KEDRION
the fourth pillar for the Italian Blood System

Danilo Medica
Italy Country Manager
ITALIAN BASED COMPANY WITH A WORLDWIDE PRESENCE

1ST LARGEST SUPPLIER OF PLASMA DERIVED PRODUCTS IN ITALY

DISTRIBUTION IN MORE THAN 80 COUNTRIES

SUBSIDIARIES IN EU, US AND LATIN AMERICA

4 MANUFACTURING PLANTS IN 3 COUNTRIES

15 COLLECTION CENTERS
BUSINESS AREAS

2012 DISTRIBUTION OF REVENUE BY BUSINESS AREA

- 95.2% PLASMA DERIVATES
- 1.3% OTHER
- 3.5% PLASMA

REVENUES (€ MLN)

2010: 247.8
2011: 277.3
2012: 378.0

CAGR: 23.5%↑

11.9%↑  36.3%↑
### HAEMOPHILIA AND OTHER BLEEDING CONDITIONS
- **EMOCLOT / PLASMACLOT / Koate-DVI**
- Factor VIII / von Willebrand Factor concentrate
- **HUMAACL**
- Factor VIII / von Willebrand Factor concentrate
- **WILFACTIN**
- von Willebrand Factor concentrate
- **AIMAFIX / HUMAFACTOR -9**
- Factor IX concentrate
- **EMOSINT**
- DDAVP Desmopressin
- **UMAN COMPLEX**
- Prothrombin Complex concentrate

### CRITICAL CARE
- **UMAN ALBUMIN / UMAN SERUM / ALBITAL / HUMAN ALBUMIN / KEDRIALB / PLASBUMIN / KEDBUMIN**
- Human Albumin solution
- **AT III KEDRION**
- Antithrombin concentrate
- **K FLEBO**
- Potassium aspartate
- **PLASMASAFE**
- Pharmaceutical grade plasma

### PRIMARY IMMUNE DEFICIENCIES AND IMMUNE-MEDIATED CONDITIONS
- **Ig VENA / HUMAGLOBIN / KEDRIGAMMA / VENITAL**
- Standard i.v. Immunoglobulin
- **16% GAMMAGLOBULIN**
- Standard i.m. Immunoglobulin
- **VENBIG / KEYVENB**
- Anti-hepatitis B i.v. Immunoglobulin
- **IMMUNOHBs / UMAN BIG**
- Anti-hepatitis B i.m. Immunoglobulin
- **TETANUS GAMMA / TETIG**
- Anti-tetanus i.m. Immunoglobulin
- **IMMUNORHO / RhoGAM**
- Anti-D i.m. Immunoglobulin

---

* products only available for the US market
** products only available for the Hungarian market
*** products only available for the Italian market

---

**Hemolytic disease of the newborn**

Rh-negative women’s babies are at risk for a potentially fatal blood disease if they turn out Rh-positive *

*The gift of babies’ lives flows in women’s veins USA TODAY*
TOTAL NUMBER OF EMPLOYEES

830 ITALY
17 AUSTRIA
232 HUNGARY
2 PORTUGAL
1494 EMPLOYEES
MEXICO 4
GERMANY 78
USA 331

TURNOVER 2012: 378,000,029 €
REVENUES GENERATED OUTSIDE ITALY: 234,300,000 €
GEOGRAPHICAL AREAS

- **Italy**: CAGR -2.1% (2010: 149.9, 2011: 149.9, 2012: 143.8)
  - 2010: 60.5%, 2011: 54.0%, 2012: 38.0%

- **EU**: CAGR -0.8% (2010: 27.6, 2011: 25.1, 2012: 27.2)
  - 2010: 11.2%, 2011: 9.1%, 2012: 7.2%

- **USA**: CAGR 3.0% (2010: 117.1)
  - 2010: 12.8%, 2011: 7.3%

- **Row**: CAGR 19.6% (2010: 62.9, 2011: 67.0, 2012: 90.0)
  - 2010: 25.4%, 2011: 24.1%, 2012: 23.8%
The Italian blood system is part of the NHS
The system aims to achieve national self sufficiency

**Law n° 219, October 21st, 2005**
Legislative Decree April 12th 2012

Voluntary, periodic, responsible, anonymous, non-remunerated blood donation

- **National and regional Institutions**
  - MoH
  - ISS
  - CNS
  - CRS
  - AIFA

- **Blood transfusion system**
  - Blood Collection Centers
  - BTC (NHS Transfusion centres)
  - Blood Collection units

- **Donor Associations and Federations**
  - AVIS
  - FIDAS
  - Fratres
  - CRI
  - Others Regional

- **Industrial Partner**
  - To date
    - KEDRION
In Italy there are 1,700,000 donors organized in Associations/Federations (AVIS, FIDAS, FRATRES and CRI).

The system currently collects 773 tons of plasma, all of which is fractionated by Kedrion through contract manufacturing agreements.

Regions retain the ownership of plasma, plasmaderived products, intermediates and fractions discarded.

On behalf of the Regions, Kedrion manufactures: HA, IVIG, FVIII, FIX, PCC, AT, also offering the following services:

- pre-production: collection and storage of plasma
- post-production: batch release, storage and delivery of finished products

National consumption of plasma derived products is partially covered thanks to the manufacturing fractionation contract of collected plasma.
SELF SUFFICIENCY LEVEL

2011, Plasma derived products consumption in Italy

- **Immunoglobulin**
  - 80% from Italian plasma
  - 20% from commercial market

- **Albumin**
  - 60% from Italian plasma
  - 40% from commercial market

- **Plasmatic FVIII**
  - 50% from Italian plasma
  - 50% from commercial market
  - 70% of the demand of commercial pFVIII should be covered by further availability from Italian plasma.

Surplus/Shortage (%) vs HNS refunded demand - splitted by region

### IGIV

<table>
<thead>
<tr>
<th>2011</th>
<th>+4%</th>
<th>-31%</th>
<th>+28%</th>
<th>-7%</th>
<th>+14%</th>
<th>-11%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-14%</td>
<td>-2%</td>
<td>+28%</td>
<td>-7%</td>
<td>+14%</td>
<td>-11%</td>
</tr>
<tr>
<td></td>
<td>-14%</td>
<td>-44%</td>
<td>-20%</td>
<td>-20%</td>
<td>-26%</td>
<td>+13%</td>
</tr>
<tr>
<td></td>
<td>-42%</td>
<td>-53%</td>
<td>-49%</td>
<td>-50%</td>
<td>+13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-45%</td>
<td>-50%</td>
<td>-40%</td>
<td>-19%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Albumin

<table>
<thead>
<tr>
<th>2011</th>
<th>+49%</th>
<th>+49%</th>
<th>+119%</th>
<th>+18%</th>
<th>+3%</th>
<th>+45%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-5%</td>
<td>-16%</td>
<td>+119%</td>
<td>+18%</td>
<td>+3%</td>
<td>+45%</td>
</tr>
<tr>
<td></td>
<td>-27%</td>
<td>-27%</td>
<td>-41%</td>
<td>-44%</td>
<td>-44%</td>
<td>-73%</td>
</tr>
<tr>
<td></td>
<td>-51%</td>
<td>-75%</td>
<td>-82%</td>
<td>-53%</td>
<td>-53%</td>
<td>-74%</td>
</tr>
<tr>
<td></td>
<td>-84%</td>
<td>-55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The discussion on the appropriate use of albumin is currently undergoing, without forgetting the recent events concerning HES.
Increase in demand and plasma pricing

• The consumption of plasma derived products in the World and in Italy has grown and will continue to grow, thanks to new therapeutic indications and major access to patient care
• Prices of plasma derived products are expected to increase, due to increased demand and "constraints" related to raw material (plasma)

Slowdown in the demand for red blood cells

• Italy has achieved self-sufficiency in the collection and consumption of red blood cells
• From this year there has been a decline in the demand for red blood cells

Compliance accomplishment to European standards

• By the end of 2014, the Italian Blood System should be in compliance to EU standards. Italian Regions are at different levels of implementation

Value Partners analysis, 2013
Plasma derived products market evolution (CAGR volumes and price), 2012-2018

<table>
<thead>
<tr>
<th>Region</th>
<th>IGIV</th>
<th>Factor VIII</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>5%</td>
<td>-2%</td>
<td>0,5%</td>
</tr>
<tr>
<td>USA, Canada</td>
<td>7%</td>
<td>2%</td>
<td>0,5%</td>
</tr>
<tr>
<td>Rest of the World</td>
<td>10%</td>
<td>1%</td>
<td>1,5%</td>
</tr>
</tbody>
</table>

- How to achieve self-sufficiency *(L219/2005)*, securing the supply and **mitigate the "price" risk**
- Is it possible to **improve the appropriateness** of consumption?

RBC NEED IS SLOWING

% growth YoY, Red Blood Cells collected and consumed

- Opportunity to modulate the collection of whole blood, in order to meet the demand, focusing on the specific needs (phenotypes) and reduce waste
- Need to reconsider the model of plasma collection, to ensure the supply of plasma, reducing exposure to fluctuations in prices

Analisi Value Partners, 2013
Fonte: CNS, Gazzetta ufficiale Repubblica Italiana: «Programma di autosufficienza del sangue e suoi prodotti per l’anno 2013»
PLASMA COLLECTION IN ITALY (x 000 kg)

To date recovered plasma amounts to 75% of the total plasma sent to the industry.

In 2012 apheresis obtained a plasma (source) increase of +2.7% vs 2011.

In the first eight months of 2013 apheresis obtained a plasma increase by +5% vs py.

In the first eight months of 2013 total plasma sent to the industry increased by 1.1%.

SOURCE COLLECTION IS CRUCIAL TO MEETING SELF-SUFFICIENCY TARGETS.
“... it is estimated that about 20 million people (one third of the Italian population) are not aware of plasmapheresis donation”

- 318 Transfusion Centres*
- 240 (73%) active for plasmapheresis production
- AVG = 319 procedures/equipments/year
  \(<1 \text{ procedure/equipments/day}\)

* Summing up the 7 different types of transfusion collection units, which include 4 military units

Source: National Register of Productive Apheresis (2009)
FULL COST OF PLASMA FROM VOLUNTARY NON REMUNERATED DONORS IN ITALY

(1) AdRes HE&OR, Turin, Italy; (2) University of Verona, Verona, Italy; (3) University of Torino, Torino, Italy

RESULTS

- Total cost per liter of plasma sent for processing is estimated in €114 and €286, respectively, depending on whether it is separated from whole blood or is obtained by apheresis.
- Given the current mix of plasma sources, the weighted average cost of plasma to the Regions excluding processing charges is estimated in €157.
- When considered as a by-product, the cost per liter of plasma recovered from whole blood donations and sent to the industry is estimated at €27, and the corresponding weighted average cost is €92.
Plasma currently collected in Italy could satisfy approx 25% of total demand of FVIII.

Significant «excess» of pd factor VIII product and intermediate «cryo paste» from Italian plasma.

Humanitarian aid programs:
- India
- Albania
- Afghanistan
- Armenia
- Egypt

Source: ISSN 2012 (Rappoti ISTISAN 12/53)
SOME UNCERTAINTIES

State-Regions Agreement of 16 December 2010

- Total compliance of Italian collection and transfusion system at the European standards relating to structural, technological and operational requirements within December 31, 2014

- What is the future of those BTC that fail to meet the deadline?

- Can we afford a system with Regions and BTC at different speeds?

- What will happen if some centers will not reach the target? Red blood cells will be usable, but the plasma can not be sent to industry? Blood red cells will not be transfused too?

- Can we afford to jeopardize RBC self-sufficiency?

- …

Kedrion is making its Quality Expertise available to the Italian Regions to support them in the achievement of these mandatory standards.
SEMINARIO INTERREGIONALE SUL SISTEMA SANGUE ITALIANO
Le regioni a confronto per affrontare insieme il cambiamento.
Firenze, 18 e 19 ottobre 2013
Convitto della Calza - Sala Pontevecchio

RSVP Dott.ssa Matilde Pellegrineschi tel. 0583.333420 info@fondazionecampus.it
Kedrion will continue to focus on the following objectives:

- Consolidating its national market leadership
- Developing its presence abroad
- Continuing to invest in product and process innovation
- Increasing its production capacity and research activities into orphan drugs
**Prevalence/Incidence**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 PLG Deficiency</td>
<td>1:1,000,000</td>
<td>1:2,000,000</td>
</tr>
<tr>
<td>FV+FVIII</td>
<td>1:1,000,000</td>
<td>1:2,000,000</td>
</tr>
<tr>
<td>Membr. Glomerul. II</td>
<td>2-3: 1,000,000</td>
<td>2.7:1,000,000</td>
</tr>
<tr>
<td>HUS</td>
<td>70-80% of patients with TTP</td>
<td>3.7:1,000,000</td>
</tr>
</tbody>
</table>

* Compassionate use already started

**Rare diseases are rare, but the people affected by these are many**
Kedrion works in close cooperation with the National Health Service, sharing its strategy of pursuing plasma derivatives self-sufficiency, motivated by the core aim of caring for the ill.
THANK YOU

d.medica@kedrion.com