Manufacturing Plasma Derivatives
An Industrial Partnership

Jan M. Bult
President & CEO

10th Convention dei CRS
Senigalia, June 13, 2014
The mission of PPTA is to promote the availability of and access to safe and effective plasma protein therapeutics for all patients in the world.
<table>
<thead>
<tr>
<th>Company</th>
<th>Products Provided</th>
<th>Manufacturing Sites</th>
<th>Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter BioScience</td>
<td>Plasma derived therapies and Recombinant therapies; Manufacturing sites in USA, Austria, Belgium, Switzerland, and Italy</td>
<td>75 Collection centers</td>
<td></td>
</tr>
<tr>
<td>GRIFOLS</td>
<td>Plasma derived therapies; Manufacturing sites in Spain and USA</td>
<td>149 Collection centers</td>
<td></td>
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<tr>
<td>Biotest</td>
<td>Plasma derived therapies; Manufacturing sites in Germany, USA</td>
<td>22 Collection centers</td>
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<tr>
<td>KEDRION</td>
<td>Plasma derived therapies; Manufacturing sites in Italy, USA, Hungary</td>
<td>15 Collection centers</td>
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<tr>
<td>CSL Behring</td>
<td>Plasma derived therapies and Recombinant therapies; Manufacturing sites in USA, Switzerland, Germany and Australia</td>
<td>86 Collection centers</td>
<td></td>
</tr>
</tbody>
</table>

June 2014
IT IS ALL ABOUT HOW TO PROVIDE PATIENTS WITH THERAPIES THEY NEED
Standards and Certification

From the general public to the patient

Donor population → Donor selection → Testing donations → NAT testing → Inventory Hold → Dilution by pooling → Virus inactivation / removal steps → Finished product

Relative risk
Certification

• Facilities audited/ companies certified
• Certification of adherence to PPTA’s voluntary standards
• All Global member companies are QSEAL Certified
Risk Reduction is the Result of Combined Measures

Donor

Safety Step 1: Screening

Safety Step 2: Testing Donation

Safety Step 3: Inventory Hold/ Lookback

Safety Step 4: Plasma pool testing

Safety Step 5 & 6: Quality Assurance GMP

Safety Step 7: Virus Inactivation/ Removal

TSE/CJD Removal

Patient

Safety Step 9: Post-Marketing Surveillance

Donation Management

Complete Manufacture

Safety Step 8: Quality Assurance Packaging Guidance

Manufacturing

Complete Manufacture

June 2014
US Source Plasma Collections 2003-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Collection (Units)</th>
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<tbody>
<tr>
<td>2003</td>
<td>12,644,462</td>
</tr>
<tr>
<td>2004</td>
<td>10,317,674</td>
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<tr>
<td>2005</td>
<td>10,368,480</td>
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<tr>
<td>2006</td>
<td>12,442,214</td>
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<tr>
<td>2007</td>
<td>15,326,821</td>
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<td>2008</td>
<td>18,817,869</td>
</tr>
<tr>
<td>2009</td>
<td>22,028,860</td>
</tr>
<tr>
<td>2010</td>
<td>23,573,488</td>
</tr>
<tr>
<td>2011</td>
<td>23,573,488</td>
</tr>
<tr>
<td>2012</td>
<td>26,214,019</td>
</tr>
<tr>
<td>2013</td>
<td>29,391,097</td>
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</table>
There is nothing wrong in compensating / recognizing a donor for the time and effort made when it is done in a well regulated environment.
Safety in all aspects

- Plasma products are proven safe, time and again
- Manufacturers recognize importance of safety at all levels, in order to achieve safe and effective products. Includes:
  - donor health,
  - safe collection practices
  - safe manufacturing practices
Every country has the right and obligation to provide its population with safe and effective medicines

Self sufficiency is a goal

Self sufficiency is not a dogma
SELF SUFFICIENCY

Self sufficiency in labile products is achievable on a national level

Self sufficiency in finished products has its challenges
SELF SUFFICIENCY

Facts to consider:

- Clinical need
- Recovered plasma / Source plasma
- Plasma for fractionation
- Fractionator experience
- Yield
- Economics
Observations:

- Collecting plasma is expensive (Italy)
- Plasma on the market is cheaper than collecting in the country (NL)
- Economy of scale is important (Japan)
- Many countries cannot afford own fractionation (Norway, Finland, Scotland, Switzerland, England)
21 Regional health authorities
MOH overall responsible
Collection regional Blood Centers
Toll Fractionation (Kedrion)
New system open for multiple bidders
No ownership for fractionator
Self sufficiency of blood and blood products (including PDMP’s) is supra-local and supra-regional goal of the NHS

Promotion and continuous development of Voluntary Non remunerated Donations
Annual national self-sufficiency program
Consultation with Regional Blood Centers and Blood Donor Associations
Annual program includes prescriptions, recommendations and objectives
Drivers Red cells and PfF

June 2014
PDMP production is national essential health care service
Exchange between regions
Driving products: IVIG, albumin
Central and north / south central and south
WHAT ABOUT FACTOR VIII?
Italian Centro Nazionale Sangue answers global call to action

Yesterday, WFH and representatives from the Italian Centro Nazionale Sangue (CNS) announced a groundbreaking initiative to donate up to 30 million IUs of factor VIII per year over a five-year period to the WFH for humanitarian interventions.

The idea for this ambitious initiative, dubbed Project WISH, occurred after several Italian Regional Blood Centres concluded that they had a large surplus of fractionated product that had been derived from donated plasma. Rather than letting the product expire, the CNS convened a panel of national experts in 2008 to brainstorm how they could donate the product to people in need around the world.

In Italy, Blood Establishments are responsible for every aspect of the collection, testing, processing, storage and distribution of human blood and blood components. The main goal of the transfusion system is to achieve national self-sufficiency in blood, blood components and plasma-derived medicinal products (PDMP) in order to provide uniform standards of services. This ensures a more effective health care system for citizens in terms of quality and safety of blood and products.

There were many issues and regulatory hurdles to overcome before the donation could occur, but all of the stakeholders agreed that they could not allow surplus clotting factor concentrates to simply expire when there is such a great need in other countries. In 2008 the CNS convened a panel of national experts with the following mandate: to monitor the situation, to identify the potential area of interventions, to analyze the current regulatory framework and to define and share recommendations.

“At the beginning it was very difficult to think that we could change the legislation and get the political commitment to get all the regions to agree on the project, but the main goal, the main target is to provide patients in Italy and people around the world with a better quality of life,” said Dr. Gabriele Calizzani of CNS. “There is a strong commitment from the donor associations that their gift can help the lives of other patients.” Different humanitarian cooperation projects have already developed for the export of PDMP.

CNS hopes its efforts, working with the Italian regional blood authorities, will encourage other entities to implement their own programs that advance the WFH vision of closing the gap in care in developing countries in sustainable and transparent ways.

WFH president Alain Weill and CNS representative Dr. Gabriele Calizzani.

“If it could be of some help to some countries, stakeholders or NMOs to adopt the Italian plan for consensus building, we are available to share our experience and knowledge on how this can be done,” added Dr. Fabio Candura, of CNS.

A lot of similarities
Toll Fractionation (Grifols, CSL)
Not self sufficient
Cryoprecipitate discarded
Round Table Discussion on Payment of Plasma Donors in Canada

April 20, 2013
Dr. Graham Sher
Chief Executive Officer
Summary

- PPPs from paid plasma equally safe to those from non-remunerated donors

- Without paid plasma donors, 70% of Ig for Canadian patients could be unavailable as well as other niche products

- @ 600,000 incremental liters plasma for fractionation required to close the gap operationally and economically unfeasible in a volunteer non-remunerated model
BIOTEST supports 'Project Recovery,' turning unused cryoprecipitate from Canadian plasma donations into Factor VIII concentrate for developing countries

BIOTEST AG, together with the World Federation of Hemophilia (WFH), Canadian Blood Services (CBS) and Grifols, has entered into an agreement called Project Recovery, which will transform previously discarded cryoprecipitate from Canadian blood donors into BIOTEST's Factor VIII concentrate, HAEMOCTIN®.

This is the first time anywhere in the world that such a partnership has been created, transforming surplus cryoprecipitate into FVIII for humanitarian use. With Project Recovery, the cryoprecipitate will be harvested by Grifols at its plant in the US and then transported by BIOTEST AG to Germany for manufacturing.

This international cooperation contract was signed in July 2013 and the first production steps have begun and the first batch has been produced and released. BIOTEST AG will deliver the first product donation in 2014; it will be a milestone for WFH in donation history. For the first time WFH can plan quantities that they will receive and the donation supplied will have a full two-year shelf life. It is estimated that each year of this project at least five million International Units of FVIII, HAEMOCTIN®, will be donated.

According to Alain Weill, WFH President, "Project Recovery has a potential to improve the lives of thousands of people with haemophilia all over the world. It allows WFH to carefully plan where and when these essential medicines will be distributed and thereby the benefits of this wonderful humanitarian endeavor."

"This agreement is an important milestone for BIOTEST's approach to improve the haemophilia care worldwide and BIOTEST is proud to be part of this important humanitarian project," says Prof Gregor Schulz, CEO BIOTEST AG.
WFH president Alain Weill speaks during Monday’s plenary.

Alan Weill, World Federation of Hemophilia President
GLOBAL IVIG SALES FROM 1984 TO 2010 (Metric Tons)

IVIG + SCIG
+10.3% per year since 1984
+7.2% per year since 2000

June 2014
IG Distribution in USA and Europe

US – Immune Globulin

Europe: IG (iv + sc)
Self-sufficiency rate

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<tr>
<td>Anti-Thrombin III</td>
<td>88.0</td>
<td>94.9</td>
<td>96.3</td>
<td>97.4</td>
<td>98.1</td>
<td>100.0</td>
<td>100.0</td>
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<tr>
<td>Immunoglobulin</td>
<td>87.5</td>
<td>88.6</td>
<td>91.2</td>
<td>95.9</td>
<td>95.9</td>
<td>95.1</td>
<td>95.1</td>
<td>95.2</td>
<td>93.8</td>
<td>95.3</td>
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<tr>
<td>Tissue sealant</td>
<td>40.7</td>
<td>45.3</td>
<td>49.6</td>
<td>48.3</td>
<td>47.9</td>
<td>45.0</td>
<td>45.7</td>
<td>45.1</td>
<td>44.0</td>
<td>44.3</td>
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<tr>
<td>Factor VIII, incl rFVIII</td>
<td>39.9</td>
<td>39.3</td>
<td>35.6</td>
<td>30.5</td>
<td>29.6</td>
<td>24.8</td>
<td>21.8</td>
<td>18.9</td>
<td>20.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Albumin, excl rec ALB</td>
<td>50.2</td>
<td>53.7</td>
<td>56.8</td>
<td>62.8</td>
<td>60.5</td>
<td>58.5</td>
<td>58.2</td>
<td>57.4</td>
<td>57.2</td>
<td>58.3</td>
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<tr>
<td>Anti HBs IG</td>
<td>2.7</td>
<td>2.6</td>
<td>2.2</td>
<td>2.8</td>
<td>2.4</td>
<td>2.2</td>
<td>2.0</td>
<td>2.1</td>
<td>2.6</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Blood Committee December 26, 2012
Every country has the right and obligation to provide its population with safe and effective medicines

Self sufficiency is a goal

Self sufficiency is not a dogma
ROME DECLARATION

High level policy makers forum, October 2013 Rome, Italy

Forum organized by

Ministry of Health Italy
Ministry of Health, Labor and Welfare, Japan

In collaboration with:

- World Health Organization
- Council of Europe
- European Commission
- International Federation of Red Cross and Red Crescent Societies
- International Society of Blood Transfusion
- International Federation of Blood Donor Organizations
- European Blood Alliance

Followed by Technical Event on May 19, 2014 in Geneva

June 2014
Self sufficiency in blood and blood products based on VNRD
Prohibit payment in cash
Labeling requirements to distinguish
Provide financial and other resources to move to self sufficiency
Formal agreements with fractionators to use surplus recovered plasma
…phase out in a programmed manner, the use of blood components for transfusion, intermediates and PDMP obtained from paid or compensated donors and family/replacement donors….

Massive reactions to WHO from various organizations, including:
  Plasma Protein Therapeutics Association
  International Plasma Fractionation Association
  PLUS (Platform of Plasma users
  APLUS (Platform of US Plasma Users)
Two requests sent to attend Technical Meeting on May 19

October meeting no representation from:
- Patients
- Regulatory agencies regulating these therapies
- Countries that collect plasma from compensated donors
- Private sector industry

Introduction legislation to prohibit compensation will lead to catastrophic undesired outcomes

We would like to have opportunity to be part of the discussion
WHO response

• WHO logo removed from Declaration

• Disclaimer changed to include: “it does not necessarily represent the decision or policies of the World Health Organization”

• Apology for not receiving an answer on previous letters

“WHO understand that for the time being access for many patients to life-saving blood factors is dependent upon paid plasma donations in high income countries, and we completely support the fact that these patients should continue to benefit from these products. For the future, we look forward towards working with PPTA and others towards a sustainable quality plasma supply based on VNRD in a non-business model”
Global supply of plasma for fractionation dependent largely (70-80%) on plasma from paid plasma donors from US, Germany, Austria and Czech Republic

Inadequate supply of plasma suitable for fractionation from national blood establishments

Unable to support Rome Declaration as drafted

Reservations concerning call to:
- Introduce legislation to prohibit cash
- To phase out in a programmed manner

Any policy which would endanger PDMP supplies to dependent patients cannot and should not be endorsed
We are extremely concerned with the Rome Declaration which in our view puts forward dangerous recommendations that could seriously impact access to treatments for patients relying on life-saving and life-enhancing plasma derived medicinal products, several of which are classified by WHO as essential medicines for both adults and children.

PLUS consensus statements supported by 29 patient organizations and other stakeholder organisations active in the field:

“the absolute focus of the blood and plasma sectors in health care must be the patient (...) Patients whose continued health is dependent on the use of blood components or PDMP’s have a right through their representative organisations to be consulted on any issue which may have an impact on the safety, efficacy or supply of the treatment they receive…”

June 2014
While we support the importance of voluntary blood and plasma donation for labile products, we believe that if recommendations in the Rome Declaration are implemented, there will be a serious decline in the supply of plasma derived medicinal products, which will leave patients who need life-saving treatments at severe risk of not having access to their treatments. On several occasions we have indicated our support for the importance of and necessary coexistence of both voluntary and remunerated systems as essential.
IT IS ALL ABOUT HOW TO PROVIDE PATIENTS WITH THERAPIES THEY NEED
TYPE OF PLASMA PROCESSED IN NORTH AMERICA
FROM 1993 TO 2010
NON-PROFIT ORGANIZATIONS
(Thousand Liters)

Source Plasma
Recovered Plasma

TYPE OF PLASMA PROCESSED IN NORTH AMERICA
FROM 1993 TO 2010
COMMERCIAL COMPANIES
(Thousand Liters)

Source Plasma
Recovered Plasma

TYPE OF PLASMA PROCESSED IN NORTH AMERICA
FROM 1993 TO 2010
COMMERCIAL COMPANIES & NON-PROFIT ORGANIZATIONS
(Thousand Liters)

Source Plasma
Recovered Plasma

June 2014
NO COMPETITION BETWEEN RECOVERED AND SOURCE PLASMA

SOURCE PLASMA IS THE PATH FORWARD

ITALY WALKS THE TALK

WHY LIMIT SUFFICIENCY TO SELF, COLLECT MORE

ACCEPT GLOBAL RESPONSIBILITY
It is always better to talk with each other than talk about each other