one assay system there is an abundance of permutation between the individual assay systems, which could create different test results.

Discussions during the workshop led to noting steps to help remedy the problem. One remedy to improve the situation is the usual call for harmonized approaches among the different global regulatory agencies. In addition, there should more exchange of information between and within the regulatory agencies and the medical community.

The ultimate goal is to assist the clinician in managing his patients. It is generally known and accepted that the current testing technologies and measurements are crude. So when observed variability is the reality, what implications does it have for clinical decision making? How much variability can be tolerated when transferring the labelled potency into the clinical laboratory? A similar decision tree as in the above mentioned ISTH/SSC recommendations would be helpful for clinical decision making, providing different evidence based options. It could also be considered to provide information on how the individual product performs in real life.

There is evidently no "one size fits all" solution. But it should be kept in mind that there is a significant amount of clinical experience which should not be underestimated. In view of the fact that variability within assays of up to 40% has not caused an issue, one may conclude that the most important factor is still the knowledge, experience and judgment of the clinician. •

ILKA VON HOEGEN, *Senior Director, Quality and Safety*

[1] Hubbard et al. Journal of Thrombosis and Haemostasis Volume 11, Issue 5, pages 988–989, May 2013

New Government - Old Arguments

BY STEFAN GRAFENHORST

On September 22, 2013, about 61.8 million voters in Germany cast their ballot. The results of the Federal elections led to difficult and rather long coalition negotiations, but finally resulted in the formation of a government of the two strongest parties, the conservative Christian Democratic Union (CDU)/ Christian Social Union (CSU) and the Social Democratic Party (SPD).

The newly formed so-called "big coalition" is led by Chancellor Angela Merkel (CDU), who has been in power since 2005. Vice-chancellor became the leader of the social democrats, Sigmar Gabriel (SPD).

While the new cabinet offered little surprise, the appointment of Hermann Gröhe as new Federal Health Minister came rather unexpected. Gröhe, a trained lawyer, used to serve as the secretary-general of conservative party CDU from 2009 to 2013 and was not on the list of potential candidates for the position of health minister; it has yet to be seen what his priorities will be. He follows Daniel Bahr from the Liberal Democrats whose party did not enter the German Parliament again.

The start of the newly formed coalition government began badly for pharmaceutical companies. As one of its first initiatives, the new government swiftly produced two bills preventing pharmaceutical companies from raising their prices past 2009 levels. The bills ensure that there will be continuation of Germany's price freeze for patented and innovative drugs, which was to expire December 31, 2013. The price freeze was initiated in the midst of the financial crisis in 2010 to ease fears that the German health insurance system would financially collapse. The first bill prolonged the price freeze until March 31, 2014 and came into effect on January 1, 2014. The second, which does not come into effect until April 1, 2014, prolongs the price freeze from April 1, 2014 until December 31, 2017. It also increases the mandatory rebate that companies have to pay for patented and innovative drugs from 6% to 7%.

The bright spot for drug companies is that the new government made legal changes to the Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance (AMNOG). AMNOG brought major changes in 2011. Since 2011, pharmaceutical companies have to go through an early benefit assessment procedure for their new drugs. The government now made an end to the legal provision that allowed the Federal Joint Committee (G-BA) to do retrospective assessments of products that were on the market before the AMNOG law came into effect. The companies who have been through this retrospective assessment process have not fared well.

The price moratorium is a huge blow for pharmaceutical companies, while the end of the retrospective assessments is on the positive side of the package. Nevertheless, at the end of 2017, the price moratorium will have been in place for eight years. With the price freeze, the government completely ignores boosters such as the inflation rate or the increase of production costs for pharmaceutical companies for almost a decade. For the plasma protein therapies industry, where production costs are comparably high and where potential savings are exhausted, the renewal of the price freeze and the mandatory rebate will pose a very special challenge. The government will regularly review the price moratorium but it seems unlikely that the regulation will be ended before 2017. •

STEFAN GRAFENHORST, *Senior Manager, Germany*

NEWS FROM AROUND THE GLOBE

Inside PPTA

A Look at Plasma Collection in Austria and Beyond

AN INTERVIEW WITH DR. MATTHIAS GESSNER,

Director Plasma Sourcing Europe, Baxter AG, Austria; Chair Austrian Plasma Collectors Association (IG Plasma)

BY ILKA VON HOEGEN

The annual International Plasma Protein Congress (IPPC) will be held in Vienna, Austria March 11-12, 2014. PPTA looks at the history of plasma collection in Austria and the landscape of European regulation in the industry.

Q Could you briefly describe the environment for plasma collection in Austria?

Austria was the first European country to start with the collection of source plasma by apheresis as early as 1964. Consequently, plasma collection was already regulated in 1975 with the adoption of the Plasmapheresis Act (Plasmapheresegesetz), which later served as a solid foundation for the plasmapheresis section of the new Blood Safety Act (Blutsicherheitsgesetz), when implemented in 1999, replacing the Plasmapheresis Act. EU Directive 2002/98/EC is implemented in Austria via the Blood Safety Act and the Blood Donor Regulation (Blutspenderverordnung). In addition, plasma centers in Austria are also regulated under the Austrian Pharmaceuticals Act, implementing EU Directive 2001/83/EC, as plasma is listed as an active pharmaceutical ingredient.

Austria, with now 50 years of history in source plasma collection, has a leading role in Europe in providing source plasma for the manufacture of stable plasma products.

The Austrian MoH's Federal Agency for Safety in Public Health (Bundesamt für Sicherheit im Gesundheitswesen, BASG) is responsible for licensing and regulatory control of plasma centers with the Austrian regulatory agency AGES (Österreichische Agentur für Gesundheit und Ernährungssicherheit-Medizinmarktaufsicht) performing inspections on behalf of BASG.

In 2006, the MoH established the Austrian "Blood Commission" (Blutkommission) to provide advice to the MoH in all matters related to blood and blood safety. Blood Commission members are appointed for 3 years by several Austrian institutions involved in blood and plasma collection, transfusion and public health comprising MoH, AGES, Red Cross, local plasma collector organization IG Plasma and industry associations Pharmig, WKÖ.

Collection of source plasma in Austria is done in privately and industry owned plasma centers operating under a medical head physician with legal responsibility for donor and product safety. Donors can donate up to 50 times per year and are compensated for their time and effort.

Q How do you see the contribution of Austrian plasma collection to plasma supply in Europe?

Austria, with now 50 years of history in source plasma collection, has a leading role in Europe in providing source plasma for the manufacture of stable plasma products. On a per capita basis, Austrian donors donate the highest volume of source plasma among all European countries. Collections in Austria in 2013 totaled nearly 550,000 liters of source plasma, for the benefit not only of Austrian patients, but also for patients from other countries that do not collect sufficient plasma to supply their patients in need of plasma products.

Q What is the relevance of EU plasma collection to global plasma supply?

Significant source plasma collection in the EU is currently limited to only three countries, Austria, the Czech Republic, and Germany with a total of about 2.5 million liters annually. The other EU countries only perform minor or no source plasma collection at all; some are using recovered plasma from whole blood donations for the production of plasma products.

Comparing these numbers to the U.S., where source plasma collections in 2012 totaled 26 million liters, it is obvious that the contribution of the EU to the global supply of source plasma is still fairly small in relation to its population of more than 500 million inhabitants. Based on the number of patients living in the EU member states, a much larger contribution of the EU to the global source plasma supply would be desirable.

Q How could the regulatory environment for plasma collection in Europe be improved?

Countries like Austria, the Czech Republic and Germany show that plasma collection in Europe can be done, provided there is a supportive regulatory environment. In this respect, it is, however, very difficult speaking of the EU, considering the wide range of regulations and the varying approaches to plasma collection in the various member countries. In my point of view, improvements in three major areas are needed:

1. Facilitation of compensation of donors for time and efforts spent: There is a long ongoing debate globally and also in Europe about compensation of donors for the time and effort invested in plasma donation. Experience in all countries with significant source plasma collection demonstrates the need to compensate donors financially (with a lump sum) for their time and efforts spent. Motivating donors to one or two weekly 1-2 hour visits to a plasma center requires some kind of compensation for this significant investment in terms of time and effort. All countries with significant source plasma collection compensate their plasma donors this way.
2. Harmonization of regulations on plasma donations: Regulations worldwide vary extensively mainly concerning the frequency and absolute numbers of plasma donations per donor. This needs a reasonable harmonization. These factors of course have a lot of influence on the economy of source plasma collection. Five decades of experience in plasma collection in Austria could serve as a sound basis for the establishment of regulations in other European countries.

3. Acceptance of plasma products made from European plasma on other markets, especially the U.S.: Currently, plasma products made from European plasma cannot be sold on the U.S. market. This is one major limitation for European source plasma. Most fractionators, however, are global companies and are looking for maximum flexibility, thus using preferably the raw material whose product can be placed on a maximum number of markets. Together with the general importance of the U.S. market for plasma products, this is one reason for the booming U.S. source plasma collections. However, it remains questionable in my point of view, whether it is long and medium term very wise to rely on plasma collection so much on a single country as we do with the U.S. today. Any modern risk management approach would try to avoid a scenario, in which so much depends on a single global supplier. If European plasma was as universally usable and accepted as U.S. plasma, this would, of course, significantly balance any potential risk and at the same time support European plasma production. This is why reaching that U.S. FDA accepts the licensing of European plasma as a raw material for plasma products to be marketed in the U.S. appears as a highly desirable goal.

Q The European Commission (EC) is considering revising the Blood Directive. What would be the major elements to ensure a healthy environment for plasma collection in Europe?

Today, the EU overall does not collect sufficient plasma to cover the potential need for plasma products for the patients in the EU. Shrinking volumes of recovered plasma, due to aging populations and improved patient blood management, in combination with increasing demand, will most likely widen this gap in the coming years if no additional source plasma is collected.

Currently, the global plasma supply is assured nearly exclusively by the plasma collection in the U.S., which carries some inherent risk as mentioned above. To allow sufficient supply also for the coming years, it would seem prudent for the EU to increase the European contribution to the global source plasma supply, what can only be reached by an increase of source plasma collection.

There are good examples of countries in Europe - Austria foremost amongst them - that show how a significant contribution to the source plasma supply can be combined, at the same time, with assuring sufficient supply of blood products for transfusion. Any potential revisions of the Blood Directive should be oriented (i) towards protecting the existing source plasma collection in the EU on a donor compensation basis, and (ii) towards facilitating a legislative wording that will allow introducing such source plasma collection also into EU Member States, that currently do not participate in source plasma collection, e.g. that a EU Directive revision comprises wording on express encouragement to proceed to compensated source plasma donations. With 50 years of experience in source plasma collection, Austria would be a good place to look at how successful source plasma collection is done. ●

ILKA VON HOEGEN, *Senior Director, Quality and Safety*

PPTA is pleased to announce the second International Plasma Awareness Week (IPAW) to be celebrated globally October 12-18, 2014.

PPTA will again work with industry partners and stakeholders to make this event a success. This annual event is designed to:

- Raise global awareness about source plasma collection.
- Recognize the contributions of plasma donors to saving and improving lives.
- Increase understanding about lifesaving plasma protein therapies and rare diseases.

Events will be held at plasma collection centers in both Europe and the U.S. More information to follow.

MEET THE

PPTA Staff

Carrie Fiarman Zlatos

MANAGER, FEDERAL AFFAIRS

Q How long have you been with PPTA?

I joined the Association in January 2013.

Q What is your role in the organization?

In my role as Manager, Federal Affairs, I am responsible for representing the Association to Congressional policy makers. My work includes identifying key legislative and administrative policy issues, educating Members of Congress and their staff about the unique nature of plasma protein therapies and the industry and advocating for policies that protect patient access to care.

Q Tell us about your background.

After growing up in South Florida, I ventured up the East Coast to the University of Maryland. While at the University of Maryland, I did an internship at the U.S. House of Representatives and received a B.A. in Government and Politics. After college, I spent seven and a half years working at the U.S. House of Representatives, where I was a primary policy advisor for healthcare policy, among other issues, for Representative Shelley Berkley (NV-1) on the House Ways and Means Committee. During my tenure handling healthcare policy on Capitol Hill, I was fortunate to work on the Affordable Care Act as it moved through Congress and became public law.

Q What is your proudest professional achievement?

In my years on Capitol Hill, I had the privilege of working on policy matters relating to veterans' healthcare. While supporting Rep. Berkley on the House Veterans' Affairs Committee, I engaged with committee staff to steer the Congresswoman's initiatives through the committee – including mental health legislation honoring a veteran from the Congresswoman's district who died while in the care of the Department of Veterans Affairs. Working closely with this veteran's family, we were able to work the legislation into a broader package of veterans' mental health policy reforms (P.L. 110-387). The life-long connection I formed with the veteran's family during this experience really provided me with the understanding of how policy changes affect many lives. My goal is to use my past experience working with constituents to better understand the needs of those who rely on life-sustaining plasma protein therapies.

"My goal is to use my past experience working with constituents to better understand the needs of those who rely on life-sustaining plasma protein therapies."

Q What is most rewarding about working in this industry?

I enjoy working in conjunction with the patient communities and seeing the connection between Capitol Hill advocacy and patient access to therapies.

GLOSSARY OF TERMS

ACA	AFFORDABLE CARE ACT
ADR	ADVERSE DRUG REACTIONS
AGES	(ÖSTERREICHISCHE AGENTUR FÜR GESUNDHEIT UND ERNÄHRUNGSSICHERHEIT
AMNOG	ACT FOR THE RESTRUCTURING OF THE PHARMACEUTICAL MARKET IN STATUTORY HEALTH INSURANCE
ANSM	AGENCE NATIONALE DE SÉCURITÉ DU MÉDICAMENT ET DES PRODUITS DE SANTÉ
BASG	BUNDESAMT FÜR SICHERHEIT IM GESUNDHEITSWESEN
CA	COMPETENT AUTHORITIES
CDU	CHRISTIAN DEMOCRATIC UNION
CHIP	CHILDREN'S HEALTH INSURANCE PROGRAM
CMS	CENTERS FOR MEDICARE AND MEDICAID SERVICES
COE	COUNCIL OF EUROPE
CSU	CHRISTIAN SOCIAL UNION
EC	EUROPEAN COMMISSION
EDQM	EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES AND HEALTH CARE
EFS	L'ÉSBLISSEMENT FRANÇAISE DU SANG
EHB	ESSENTIAL HEALTH BENEFITS
EMA	EUROPEAN MEDICINES AGENCY
EU	EUROPEAN UNION
EUNETHTA	EUROPEAN NETWORK OF HEALTH TECHNOLOGY ASSESSMENT
FDA	FOOD AND DRUG ADMINISTRATION
ICH	INTERNATIONAL CONFERENCE ON HARMONISATION
IPAW	INTERNATIONAL PLASMA AWARENESS WEEK
ISTH/SSC	THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HEMOSTASIS
MAH	MARKETING AUTHORIZATION HOLDERS
MOH	MINISTRY OF HEALTH
NIH	NATIONAL INSTITUTES OF HEALTH
PBRER	PERIODIC BENEFIT RISK EVALUATION REPORT
PH.EUR.	EUROPEAN PHARMACOPOEIA
PHV	PHARMACOVIGILANCE
PRAC	PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE (EUROPEAN MEDICINES AGENCY)
PSUR	PERIODIC SAFETY UPDATE REPORT
RMP	RISK MANAGEMENT PLAN
SCP	SERVICE CAPABILITY AND PERFORMANCE
SPD	SOCIAL DEMOCRATIC PARTY
TFEU	TREATY ON THE FUNCTIONING OF THE EUROPEAN UNION
TGA	AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION
VNRD	VOLUNTARY NON-REMUNERATED DONORS
WKÖ	WIRTSCHAFTSKAMMER ÖSTERREICH


Washington, D.C.

Upcoming Events

CONFERENCES & SYMPOSIUMS

March

5–8 2nd International Congress on research of Rare & Orphan Diseases
Basel, Switzerland

7–9 Advanced Learning on Platelets & Thrombosis International Course
Ioannina, Greece

8–9 2nd National Conference on Primary Immunodeficiency Diseases (PIDCON 2014)
Varanasi, India

11–12 **International Plasma Protein Congress (IPPC)**
Vienna, Austria

18–21 34th International Symposium on Intensive Care and Emergency Medicine (ISICEM 2014)
Brussels, Belgium

26–30 9th International Congress on Autoimmunity
Nice, France

27–29 Hemophilia Federation of America (HFA) 2014 Annual Symposium
Tampa, Florida

April

2–6 Platelets 2014 Educational Course; Platelets 2014: 8th International Symposium
Ma'ale Hachamisha, Israel

10–12 Thrombosis and Hemostasis Summit of North America
Chicago, Illinois

10–13 2014 Clinical Immunology Society (CIS) Annual Meeting: Primary Immune Deficiency Diseases North American Conference
Baltimore, MD

17 World Hemophilia Day

22–29 World Primary Immunodeficiency Week (WPIW)

May

2–6 American Academy of Immunology (AAI) Annual Meeting
Pittsburgh, PA

8–10 European Conference on Rare Diseases & Orphan Products
Berlin, Germany

10–13 24th European Congress of Clinical Microbiology and Infectious Diseases
Barcelona, Spain

11–15 World Federation of Hemophilia (WFH) World Congress
Melbourne, Australia

21–22 IPFA/PEI 21st Annual International Workshop
Rome, Italy

24–25 5th JSH (Japanese Society of Hematology) International Symposium
Hamamatsu, Japan

31–June 5 33rd International Congress of the ISBT
Seoul, South Korea

June

10–11 World Orphan Drug Congress Asia 2014
Singapore

26–27 **Plasma Protein Forum (PPF)**
Washington, DC

September

18–20 66th Annual Meeting of the National Hemophilia Foundation (NHF) *Washington, DC*

28–30 3rd International conference on Immune Tolerance
Amsterdam, The Netherlands

October

3–5 8th Bari International Conference (BIC)
Bari, Italy

12–18 **International Plasma Awareness Week (IPAW)**

25–28 AABB Annual Meeting
Philadelphia, PA

26 **PPTA Business Forum** (For Members Only)
Philadelphia, Pennsylvania

December

24–25 International Congress on Immunology (ICI) Annual Meeting
Bangkok, Thailand

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