RAPPORTI ISTISAN 20|13

ISSN: 1123-3117 (cartaceo) • 2384-8936 (online)

Italian Blood System 2017: demand for plasma-derived medicinal products. Volume 2

F. Candura, M.L. Salvatori, G. Calizzani, S. Profili,
C. Chelucci, C. Brutti, C. Biffoli, G.M. Liumbruno

EPIDEMIOLOGIA
E SANITÀ PUBBLICA

ISTITUTO SUPERIORE DI SANITÀ

Italian Blood System 2017: demand for plasma-derived medicinal products. Volume 2

Fabio Candura (a), Maria Lavinia Salvatori (a),
Gabriele Calizzani (a), Samantha Profili (a),
Cristiana Chelucci (a), Chiara Brutti (b), Claudia Biffoli (b),
Giancarlo Maria Liumbruno (a)
(a) Centro Nazionale Sangue, Istituto Superiore di Sanità, Roma
(b) Direzione Generale del Sistema Informativo, Ministero della Salute, Roma

ISSN: 1123-3117 (cartaceo) • 2384-8936 (online)

Rapporti ISTISAN
20/13

IstitutoSuperiore di Sanità
Italian Blood System 2017: demand for plasma-derived medicinal products. Volume 2.
Fabio Candura, Maria Lavinia Salvatori, Gabriele Calizzani, Samantha Profili, Cristiana Chelucci, Chiara Brutti, Claudia Biffoli, Giancarlo Maria Liumbruno
2020, vii, 121 p. Rapporti ISTISAN 20/13

With the aim of fulfilling the task assigned it pursuant to national regulations regarding coordinating and providing technical support to the planning of self-sufficiency in blood components and plasma-derived medicinal products at regional and national level, the Italian National Blood Centre has conducted an analysis in collaboration with the Information and Statistics Department of the Italian Health Ministry. The analysis of the demand for plasma-derived medicinal products and recombinant therapies included the assessment of the self-sufficiency levels achieved and the costs sustained by the Italian National Health Service for the provision of these products. The content of this document, an update of the data for the year 2016 published in the Rapporto ISTISAN 19/12, was obtained by conducting a comparative analysis of the available data sources. The document is also an invaluable tool for planning self-sufficiency at national level.

Key words: Plasma-derived medicinal products; Demand; Self-sufficiency; Expenditure

Istituto Superiore di Sanità
Sistema trasfusionale italiano 2017: analisi della domanda dei medicinali plasmaderivati. Volume 2.
Fabio Candura, Maria Lavinia Salvatori, Gabriele Calizzani, Samantha Profili, Cristiana Chelucci, Chiara Brutti, Claudia Biffoli, Giancarlo Maria Liumbruno
2020, vii, 121 p. Rapporti ISTISAN 20/13 (in inglese)

Al fine di adempiere ai compiti ad esso assegnati dalla normativa vigente in materia di coordinamento e supporto tecnico alla programmazione dell'autosufficienza regionale e nazionale di emocomponenti e medicinali plasmaderivati, il Centro Nazionale Sangue ha effettuato, in collaborazione con l'Ufficio IV della Direzione Generale del Sistema Informativo e Statistico Sanitario del Ministero della Salute, l'analisi della domanda dei prodotti medicinali plasmaderivati e delle alternative terapeutiche di natura ricombinante, le valutazioni dei livelli di autosufficienza regionale e nazionale e la stima della spesa farmaceutica a carico del Servizio Sanitario Nazionale. Il confronto delle diverse fonti dati disponibili ha consentito l'elaborazione del presente documento che riporta l'aggiornamento relativo all'anno 2016 dei dati sull'argomento pubblicati nel Rapporto ISTISAN 19/12 e che si configura come uno strumento fondamentale per la programmazione dell'autosufficienza nazionale.

Parole chiave: Medicinali plasmaderivati; Domanda; Autosufficienza; Spesa

Si ringraziano per il contributo al presente documento: Giovanna Antonini, Annalisa Di Vito, Pierluigi Russo (Area Strategia e Politiche del Farmaco, Agenzia Italiana del Farmaco), Odile Tchangmena Befeuka, Concettina Oliva, Domenico Di Giorgio (Ufficio Qualità dei Prodotti e Contrasto al Crimine Farmaceutico, Agenzia Italiana del Farmaco); Lorella Lombardozzi, Alessandra Mecozzi (Direzione Regionale Salute e Integrazione Sociosanitaria - Area Politica del Farmaco, Regione Lazio); Ilaria Mazzetti (Servizio Assistenza Territoriale - Area Farmaco e Dispositivi Medici, Direzione Generale Sanità e Politiche Sociali e per l'Integrazione, Regione Emilia-Romagna); Livia Cannata, Liviana Catalano, Anna Ceccarelli (Centro Nazionale Sangue, Istituto Superiore di Sanità); le Aziende: Kedrion SpA, Baxalta SpA, Pfizer Italia, Grifols Italia SpA, CSL Behring SpA, Takeda Italia SpA, Biotest Italia Srl, Bayer SpA, Octapharma Italy SpA, Novo Nordisk A/S.

Per informazioni su questo documento scrivere a: segreteriagenerale.cns@iss.it

Il rapporto è accessibile online dal sito di questo Istituto: www.iss.it

Citare questo documento come segue:
Candura F, Salvatori ML, Calizzani G, Profili S, Chelucci C, Brutti C, Biffoli C, Liumbruno GM. *Italian Blood System 2017: demand for plasma-derived medicinal products. Volume 2.* Roma: Istituto Superiore di Sanità; 2020. (Rapporti ISTISAN 20/13).

Legale rappresentante dell'Istituto Superiore di Sanità: *Silvio Brusaferro*
Registro della Stampa - Tribunale di Roma n. 114 (cartaceo) e n. 115 (online) del 16 maggio 2014

Direttore responsabile della serie: *Paola De Castro*
Redazione*: Sandra Salinetti e Manuela Zazzara*
La responsabilità dei dati scientifici e tecnici è dei singoli autori, che dichiarano di non avere conflitti di interesse.

viale Regina Elena, 299 – 00161 Roma

TABLE OF CONTENTS

PART B

Other plasma-derived medicinal products

PART C

National self-sufficiency in toll-fractionated plasma derived medicinal products

ACRONYMS AND ABBREVIATIONS

3F-PCCs	3-Factor Prothrombin Complex Concentrates
4F-PCCs	4-Factor Prothrombin Complex Concentrates
AIC	Autorizzazione di Immissione in Commercio (Marketing Authorisation)
AIFA	Agenzia Italiana del FArmaco (Italian Medicines Agency)
AP	Autonomous Province
aPCCs	Activated Prothrombin Complex Concentrates
AT	AntiThrombin
ATC	Anatomical Therapeutic Chemical classification system
BE/s	Blood Establishment/s
BCU/s	Blood Collection Unit/s
BHK	Baby Hamster Kidney fibroblasts
BZ	Bolzano
CHO	Chinese Hamster Ovary cells
CMV	CytoMegaloVirus
DL	Decreto Legge (Decree Law)
DL.vo	Decreto Legislativo (Legislative Decree)
DM	Decreto Ministeriale (Ministerial Decree of the Ministry of Health)
ELC	Essential Levels of Care
ER	Emilia-Romagna
F	Factor
FVIIpd	Plasma-derived factor VII
pdFVIII	Plasma-derived factor VIII
pdFIX	Plasma-derived factor IX
Friuli-V. Giulia	Friuli-Venezia Giulia
FU/s	FEIBA Unit/s
FVG	Friuli-Venezia Giulia
IG	ImmunoGlobulin
ISTAT	Istituto Italiano di Statistica (Italian National Statistics Institute)
IU/s	International Unit/s
IVIG	IntraVenous ImmunoGlobulin
L	Law
LHC	Local Health Centre
LPS	Lombardy-Piedmont-Sardinia Agreement
Min	Ministry
MoH	Ministry of Health
NAIP	Nuovo Accordo Interregionale per la Plasmaderivazione (New Interregional Agreement for plasma-derived medicinal products)
NHS	National Health Service
NSIS	Nuovo Sistema Informativo Sanitario (New Health Information System)
PDMP/s	Plasma-Derived Medicinal Product/s
rFVIIa	Recombinant activated Factor VII
rFVIII	Recombinant Factor VIII
rFIX	Recombinant Factor IX
SC/IM	SubCutaneous/IntraMuscular
ST/s	Transfusion Service/s
UdR	Collection Units run by Donor Associations
VAT	Value Added Tax
vWF	von Willebrand Factor
WHO	World Health Organization

PRESENTATION

The Italian National Blood Centre (Centro Nazionale Sangue, CNS) is a technical body of the Italian Ministry of Health (MoH) which operates under the Istituto Superiore di Sanità (the National Institute of Health in Italy). In compliance with the laws in force, its tasks include the coordination and technical-scientific support on all matters concerning the production of Plasma and Plasma-Derived Medicinal Products (PDMPs).

In particular, the CNS provides guidelines regarding the strategic objectives of the transfusion system, which include achieving and maintaining self-sufficiency at regional and national level in labile blood components and PDMPs.

This report relating to calendar year 2017, also contains the PDMP demand included in the new calls for tender at regional level regarding industrial toll fractionation. In fact, the management of contracts for toll fractionation services is one of the well-established activities that contributes towards both the planning of plasma and PDMP production and the monitoring of their consumption and pharmaceutical expenditure. The main aim of this report, as that of similar reports published annually from 2007 to 2016, is to provide indications and the necessary strategic instruments to achieve and maintain self-sufficiency at regional and national level in plasma and PDMPs in accordance with the objectives set forth in the national planning scheme drafted within the national plasma and plasma-derived medicinal products programme 2016-2020, established by Ministerial Decree (DM) of 2 December 2016 and in the National self-sufficiency in blood and blood products programme 2017, established by DM of 20 July 2016.

Dr Giancarlo Maria Liumbruno
Director General
Italian National Blood Centre

INTRODUCTION

Plasma-Derived Medicinal Products (PDMPs) are pharmaceutical specialties produced through the industrial processing of plasma that is the liquid component of the blood collected from voluntary donors through apheresis or recovered from the whole blood by centrifugation. PDMPs play a key, and sometimes irreplaceable, role in the treatment of many acute and chronic clinical conditions (1).

Given their biological nature, the quality and safety of PDMPs are based on the controls carried out on the raw material – "plasma"– and its origin, as well as on the industrial manufacturing processes, which include removal and viral inactivation steps (2).

In Italy, plasma comes exclusively from the voluntary, anonymous and unremunerated donations of mainly periodic donors. Regions and Autonomous Provinces (APs) (hereinafter Regions), individually or in association, supply the plasma collected by Blood Establishments (BEs), to the Company(s) holder(s) of the agreements for the industrial transformation of plasma for the production of PDMPs.

The contract with companies, which operate as service providers, is considered a "third party processing" method, the acquisition of which by the Regions is implemented by means of a tender procedure in accordance with current legislation (3).

In June 2017, the New Interregional Agreement for Plasma-Derived Medicinal Products (Nuovo Accordo Interregionale per la Plasmaderivazione, NAIP), led by the Veneto Region, started to send plasma for fractionation to CSL Behring, the company that won the tender launched in 2015 pursuant to Law 219 of 21 October 2005, (L 219/2005) (4), whose contract provides for the production of the following PDMPs: albumin, normal human immunoglobulins for intravenous use (IntraVenous ImmunoGlobulin, IVIG), subcutaneous (SC)/ intramuscular (IM) immunoglobulins (IG), factor VIII concentrates of plasma origin (pdFVIII), plasma-derived factor VIII (pdFVIII) and von Willebrand factor (vWF) in combination concentrates (pdFVIII/vWF), andfibrinogen.

Pending the launching of other tenders for the assignment of the plasma toll-fractionation service, the other Regions were still affiliated exclusively with the company Kedrion SpA (hereinafter Kedrion), whose contract provided for the production of the following PDMPs: albumin, IVIG, Anti-Thrombin (AT), pdFVIII, plasma-derived Factor IX concentrates (pdFIX), and 3-factor Prothrombin Complex Concentrates (3F-PCCs).

In consideration of the clinical interest and their impact on pharmaceutical expenditure, the Report describes the demand for the other PDMPs and for the recombinant medicinal products used for the treatment of congenital and acquired bleeding disorders distributed through commercial channels.

For each of the PDMPs whose supply is included in the contracts between the Regions and the fractionator (i.e. Kedrion), the level of regional and national self-sufficiencies is estimated.

Finally, the pharmaceutical expenditure incurred by the NHS for procurement on the market is described, whether it is or is not the portion of the NHS demand not covered by toll fractionation agreement.

The report, after a description of data sources and the methodology used, analyses the demand for each active ingredient, the level of self-sufficiency, for the PDMPs produced by toll fractionation, and pharmaceutical expenditure.

It is divided into four analytical sections:

- *Part A*
  The demand for PDMPs currently provided by toll fractionation agreements.
- *Part B*
  The demand for other PDMPs.
- *Part C*
  National PDMP self-sufficiency.
- *Part D*
  Pharmaceutical expenditure on plasma-derived and recombinant medicinal products.

SOURCES AND METHODOLOGY

Data sources

Drug traceability flow

Since January 2005, the medicinal products traceability database (5) has been updated daily with data gathered from the delivery notes of drugs belonging to each reimbursement and dispensation regime. As every actor involved in their production and distribution – production sites, warehouses and wholesalers, pharmacies, hospitals, etc. – is assigned a unique identifying code and each single package is tracked through a marketing authorisation code (Autorizzazione all'Immissione in Commercio, AIC code) during every step of the entire supply chain process (Figure 1).

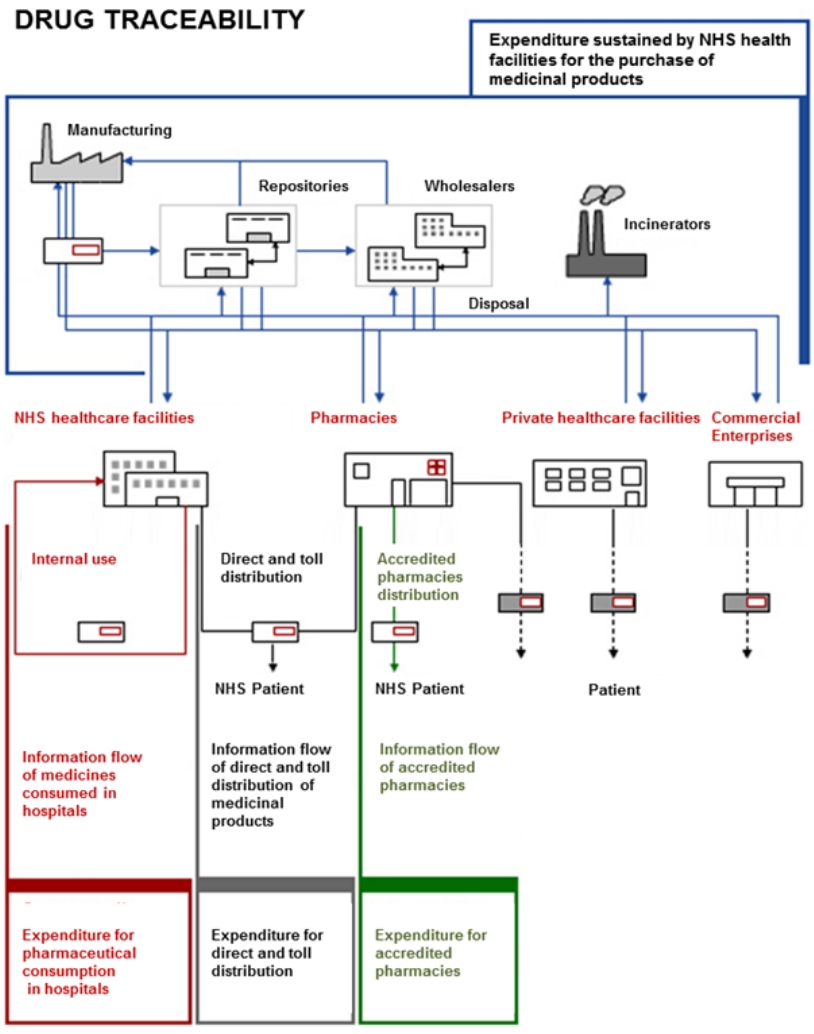

Figure 1. The drug traceability system in Italy (adapted by the CNS on data from www.salute.gov.it)

Pursuant to Italian law, if the final receiver is a public entity (hospital pharmacy, public healthcare facility, etc.), also the payment due is detected along with the quantity of the product in order to monitor pharmaceutical expenditure. Thus, the drug traceability system keeps track of all medicinal product movements identified by the AIC code and quantified by the number of packages, from one logistics site to another (all that is placed below the dotted horizontal line in Figure 1) without considering any final user.

Therefore, the drug traceability system is suitable to quantify the total demand for PDMPs because it takes into account the quantities distributed to both public and private health facilities, and to pharmacies regardless of the dispensation regime, and whether or not charged to the Italian NHS.

Information flow of accredited pharmacies

The "Health Card" project (Law 326/2003) (6), established the information flow that records all data related to prescription drugs with the aim of monitoring the pharmaceutical services funded by the NHS and provided by public pharmacies.

This dispensation regime concerns the medicinal products included in the Essential Levels of Care (ELC).

This information flow is the most suitable for calculating the demand for PDMPs provided through public pharmacies and it is managed and supplied by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) (Figure 2).

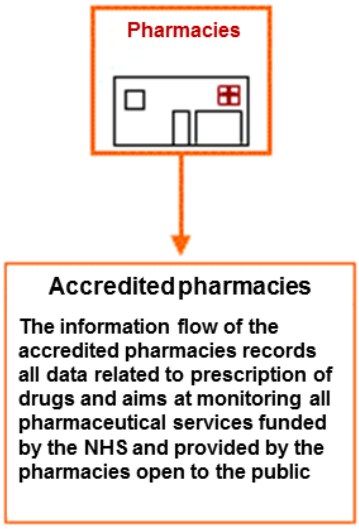

Figure 2. Scope of the information flow of accredited pharmacies (adapted by the CNS on data from www.salute.gov.it)

Information flow of the direct provision of medicinal products

The institutional information flow of the direct provision of medicinal products registers the home utilisation of medicinal products distributed by public healthcare facilities; direct provision can also occur through specific agreements with public pharmacies (toll distribution). This information flow, established by DM of 31 July 2007 (7), considers:

- medicinal products given to the patient to be utilised at home;
- medicinal products provided directly by healthcare facilities after hospital discharge or medical examination;
- medicinal products provided to chronic patients within disease-specific therapeutic plans and to patients for home care;
- medicinal products distributed to prison facilities;
- medicinal products provided by public and private pharmacies on behalf of Local Health Centres (LHCs) (toll distribution).

The medicinal products considered in this information flow are all drugs with an AIC code, regardless of the class of reimbursement (A-C-H), magistral formulations, officinal formulas and foreign medicines not authorised to be sold in Italy and used pursuant to DM of 11 February 1997 (8). In the latter cases, the pharmaceutical performance is identified through the Anatomical Therapeutic Chemical (ATC) classification system, (see dedicated paragraph).

This information flow consists of the following details that are submitted monthly to the MoH: providing structure, prescription barcode (which through the prescription pad database can be traced to the prescriber), patient, medicinal product code, date of delivery, quantity delivered and related expenditure. Until 2009, only the costs, and not the related quantities, were recorded.

The institutional information flow of the direct provision of medicinal products, shown in Figure 3, records the medicinal product delivery on a nominal basis.

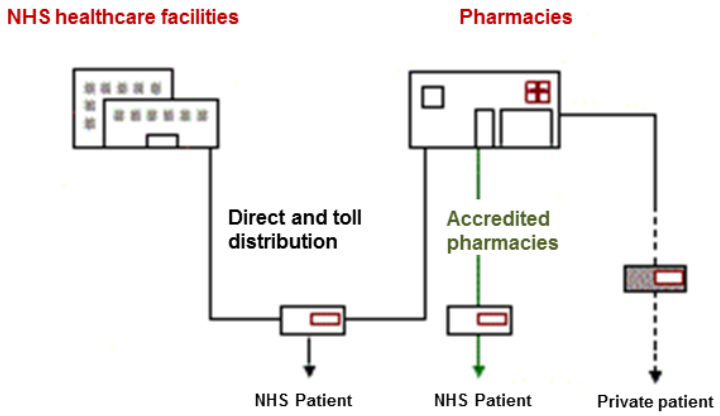

Figure 3. Medicinal products information flow (adapted by the CNS on data from www.salute.gov.it)

This information flow is the most suitable for quantifying the NHS's demand for PDMPs, provided through the direct distribution channel. The information recorded by this flow makes it possible to assess the appropriateness of the prescription and the appropriateness of the total number of medicinal products consumed by patients, as well as to compare the drug acquisition costs incurred by single health facilities, thus allowing an indirect evaluation of the purchase tenders.

Information flow of medicines consumed in hospitals

The information flow to monitor the consumption of medicinal products in hospitals takes into consideration the medicinal products utilised by public healthcare facilities.

These include all medicinal products with an AIC code, regardless of their reimbursement class (A, C, H), masterly formulations, medicinal formulas and foreign medicines not authorised to be sold in Italy and used in accordance with DM of 11 February 1997 (8). In the latter cases, pharmaceutical performance is identified by the ATC code.

The information flow includes the following details submitted monthly to the MoH: providing structure, receiving operating unit, recipient activity regime, drug code, disbursement date, quantity delivered and related expenditure.

The movement of toll-manufactured PDMPs is not associated with a purchase cost; however, an estimate of the aforementioned costs can be made through the exchange fees defined in the State-Regions Agreement of 20 October 2015 (9).

The information flow to monitor the consumption of medicinal products in hospitals thus detects the internal movements of drugs purchased or made available for use by healthcare facilities directly managed by the Italian NHS, with the exception of those delivered through direct distribution. Therefore, the hospital information flow records the movements of single packages to the operating units, as shown in Figure 4. This flow is the most suitable for quantifying the consumption of those PDMPs whose costs are covered by the NHS and which are used during hospitalisation or outpatient regimens.

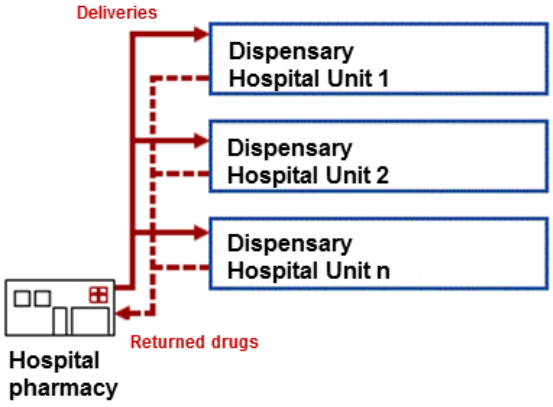

Figure 4. Information flow of medicines consumed in hospitals (adapted by the CNS on data from www.salute.gov.it)

Data on plasma-derived medicinal products produced from Italian plasma

The CNS receives the data regarding PDMPs distributed by Kedrion on behalf of the Regions as part of toll-manufacturing contracts from Kedrion itself and these figures go to form the database for the analysis of PDMP production from national plasma.

Data on plasma-derived medicinal products subject to import procedures

Data related to the PDMPs imported by Italy due to a national shortage, registered abroad and subject to import procedures pursuant to DM of February 11, 1997 (8), and DM of May11, 2001 (10), are provided by the Product Quality Office of the AIFA.

Data processing and the ATC drug classification system

For this report, different data sources were accessed to detect the number of packages, by reference year and by single AIC code, and to identify quantities of active ingredients of distributed PDMPs. The individual AIC codes were traced back to the relevant active ingredient and to the related ATC code.

The ATC system is a drug classification system managed by the Nordic Council on Medicine and the Collaborating Centre for Drug Statistics Methodology of the World Health Organisation (WHO) in Oslo, Norway (www.whocc.no).

Under the ATC system, drugs are classified in different groups according to the target organ, their mechanism of action and chemical and therapeutic properties. The main groups of the ATC system are further divided into 5 hierarchical levels, shown in Table 1.

Table 1. ATC classification system

Level	Description	Note
I	anatomical main group	consists of one letter
II	therapeutic main group	consists of two digits
III	therapeutic subgroup	consists of one letter
IV	chemical/therapeutic subgroup	consists of one letter
V	chemical subgroup	consists of two digits

For example, the classification of FVIII and von Willebrand Factor (vWF) in combination is B02BD06 and is based on the composition as shown in Table 2.

Table 2. ATC classification system of FVIII and von Willebrand Factor (vWF) in combination

Level	Description
B	Blood and Blood forming organs
B02	Antihaemorrhagics
B02B	Vitamin K and other haemostatics
B02BD	Blood coagulation factors
B02BD06	Von Willebrand factor and coagulation factor VIII in combination

The ATC classification system is based on the principle of assigning a single code to individual pharmaceutical products (AIC code). Medicinal products are therefore classified according to their main therapeutic use. A medicinal product, however, can be used for two or more therapeutic indications of equal importance with different classification possibilities. When a drug is available in two or more dosages or pharmaceutical forms for different therapeutic uses, the classification

is determined on the basis of the actual therapeutic use. Finally, preparations that cannot be uniquely classified in a particular group are coded in the fourth level with the letter X.

Therefore, the ATC classification makes it possible to perform a progressively more detailed identification of all drugs and substances for therapeutic use and, indirectly, through the analysis of active ingredients or of the prescribed therapeutic groups, it makes it possible to formulate hypotheses on the incidence of specified pathologies or prevalence in the general population (11).

When a medicinal product is placed on the market, the AIFA assigns it an AIC code. Based on the active ingredient and the therapeutic indications, it is possible to associate an ATC code and the quantity of active ingredient contained (expressed in specific units of measurement: mg, IU, g, etc.) to it.

In order to make aggregate data comparable at regional level, the absolute quantities were standardised for the resident population as of January 1st, 2017 of each year in question taken from the figures of the Italian National Statistics Institute (Istituto Italiano di Statistica, ISTAT) (12) (Table 3).

Table 3. Resident population by Region and Autonomous Province, 2016-2017 (adapted by the CNS on data from ISTAT, 31/8/2017)

Region	2016	2017
Abruzzo	1,326,513	1,322,247
Aosta Valley	127,329	126,883
AP Bolzano	520,891	524,256
AP Trento	538,223	538,604
Apulia	4,077,166	4,063,888
Basilicata	573,694	570,365
Calabria	1,970,521	1,965,128
Campania	5,850,850	5,839,084
Emilia-Romagna	4,448,146	4,448,841
Friuli-Venezia Giulia	1,221,218	1,217,872
Latium	5,888,472	5,898,124
Liguria	1,571,053	1,565,307
Lombardy	10,008,349	10,019,166
Marche	1,543,752	1,538,055
Molise	312,027	310,449
Piedmont	4,404,246	4,392,526
Sardinia	1,658,138	1,653,135
Sicily	5,074,261	5,056,641
Tuscany	3,744,398	3,742,437
Umbria	891,181	888,908
Veneto	4,915,123	4,907,529
Italy	60,665,551	60,589,445

AP: Autonomous Province

Active ingredients and measurement units

In order to quantify the demand for PDMPs, measurement units used for each active ingredient are shown in Table 4. As regards local haemostatics and combinations (ATC B02BC and B02BC30), the various commercial products are composed of a mixture of different active ingredients, the related data of which are expressed in millilitres, with the exception of formulations where the number of sponges utilised are provided per year.

Table 4. Active ingredients, ATC codes and measurement units

Active ingredient	ATC Code	Measurement unit
Albumin	B05AA01	g
Normal human Immunoglobulins for extravascular administration	J06BA01	g
Normal human Immunoglobulins for intravascular administration	J06BA02	g
Antithrombin	B01AB02	IU
Plasma-derived and recombinant coagulation factor VIII	B02BD02	IU
Von Willebrand factor and coagulation factor VIII in combination	B02BD06	IU
Plasma-derived coagulation factor IX	B02BD04	IU
Recombinant coagulation factor IX	B02BD09	IU
3-factor Phrothrombin complex concentrates	B02BD	IU
4-factor Phrothrombin complex concentrates	B02BD01	IU
Hepatitis B immunoglobulins	J06BB04	IU
Tetanus immunoglobulins	J06BB02	IU
Anti-D (Rh) immunoglobulin	J06BB01	IU/µg
Cytomegalovirus immunoglobulins	J06BB09	IU
Varicella/zoster immunoglobulins	J06BB03	IU
Rabies immunoglobulins	J06BB05	IU
Local haemostatics and combinations	B02BC B02BC30	mL/sponges
Coagulation factor VII	B02BD05	IU
Coagulation factor VIIa	B02BD08	mg
Factor VIII inhibitor bypassing activity	B02BD03	FU
Human fibrinogen	B02BB01	g
Alfa-1 antitrypsin	B02AB02	mg
Plasma-derived C1-inhibitor	B06AC01	IU
Coagulation factor X	B02BD13	IU
Coagulation factor XI	B02BD	IU
Plasma-derived coagulation factor XIII	B02BD07	IU
Recombinant coagulation factor XIII	B02BD11	IU
Protein C	B01AD12	IU
Other plasma proteins fractions	B05AA02	mL

Self-sufficiency and pharmaceutical expenditure

For every PDMP included in the agreements between the Regions and their affiliated Companies (Kedrion and CSL Behring), the degree of the achieved self-sufficiency was assessed by comparing the actual supply with NHS demand. However, it is worth underlying that CSL Behring started to collect plasma only in May 2017, therefore, there was not enough time to return any PDMPs to NAIP Regions. As a result, self-sufficiency of NAIP Regions is estimated only on the basis of the PDMPs made available by Kedrion from plasma collected before May 2017 under the conditions of their expiring contract. In this report, productive capacity (or potential supply) means the theoretic quantity of PDMPs derivable from the plasma sent by each Region for fractionation from July 2016 to June 2017. By contrast, effective supply (or toll fractionation) means the quantity of PDMPs *de facto* distributed by Kedrion to each Region, during the 2017 calendar year. Data related to the productive capacity and effective supply are provided by companies. Both productive capacity and effective supply are strictly influenced by the quantity and quality of plasma sent by the Regions, industrial yields and planning.

Total demand refers to the regional PDMP utilisation considering all distribution channels (public and private healthcare facilities, pharmacies, etc.). NHS demand means the share of the total demand funded by the NHS.

Potential self-sufficiency means the percent ratio between the productive capacity and NHS demand. Effective self-sufficiency means the percent ratio between the effective supply and NHS demand.

In the dedicated chapter, pharmaceutical expenditure is defined as the expenditure for the supply of PDMPs covered by the NHS through public health facilities and pharmacies. As far as the first channel is concerned, the aggregate purchase cost of PDMPs incurred by public facilities was detected and quantified by means of the traceability information flow. The quantities and the monetary value of PDMPs delivered to public pharmacies were calculated by using the price in force on 31/12/2017, and applying any eventual discounts provided for by Law 662/1996 (13), amended by Law 122/2010 (14).

For albumin, IVIG and pdFVIII, the average costs per unit purchased on the market, and the average costs per unit purchased through public health facilities and pharmacies are specified in summary tables, to which the related percentages of the demand and expenditure paid through the same distribution channels are added.

For toll-fractionated medicinal products, it is not possible to provide an estimate of the related expenditure, but only the total amount incurred by the Regions for plasma processing services not including the costs incurred by Regions for the production of plasma as “raw material”.

PART A
Plasma-derived medicinal products from toll fractionation

ALBUMIN (ATC B05AA01)

Albumin is a plasma protein produced from liver cells and accounts for about 60% of all plasma proteins. Its concentration in the blood (referred to as albuminaemia) can range between 3.5 and 5.0 g / dL. Lower albuminaemia values are mainly due to a reduced production of albumin by the liver. The ability to synthesise proteins by the hepatocyte is compromised in severe liver diseases (15,16). Table 5 shows the brand names of drugs containing albumin currently on the market in Italy and the amount of active ingredient they contain expressed in grams.

Table 5. Products containing albumin currently available on the Italian market (adapted by CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	g	Manufacturer	NHS class
011544020	ALBUMINA BEHRING*IV 50ML20%	10	CSL BEHRING SpA	A
021111024	UMANALBUMIN*INF FL 50ML 200G/L	10	KEDRION SpA	A
021111051	UMANALBUMIN*FL 250ML 5%	12.5	KEDRION SpA	C
021111087	UMANALBUMIN*INF FL 50ML 250G/L	12.5	KEDRION SpA	A
021111101	UMANALBUMIN*EV FL 100ML 200G/L	20	KEDRION SpA	A
022515136	ALBITAL*1FL 50ML 25G/100ML+SET	12.5	KEDRION SpA	A
022515163	ALBITAL*1FL 50ML SOLUZ 20%+SET	10	KEDRION SpA	A
028989046	PLASBUMIN*EV 1FL 50ML 200G/L	10	GRIFOLS ITALIA SpA	A
028989059	PLASBUMIN*EV 1FL 100ML 200G/L	20	GRIFOLS ITALIA SpA	A
028989097	PLASBUMIN*EV 1FL 50ML 250G/L	12.5	GRIFOLS ITALIA SpA	A
029251016	ALBUTEIN*IV FL 250ML 50G/L	12.5	GRIFOLS ITALIA SpA	C
029251028	ALBUTEIN*IV FL 500ML 50G/L	25	GRIFOLS ITALIA SpA	C
029251030	ALBUTEIN*IV FL 50ML 200G/L	10	GRIFOLS ITALIA SpA	A
029251042	ALBUTEIN*IV FL 50ML 25%	12.5	GRIFOLS ITALIA SpA	A
034611018	ALBUMINA GRIFOLS*1FL 50ML 20%	10	GRIFOLS ITALIA SpA	A
034611020	ALBUMINA GRIFOLS*1FL 100ML 20%	20	GRIFOLS ITALIA SpA	A
034611032	ALBUMINA GRIFOLS*1FL 100ML 5%	5	GRIFOLS ITALIA SpA	C
034611044	ALBUMINA GRIFOLS*1FL 250ML 5%	12.5	GRIFOLS ITALIA SpA	C
034611057	ALBUMINA GRIFOLS*1FL 500ML 5%	25	GRIFOLS ITALIA SpA	C
034611069	ALBUMINA GRIFOLS*50ML 25G/100M	12.5	GRIFOLS ITALIA SpA	A
034611071	ALBUMINA GRIFOLS*100ML 25G/100	25	GRIFOLS ITALIA SpA	H
036176016	ALBUMINA LFB*FL 50ML 200MG/ML	10	LBF	A
036504052	ALBUREX*INFUS 1FL 50ML 20%	10	CSL BEHRING GmbH	A
036504064	ALBUREX*INFUS 1FL 100ML 20%	20	CSL BEHRING GmbH	A
036504076	ALBUREX*INFUS 1FL 50ML 25%	12.5	CSL BEHRING GmbH	A
037566015	ALBUMINA BAXTER*1FL 250ML 50G/	12.5	BAXALTA ITALY Srl	C
037566054	ALBUMINA BAXTER*FL 50ML 200G/L	10	BAXALTA ITALY Srl	A
037566078	ALBUMINA BAXTER*1FL 100ML 200G	20	BAXALTA ITALY Srl	A
037566092	ALBUMINA BAXTER*FL 50ML 250G/L	12.5	BAXALTA ITALY Srl	A
038109017	FLEXBUMIN*24SACCHE 50ML 200G/L	240	BAXALTA ITALY Srl	H
038109031	FLEXBUMIN*12S 100ML200G/L	240	BAXALTA ITALY Srl	H
038109056	FLEXBUMIN*SAC INF 50ML 200G/L	10	BAXALTA ITALY Srl	A
038109068	FLEXBUMIN*SAC INF 100ML 200G/L	20	BAXALTA ITALY Srl	A
038109070	FLEXBUMIN*SAC INF 50ML 250G/L	12.5	BAXALTA ITALY Srl	A
038109082	FLEXBUMIN*1SACCA 100ML 250G/L	25	BAXALTA ITALY Srl	H
038747034	OCTALBIN*IV 50ML 200MG/ML	10	OCTAPHARMA ITALY SPA	A
038747046	OCTALBIN*IV 100ML 200MG/ML	20	OCTAPHARMA ITALY SPA	A
039073010	ALBIOMIN*INF 250ML 50G/L 5%	12.5	BIOTEST ITALIA Srl	C
039073022	ALBIOMIN*FL 50ML 200G/L 20%	10	BIOTEST ITALIA Srl	A
039187012	ALBUNORM*1FL 100ML 5% 50G/L	5	OCTAPHARMA ITALY SPA	C
039073034	ALBIOMIN*INF 100ML 200G/L 20%	20	BIOTEST ITALIA Srl	A
039187024	ALBUNORM*10FL 100ML 5% 50G/L	5	OCTAPHARMA ITALY SPA	C

AIC code	Brand name	g	Manufacturer	NHS class
039187036	ALBUNORM*1FL 250ML 5% 50G/L	12.5	OCTAPHARMA ITALY SPA	C
039187063	ALBUNORM*1FL 50ML 20% 200G/L	10	OCTAPHARMA ITALY SPA	A
039187087	ALBUNORM*1FL 100ML 20% 200G/L	20	OCTAPHARMA ITALY SPA	A
039187101	ALBUNORM*1FL 50ML 25% 250G/L	12.5	OCTAPHARMA ITALY SPA	A
042029013	KALBI*FL 50ML 200G/L	10	KEDRION SpA	A
042029025	KALBI*FL 50ML 250G/L+SET	12.5	KEDRION SpA	A
043358011	ALBUMEON*FL 50ML 200G/L 20%	10	CSL BEHRING SpA	A
043358023	ALBUMEON*FL 100ML 200G/L 20%	20	CSL BEHRING SpA	A
044549018	PROBUMIN*FL 50 ML 200 G/L	10	GRIFOLS ITALIA SPA	C (nn)
044549020	PROBUMIN*FL 100ML 200 G/L	20	GRIFOLS ITALIA SPA	C (nn)

Quantification and characterisation of the demand

Table 6 shows the total demand (expressed in grams) and the total standardised demand (expressed in grams per 1,000 population) of albumin[1] for the two-year period 2016-2017 with the variations in percentage, both at national and regional levels.

Table 6. Total demand (public and private) and total standardised demand for albumin, expressed in grams and grams per 1,000 population, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	856,668	645.8	791,568	598.7	-7.3
Aosta Valley	67,493	530.1	73,750	581.2	9.7
AP Bolzano	134,780	258.7	148,960	284.1	9.8
AP Trento	154,093	286.3	183,425	340.6	19.0
Apulia	1,853,633	454.6	2,088,145	513.8	13.0
Basilicata	321,773	560.9	334,825	587.0	4.7
Calabria	961,025	487.7	1,085,958	552.6	13.3
Campania	5,862,160	1001.9	5,552,418	950.9	-5.1
E.-Romagna	2,330,993	524.0	2,437,620	547.9	4.6
Friuli-V. Giulia	363,573	297.7	378,478	310.8	4.4
Latium	2,954,903	501.8	3,150,310	534.1	6.4
Liguria	693,110	441.2	672,413	429.6	-2.6
Lombardy	6,302,200	629.7	6,896,345	688.3	9.3
Marche	673,770	436.4	717,305	466.4	6.9
Molise	177,628	569.3	144,963	466.9	-18.0
Piedmont	1,365,675	310.1	1,449,118	329.9	6.4
Sardinia	1,666,375	1005.0	1,553,920	940.0	-6.5
Sicily	2,731,970	538.4	3,043,375	601.9	11.8
Tuscany	1,949,145	520.5	1,811,433	484.0	-7.0
Umbria	495,368	555.9	516,325	580.9	4.5
Veneto	2,216,603	451.0	2,308,243	470.3	4.3
ITALY	34,132,933	562.6	35,338,893	583.3	3.7

[1] The data analysed did not consider the use of the product *Umanserum*™. This product is classified as human plasma protein (ATC B05AA02, see related chapter) within the ATC system, despite its 90% albumin composition.

In 2017, the national demand for this ingredient was about 35,300 kilograms (Table 6), equal to 583 grams per 1,000 population. The two regions with the highest standardised demand were Campania and Sardinia with standardised volumes of 951 and 940 grams, respectively. The regions with the lowest demand were Friuli-Venezia Giulia and the AP of Bolzano, with about 311 and 284 grams per 1,000 population, respectively (Figure 5).

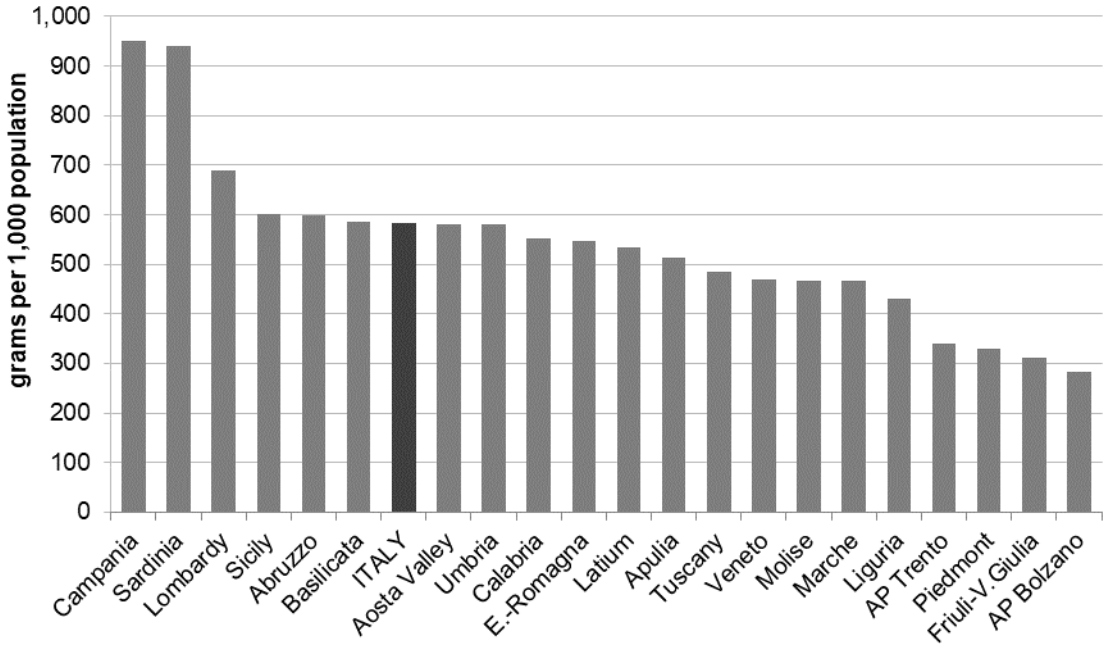

Figure 5. Total and regional demand (public and private) for albumin, expressed in grams per 1,000 population, 2017 (adapted by the CNS on data from the traceability information flow)

In this two-year period, the total standardised demand for albumin showed an upward trend respect to previous years (3.7% compared to 2016) (17). The regions where the increase in albumin utilisation was more evident, measured as a percentage change compared to the Italian mean value, were the AP of Trento (+19%), Calabria and Apulia (+13%). By contrast, a decrease was observed in Molise (-18%), Abruzzo and Tuscany (-7%).

Figure 6 highlights the six regions with a higher demand compared to national demand. Two of them show significantly higher values (> 60%).

Figure 7 shows the standardised regional demand for albumin registered in 2017 per distribution channel (public pharmacies compared to other facilities), as shown by the drug traceability system (17,18). In 2017, about 12% of the national demand – approximately 4,357 kilograms – was distributed through public pharmacies. Pharmacies as a distribution channel are particularly used in Calabria, Campania and Latium, where they account for between 20 and 30% of each regional demand, while they are used albeit to a lesser extent in Apulia, Molise and Piedmont (with percentages of between 14 and 17% of the total regional demand). As far as the other regions are concerned, they are rarely used.

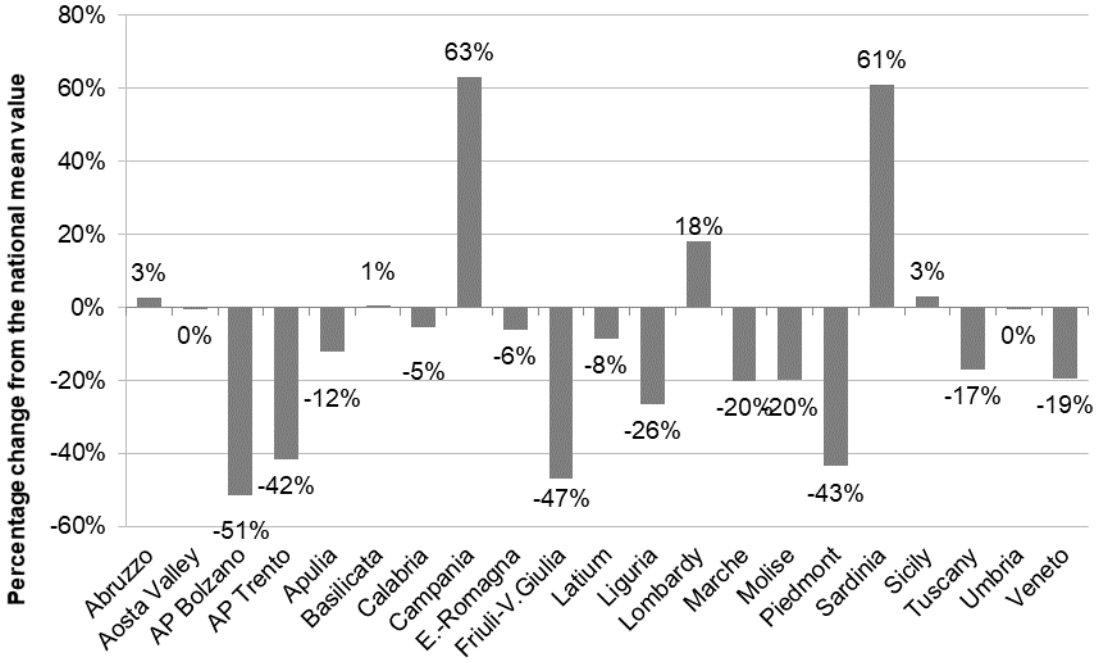

Figure 6. Percentage change from the national mean value of standardised regional demand for human albumin in 2017 (adapted by the CNS on data from the traceability information flow)

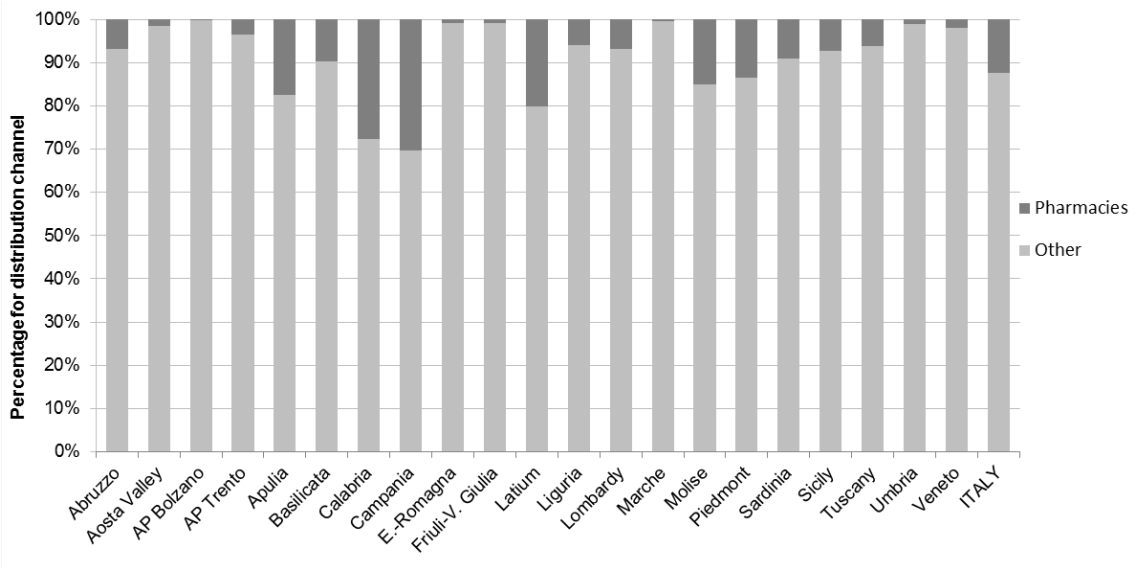

Figure 7. Standardised regional demand for albumin registered per distribution channel, 2017 (adapted by the CNS on data from the traceability information flow)

NORMAL HUMAN IMMUNOGLOBULINS FOR SUBCUTANEOUS USE (ATC J06BA01) AND FOR INTRAVENOUS USE (ATC J06BA02)

Immunoglobulins (IGs) are used in substitutive immunodeficiency therapy and in the treatment of autoimmune diseases or systemic inflammatory processes. However, in clinical practice they are used much more extensively and their use is not always fully justified by the available evidence in scientific literature. Since 2007, both soluble IG preparations for subcutaneous/intramuscular infusion (SC/IM) and those for intravenous use (IntraVenous, IV) (18) have been available in Italy. IGs, like all other PDMPs, are prepared by using human plasma pools, which guarantees the recipient a higher antibody coverage thanks to a significant idiotypical diversity. The preparations contain structurally and functionally intact IG, with normal half-life and subclass proportions: 95% of monomeric IGG, small amounts of dimers, and variable amounts of IGA and IGM (19). Tables 7 shows the names of the drugs containing IG that are currently marketed in Italy and the amount of active ingredient they contain expressed in grams.

Table 7. Products containing normal human immunoglobulins for subcutaneous/ intramuscular and intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for subcutaneous/intramuscular use				
036800011	SUBCUVIA*SC IM FL 5ML 160MG/ML	0.8	BAXALTA ITALY Srl	H
036800023	SUBCUVIA*SC IM 20FL5ML 160MG/M	16	BAXALTA ITALY Srl	H
036800035	SUBCUVIA*SC IM 20FL10ML 160MG/	32	BAXALTA ITALY Srl	H
036800047	SUBCUVIA*SC IM FL10ML 160MG/ML	1.6	BAXALTA ITALY Srl	H
Normal human immunoglobulin for subcutaneous use				
040652012	OCTANORM*1FL 10ML 165MG/ML	1.65	OCTAPHARMA ITALY SPA	H
040652024	OCTANORM*10FL 10ML 165MG/ML	16.5	OCTAPHARMA ITALY SPA	H
040652036	OCTANORM*20FL 10ML 165MG/ML	33	OCTAPHARMA ITALY SPA	H
040652048	OCTANORM*1FL 20ML 165MG/ML	3.3	OCTAPHARMA ITALY SPA	H
040652051	OCTANORM*10FL 20ML 165MG/ML	33	OCTAPHARMA ITALY SPA	H
040652063	OCTANORM*20FL 20ML 165MG/ML	66	OCTAPHARMA ITALY SPA	H
040652075	OCTANORM*1FL 6ML 165MG/ML	0.99	OCTAPHARMA ITALY SPA	H
040652101	OCTANORM*FL 12ML 165MG/ML	1.98	OCTAPHARMA ITALY SPA	H
040652137	OCTANORM*FL 24ML 165MG/ML	3.96	OCTAPHARMA ITALY SPA	H
040652164	OCTANORM*FL 48ML 165MG/ML	7.92	OCTAPHARMA ITALY SPA	H
041157013	HIZENTRA*SC 1FL 5ML 200MG/ML	1	CSL BEHRING SpA	H
041157049	HIZENTRA*SC 1FL 10ML 200MG/ML	2	CSL BEHRING SpA	H
041157102	HIZENTRA*SC 1FL 20ML 200MG/ML	4	CSL BEHRING SpA	H
041157138	HIZENTRA*SC 1FL 50ML 200MG/ML	10	CSL BEHRING SpA	H
042804017	HYQVIA*SC 1FL 25ML+1FL 1,25ML	2.5	BAXALTA ITALY Srl	H
042804029	HYQVIA*SC 1FL 50ML+1FL 2,5ML	5	BAXALTA ITALY Srl	H
042804031	HYQVIA*SC 1FL 100ML+1FL 5ML	10	BAXALTA ITALY Srl	H
042804043	HYQVIA*SC 1FL 200ML+1FL 10ML	20	BAXALTA ITALY Srl	H
042804056	HYQVIA*SC 1FL 300ML+1FL 15ML	30	BAXALTA ITALY Srl	H
043396011	NAXIGLO*SC FL 10ML 160MG/ML	1.6	KEDRION SpA	H
043396023	NAXIGLO*SC FL 25ML 160MG/ML	4	KEDRION SpA	H
043398015	KEYCUTE*SC FL 10ML 160MG/ML	1.6	KEDRION SpA	H
043398027	KEYCUTE*SC FL 25ML 160MG/ML	4	KEDRION SpA	H
044244010	CUVITRU*SC 1FL 5ML 200MG/ML	1	BAXALTA ITALY Srl	C(nn)
044244022	CUVITRU*SC 1FL 10ML 200MG/ML	2	BAXALTA ITALY Srl	C(nn)
044244034	CUVITRU*SC 1FL 20ML 200MG/ML	4	BAXALTA ITALY Srl	C(nn)
044244046	CUVITRU*SC 1FL 40ML 200MG/ML	8	BAXALTA ITALY Srl	C(nn)

AIC code	Brand name	g	Manufacturer	NHS class
Normal human immunoglobulin for intravenous use				
025266141	IGVENA*EV 1FL 20ML 50G/L	1	KEDRION SpA	H
025266154	IGVENA*EV 1FL 50ML 50G/L+SET	2.5	KEDRION SpA	H
025266166	IGVENA*EV 1FL 100ML 50G/L+SET	5	KEDRION SpA	H
025266178	IGVENA*EV 1FL 200ML 50G/L+SET	10	KEDRION SpA	H
029021019*	PENTAGLOBIN*EV FL 50MG/ML 10ML	0.5	BIOTEST ITALIA Srl	C
029021033*	PENTAGLOBIN*EV 1FL 50MG/ML50ML	2.5	BIOTEST ITALIA Srl	C
029021045*	PENTAGLOBIN*EV 1FL 50MG/ML100M	5	BIOTEST ITALIA Srl	C
029249048	PLITAGAMMA*50ML(2,5G)5%+SET	2.5	GRIFOLS ITALIA SpA	H
029249051	PLITAGAMMA*100ML (5G)5%+SET	5	GRIFOLS ITALIA SpA	H
029249063	PLITAGAMMA*200ML (10G)5%+SET	10	GRIFOLS ITALIA SpA	H
033240033	GAMMAGARD*EV 1FL 50MG/ML 96ML	4.8	BAXTER SpA	H
033240045	GAMMAGARD*EV 1FL 50MG/ML 192ML	9.6	BAXTER SpA	H
035143015	OCTAGAM*IV FL 50ML 5%	2.5	OCTAPHARMA ITALY SPA	H
035143027	OCTAGAM*IV FL 100ML 5%	5	OCTAPHARMA ITALY SPA	H
035143039	OCTAGAM*IV FL 200ML 5%	10	OCTAPHARMA ITALY SPA	H
035143041	OCTAGAM*IV FL 500ML 5%	25	OCTAPHARMA ITALY SPA	H
037107012	KIOVIG*EV FL 10ML 100MG/ML	1	BAXTER SpA	H
037107024	KIOVIG*EV FL 25ML 100MG/ML	2.5	BAXTER SpA	H
037107036	KIOVIG*EV FL 50ML 100MG/ML	5	BAXTER SpA	H
037107048	KIOVIG*EV FL 100ML 100MG/ML	10	BAXTER SpA	H
037107051	KIOVIG*EV FL 200ML 100MG/ML	20	BAXTER SpA	H
037107063	KIOVIG*EV FL 300ML 100MG/ML	30	BAXTER SpA	H
037240064	INTRATECT*INFUS FL 50G/L 50ML	2.5	BIOTEST ITALIA Srl	H
037240076	INTRATECT*INFUS FL 50G/L 100ML	5	BIOTEST ITALIA Srl	H
037240088	INTRATECT*INFUS FL 50G/L 200ML	10	BIOTEST ITALIA Srl	H
037240090	INTRATECT*INFUS FL 100G/L 10ML	1	BIOTEST ITALIA Srl	H
037240102	INTRATECT*INFUS FL 100G/L 50ML	5	BIOTEST ITALIA Srl	H
037240114	INTRATECT*INFUS FL100G/L 100ML	10	BIOTEST ITALIA Srl	H
037240126	INTRATECT*INFUS FL100G/L 200ML	2	BIOTEST ITALIA Srl	H
037254012	VENITAL*EV FL 20ML 50G/L	1	KEDRION SpA	H
037254024	VENITAL*EV FL 50ML 50G/L+SET	2.5	KEDRION SpA	H
037254036	VENITAL*EV FL 100ML 50G/L+SET	5	KEDRION SpA	H
037254048	VENITAL*EV FL 200ML 50G/L+SET	10	KEDRION SpA	H
039457015	GAMTEN*INFUS 1FL 20ML 100MG/ML	2	OCTAPHARMA ITALY SPA	H
039457027	GAMTEN*INFUS 1FL 50ML 100MG/ML	5	OCTAPHARMA ITALY SPA	H
039457039	GAMTEN*INFUS 1FL100ML 100MG/ML	10	OCTAPHARMA ITALY SPA	H
039457041	GAMTEN*INFUS 1 FL 200ML 100MG/ML	20	OCTAPHARMA ITALY SPA	H
039712017	PRIVIGEN*EV 1FL 50ML 100MG/ML	5	CSL BEHRING SpA	H
039712029	PRIVIGEN*EV 1FL 100ML 100MG/ML	10	CSL BEHRING SpA	H
039712031	PRIVIGEN*EV 1FL 200ML 100MG/ML	20	CSL BEHRING SpA	H
039712043	PRIVIGEN*EV 1FL 25ML 100MG/ML	2.5	CSL BEHRING SpA	H
040267027	FLEBOGAMMA DIF*FL 50ML 50MG/ML	2.5	GRIFOLS ITALIA SpA	H
040267039	FLEBOGAMMA DIF*FL 100ML 5G	5	GRIFOLS ITALIA SpA	H
040267041	FLEBOGAMMA DIF*FL 200ML 10G	10	GRIFOLS ITALIA SpA	H
040267054	FLEBOGAMMA DIF*FL 400ML 20G	20	GRIFOLS ITALIA SpA	H
040267066	FLEBOGAMMA DIF*EV 50ML 5G	5	GRIFOLS ITALIA SpA	H
040267078	FLEBOGAMMA DIF*EV 100ML 10G	10	GRIFOLS ITALIA SpA	H
040267080	FLEBOGAMMA DIF*EV 200ML 20G	20	GRIFOLS ITALIA SpA	H
043736014	IQYMUNE*FL INFUS 20ML 100MG/ML	2	LFB	C(nn)
043736026	IQYMUNE*FL INFUS 50ML 100MG/ML	5	LFB	C(nn)
043736038	IQYMUNE*FL INFUS100ML 100MG/ML	10	LFB	C(nn)
043736040	IQYMUNE*FL INFUS200ML 100MG/ML	20	LFB	C(nn)
044187019	GLOBIGA*INF 1FL 1G 100MG/ML	1	OCTAPHARMA ITALY SPA	C(nn)
044187021	GLOBIGA*INF 1FL 2,5G 100MG/ML	2.5	OCTAPHARMA ITALY SPA	C(nn)
044187033	GLOBIGA*INF 1FL 5G 100MG/ML	5	OCTAPHARMA ITALY SPA	C(nn)
044187045	GLOBIGA*INF 1FL 6G 100MG/ML	6	OCTAPHARMA ITALY SPA	C(nn)
044187058	GLOBIGA*INF 1FL 10G 100MG/ML	10	OCTAPHARMA ITALY SPA	C(nn)

AIC code	Brand name	g	Manufacturer	NHS class
044187060	GLOBIGA*INF 3FL 10G 100MG/ML	30	OCTAPHARMA ITALY SPA	C(nn)
044187072	GLOBIGA*INF 1FL 20G 100MG/ML	20	OCTAPHARMA ITALY SPA	C(nn)
044187084	GLOBIGA*INF 3FL 20G 100MG/ML	60	OCTAPHARMA ITALY SPA	C(nn)
044187096	GLOBIGA*INF 1FL 30G 100MG/ML	30	OCTAPHARMA ITALY SPA	C(nn)

* Normal human immunoglobulins for intravenous use with high titers of IgM indicated as support therapy along with antibiotics for serious bacterial infections and as replacement therapy in immunodepressed patients.

Quantification and characterisation of the demand

Table 8 shows the total demand (expressed in grams) and the total standardised demand (in grams per 1,000 population) for IGs for the period 2016-2017 and the relative variations in percentage, at national and regional levels. The same information is reported for both SC/IM (Table 9) and IV (Table 10) preparations.

Table 8. Total demand (public and private) and total standardised demand for normal human immunoglobulins for intravenous and subcutaneous/ intramuscular use, expressed in grams and grams per 1,000 population, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	103,807	78.3	104,627	79.1	1.1
Aosta Valley	15,144	118.9	22,234	175.2	47.3
AP Bolzano	44,193	84.8	39,369	75.1	-11.5
AP Trento	35,076	65.2	32,411	60.2	-7.7
Apulia	366,461	89.9	383,616	94.4	5.0
Basilicata	34,254	59.7	32,733	57.4	-3.9
Calabria	111,584	56.6	92,110	46.9	-17.2
Campania	329,094	56.2	358,867	61.5	9.3
E.-Romagna	382,717	86.0	419,639	94.3	9.6
Friuli-V. Giulia	108,330	88.7	116,621	95.8	7.9
Latium	460,273	78.2	500,964	84.9	8.7
Liguria	167,491	106.6	169,793	108.5	1.7
Lombardy	757,076	75.6	866,654	86.5	14.4
Marche	162,733	105.4	176,179	114.5	8.7
Molise	24,644	79.0	17,652	56.9	-28.0
Piedmont	421,785	95.8	445,952	101.5	6.0
Sardinia	69,968	42.2	73,740	44.6	5.7
Sicily	262,514	51.7	309,856	61.3	18.4
Tuscany	582,697	155.6	713,238	190.6	22.5
Umbria	64,481	72.4	82,926	93.3	28.9
Veneto	442,280	90.0	445,601	90.8	0.9
ITALY	4,946,601	81.5	5,404,781	89.2	9.4

In 2017, the total national demand for IGs was 5,404,781 grams, equal to 89.2 grams per 1,000 population (Table 8). The three regions with the highest standardised demand per 1,000 population were Tuscany, Aosta Valley and Marche, with around 191, 175 and 114 grams respectively. The demand was lower in Sardinia, Calabria and Molise, where it was between 45 and 57grams per 1,000 population. The demand for these PDMPs rose sharply in the two-year

period 2016-2017 (+9.4%), especially for the SC/IM formulations (+ 23.3%), and there were notable differences from one region to another. This trend was not observed in Liguria and Veneto, whose demands were substantially stable. A significant decrease occurred in Calabria and Molise (-17.2% and -28%, respectively).

Figure 8 shows which regions tended to use more SC/IM formulations and which preferred IV ones. More SC/IM formulations were used in Calabria (24%), Umbria and Abruzzo (22%) while fewer were used in Friuli-Venezia Giulia and in the APs of Trento and Bolzano (<5%). At national level, the demand for SC/IM IGs stood at 17% of the total demand for IGs (15% in 2016).

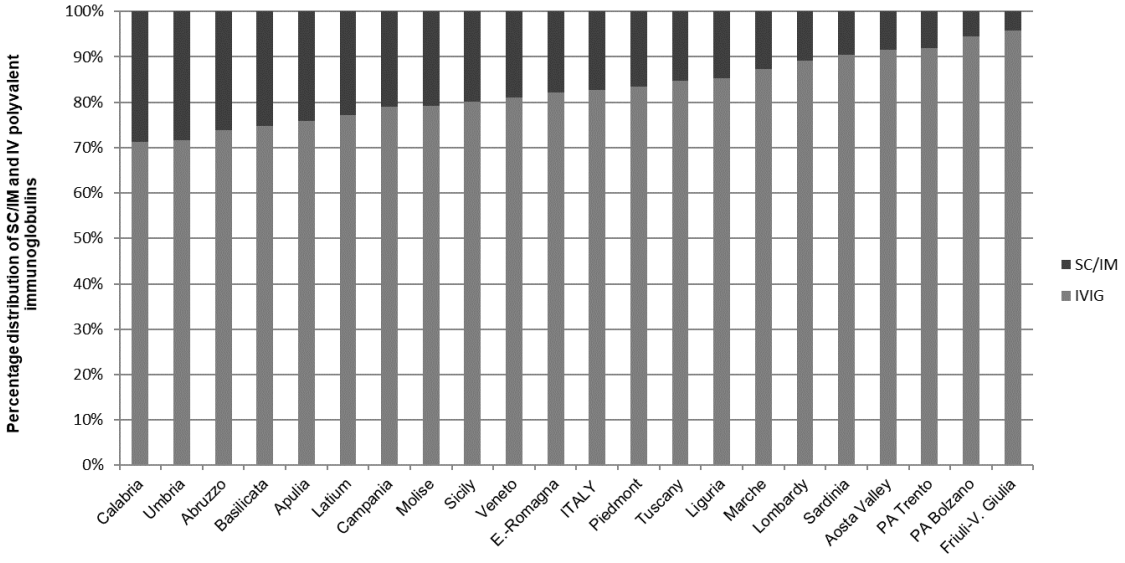

Figure 8. Total standardised demand (public and private) per administration of immunoglobulins (percentage on total), per Region, 2017 (adapted by CNS on data from the traceability information flow)

Normal human immunoglobulins for subcutaneous use

In 2017, the total demand for SC/IM IGs was about935,000 grams (15.4 grams per 1,000 population), with a 23% increase compared to 2016 (Table 9).

The regional demands were diversified and the highest values, 29.2, 26.4 and 22.8 grams per 1,000 population were recorded in Tuscany, Umbria and Apulia.

The lowest values were recorded in AP of Bolzano and Friuli-Venezia Giulia and were equal to 4.2 and 4.0 respectively (Figure 9).

In Abruzzo, Apulia, Emilia-Romagna, Latium, Liguria, Piedmont, Tuscany, Umbria and Veneto, a higher total demand compared to national demand was recorded (range: 3-89%) (Figure 10).

Table 9. Total demand (public and private) and total standardised demand for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams and grams per 1,000 population, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	20,960	15.8	27,292	20.6	30.6
Aosta Valley	1,764	13.9	1,864	14.7	6.0
AP Bolzano	3,305	6.3	2,185	4.2	-34.3
AP Trento	1,826	3.4	2,623	4.9	43.5
Apulia	87,076	21.4	92,705	22.8	6.8
Basilicata	6,580	11.5	8,233	14.4	25.9
Calabria	25,020	12.7	26,410	13.4	5.8
Campania	66,945	11.4	75,613	12.9	13.2
E.-Romagna	53,619	12.1	74,503	16.7	38.9
Friuli-V. Giulia	5,083	4.2	4,851	4.0	-4.3
Latium	74,567	12.7	114,316	19.4	53.1
Liguria	15,682	10.0	24,977	16.0	59.9
Lombardy	81,303	8.1	94,287	9.4	15.8
Marche	21,056	13.6	22,304	14.5	6.3
Molise	2,584	8.3	3,682	11.9	43.2
Piedmont	64,465	14.6	73,413	16.7	14.2
Sardinia	9,373	5.7	7,042	4.3	-24.6
Sicily	45,355	8.9	61,503	12.2	36.1
Tuscany	85,881	22.9	109,336	29.2	27.4
Umbria	14,156	15.9	23,445	26.4	66.0
Veneto	72,872	14.8	84,413	17.2	16.0
ITALY	759,473	12.5	934,996	15.4	23.3

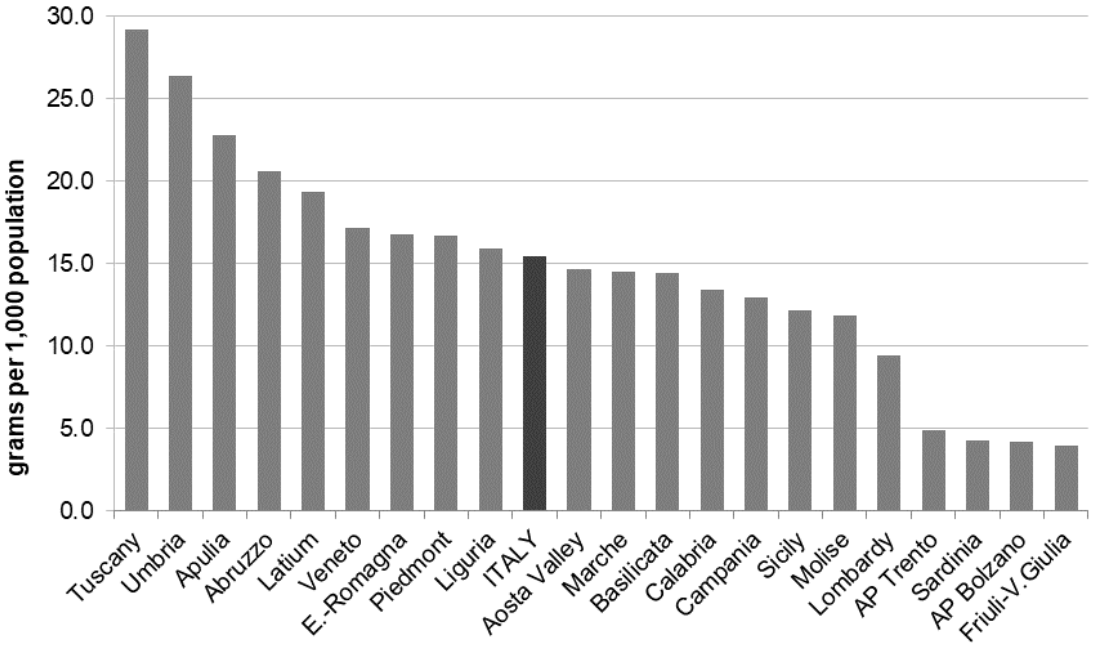

Figure 9. Total and regional demand (public and private) for normal human immunoglobulins for subcutaneous/ intramuscular use, expressed in grams per 1,000 population, 2017 (adapted by the CNS on data from the traceability information flow)

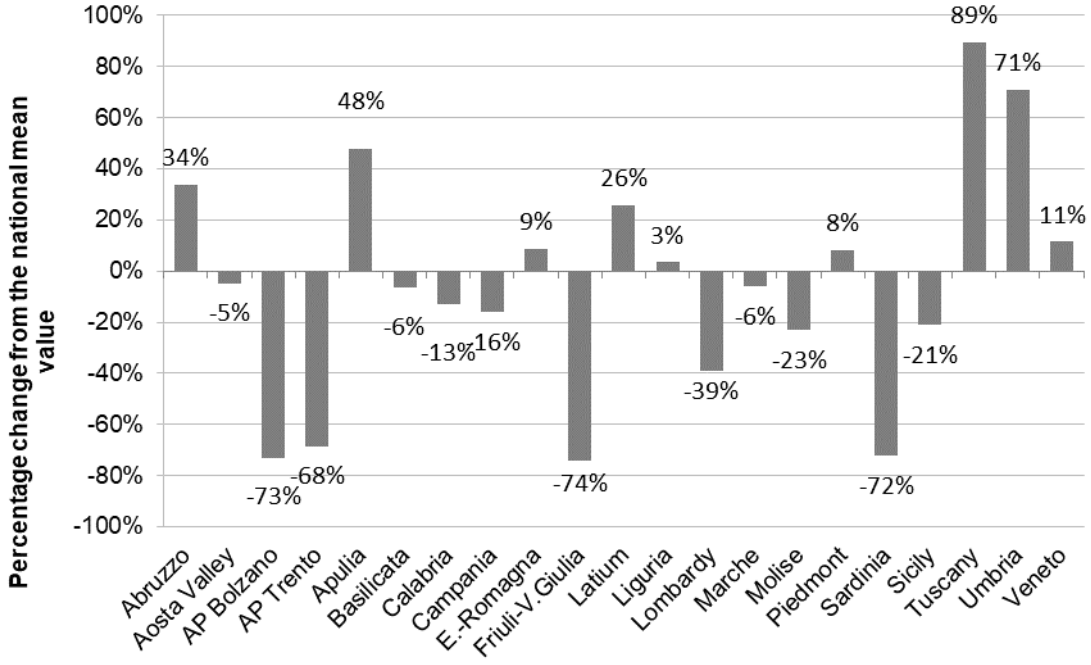

Figure 10. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for subcutaneous/ intramuscular use in 2017 (adapted by the CNS on data from the traceability information flow)

Normal human immunoglobulins for intravenous use

Finally, in Table 10, the total and standardised demands for IG for intravenous use in 2016-2017 are reported.

Also, in this case, a general upward trend (about + 6.9 %) was observed which however was not confirmed in Abruzzo, the AP of Bolzano, the AP of Trento, Basilicata, Calabria, Liguria, Molise and Veneto. Nonetheless, in three of these regions (Calabria, Abruzzo and Umbria) it is likely SC/IM preparations were preferred to IV preparations.

Figure 11 shows the standardised regional demand for IVIGs in 2017 as registered by the drug traceability system.

The highest demand for IVIGs was recorded in Tuscany, Aosta Valley, Marche and Liguria with volumes ranging between 92 and 161 grams per 1,000 population (respectively +119, +118, +36 and +25% compared to the national mean value) (Figure 12). The lowest standardised demand was observed in Calabria, Sardinia, Basilicata and Molise, with volumes of between 33 and 45 grams per 1,000 population.

Table 10. Total demand (public and private) and total standardised demand for normal human immunoglobulins for intravenous use, expressed in grams and grams per 1,000 population, and variations in percentage between 2016-2017 (adapted by CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	82,847	62.5	77,335	58.5	-6.4
Aosta Valley	13,380	105.1	20,370	160.5	52.8
AP Bolzano	40,888	78.5	37,184	70.9	-9.6
AP Trento	33,250	61.8	29,788	55.3	-10.5
Apulia	279,384	68.5	290,911	71.6	4.5
Basilicata	27,674	48.2	24,500	43.0	-11.0
Calabria	86,564	43.9	65,700	33.4	-23.9
Campania	262,148	44.8	283,254	48.5	8.3
E.-Romagna	329,098	74.0	345,136	77.6	4.9
Friuli-V. Giulia	103,248	84.5	111,770	91.8	8.6
Latium	385,706	65.5	386,649	65.6	0.1
Liguria	151,810	96.6	144,816	92.5	-4.3
Lombardy	675,773	67.5	772,367	77.1	14.2
Marche	141,678	91.8	153,875	100.0	9.0
Molise	22,060	70.7	13,970	45.0	-36.4
Piedmont	357,321	81.1	372,539	84.8	4.5
Sardinia	60,595	36.5	66,698	40.3	10.4
Sicily	217,159	42.8	248,354	49.1	14.8
Tuscany	496,816	132.7	603,902	161.4	21.6
Umbria	50,325	56.5	59,481	66.9	18.5
Veneto	369,408	75.2	361,188	73.6	-2.1
ITALY	4,187,128	69.0	4,469,785	73.8	6.9

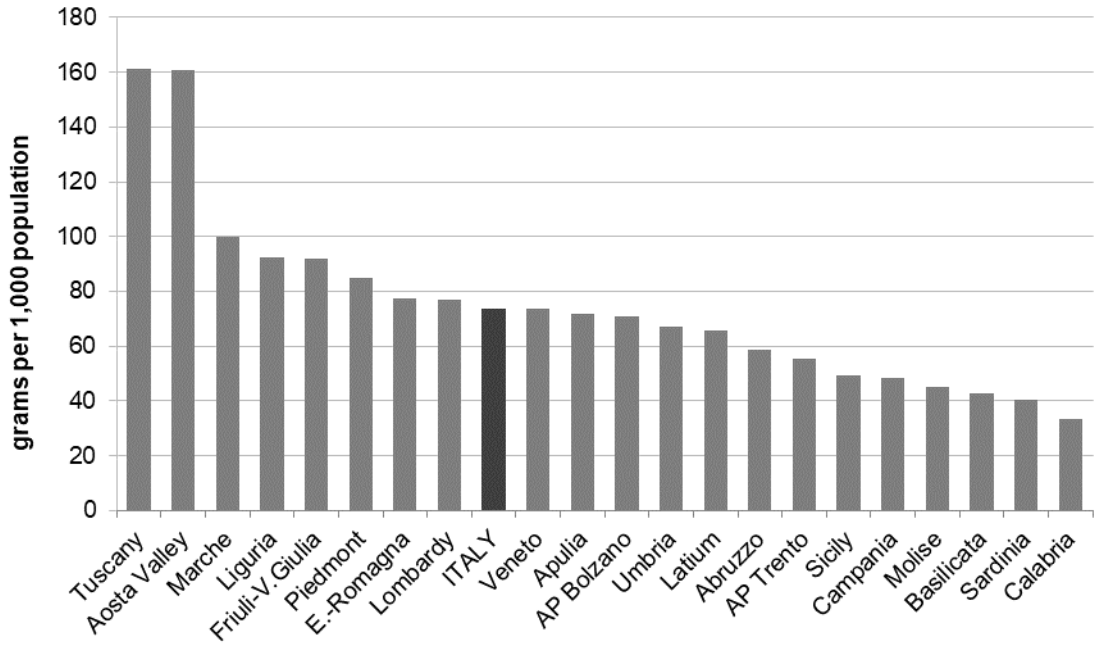

Figure 11. Total and regional demand (public and private) for normal human immunoglobulins for intravenous use, expressed in grams per 1,000 population, 2017 (adapted by the CNS on data from the traceability information flow)

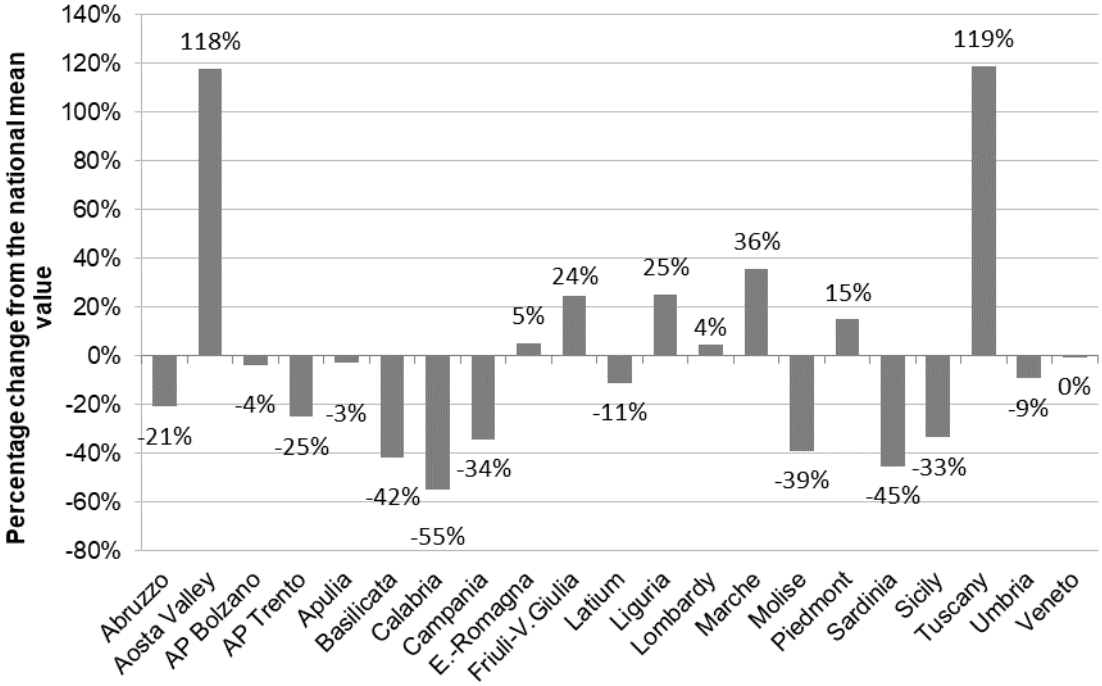

Figure 12. Percentage change from the national mean value of standardised regional demand for normal human immunoglobulins for intravenous use in 2017 (adapted by the CNS on data from the traceability information flow)

ANTITHROMBIN (ATC B01AB02)

Antithrombin (AT) is a hepatic synthesised glycoprotein present in plasma at a concentration of about 150 μg / mL (19). It is a protease inhibitor, belonging to the serpentine family or serine protease inhibitors. It is the most powerful natural coagulation inhibitor and plays a key role in haemostatic balance. It inhibits the action of all activated coagulation factors, except for FV and FVIII; it has a particular affinity for thrombin and is also called heparin cofactor, as the anticoagulant action of heparin is mediated by AT. It also has anti-inflammatory and anti-aggregating properties mediated by the release of prostacyclines by endothelial cells (20, 21).

Table 11 shows the names of AT drugs currently on the market in Italy and the relative quantity of active substance they contain measured in International Units (IUs).

Table 11. Products containing antithrombin currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
025766039	KYBERNIN P*IV FL 500UI+10ML+SE	500	CSL BEHRING SpA	H
027113012	ANTITROMBINA III IMMUNO*FL10ML	500	BAXALTA ITALY Srl	H
029378015	AT III KED*500UI+FL 10ML+SET	500	KEDRION SpA	H
031118019	ATENATIV*IV FL 500UI+FL 10ML	500	OCTAPHARMA ITALY SPA	H
034330035	ANBINEX*FL 500UI+SIR 10ML+SET	500	GRIFOLS ITALIA SpA	H
041800018	ATKED*FL 500UI+FL 20ML+SET	500	KEDRION SpA	H
044565012	ATTERTIUM FL 500UI+SIR 10ML	500	GRIFOLS ITALIA SpA	C(nn)
025766027	KYBERNIN P*IV FL 1000UI+F 20ML	1000	CSL BEHRING SpA	H
027113024	ANTITROMBINA III IMMUNO*FL20ML	1000	BAXALTA ITALY Srl	H
029378027	AT III KED*1000UI+FL 20ML+SET	1000	KEDRION SpA	H
031118021	ATENATIV*IV FL 1000UI+FL 20ML	1000	OCTAPHARMA ITALY SPA	H
034330047	ANBINEX*FL 1000UI+SIR 20ML+SET	1000	GRIFOLS ITALIA SpA	H
041800020	ATKED*FL 1000UI+FL 20ML+SET	1000	KEDRION SpA	H
044565024	ATTERTIUM FL 1000UI+SIR 20ML	1000	GRIFOLS ITALIA SpA	C(nn)
029378039	AT III KED*2000UI+FL 20ML+SET	2000	KEDRION SpA	H
041800032	ATKED*FL 2000UI+FL 20ML+SET	2000	KEDRION SpA	H

Quantification and characterisation of the demand

Table 12 shows the total demand (expressed in IUs) and the total standardised demand (expressed in IUs *per capita*) of AT for the two-year period 2016-2017 with the relative percentage changes at national and at regional levels.

In 2017, total AT demand was 119,019,500 IUs, equal to 2 IUs *per capita*, confirming a stable trend in utilisation compared to the previous years. However, in eight regions there was a significant upward trend in use [range: Aosta Valley (+82.1%), Latium (+2.1)]. The region in which the biggest drop in the use of AT was observed was the AP of Bolzano (-62.3%).

Figure 13 shows the regional and national standardised demand for AT in 2017. The regions with the highest *per capita* demand were Calabria, Molise, Sicilia and Latium, with a demand of 4.1 IUs for the first, 3.8 IUs for the second, 3.4 IUs for the third and 3.2 IUs for the fourth region.

The lowest demand, between 0.3 and 0.8 IU *per capita*, was recorded in the AP of Trento, the AP of Bolzano, in Emilia-Romagna and in Umbria.

Table 12. Total demand (public and private) and total standardised demand for antithrombin, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU*per capita*	IU	IU *per capita*	
Abruzzo	1,571,000	1.2	1,545,500	1.2	-1.3
Aosta Valley	183,000	1.4	332,000	2.6	82.1
AP Bolzano	532,000	1.0	202,000	0.4	-62.3
APTrento	123,000	0.2	181,000	0.3	47.1
Apulia	8,130,000	2.0	7,901,500	1.9	-2.5
Basilicata	1,356,500	2.4	1,247,000	2.2	-7.5
Calabria	8,342,000	4.2	8,056,500	4.1	-3.2
Campania	18,539,500	3.2	17,307,500	3.0	-6.5
E.-Romagna	2,731,500	0.6	2,351,000	0.5	-13.9
Friuli-V. Giulia	2,826,000	2.3	3,095,000	2.5	9.8
Latium	18,707,000	3.2	19,128,000	3.2	2.1
Liguria	2,936,500	1.9	2,170,500	1.4	-25.8
Lombardy	10,887,000	1.1	10,721,500	1.1	-1.6
Marche	2,062,000	1.3	2,227,000	1.4	8.4
Molise	1,305,000	4.2	1,194,000	3.8	-8.0
Piedmont	7,433,500	1.7	7,597,500	1.7	2.5
Sardinia	2,815,500	1.7	2,700,500	1.6	-3.8
Sicily	15,216,500	3.0	17,434,000	3.4	15.0
Tuscany	7,052,000	1.9	7,454,000	2.0	5.8
Umbria	692,000	0.8	714,000	0.8	3.4
Veneto	5,770,500	1.2	5,459,500	1.1	-5.2
ITALY	119,212,000	2.0	119,019,500	2.0	0.0

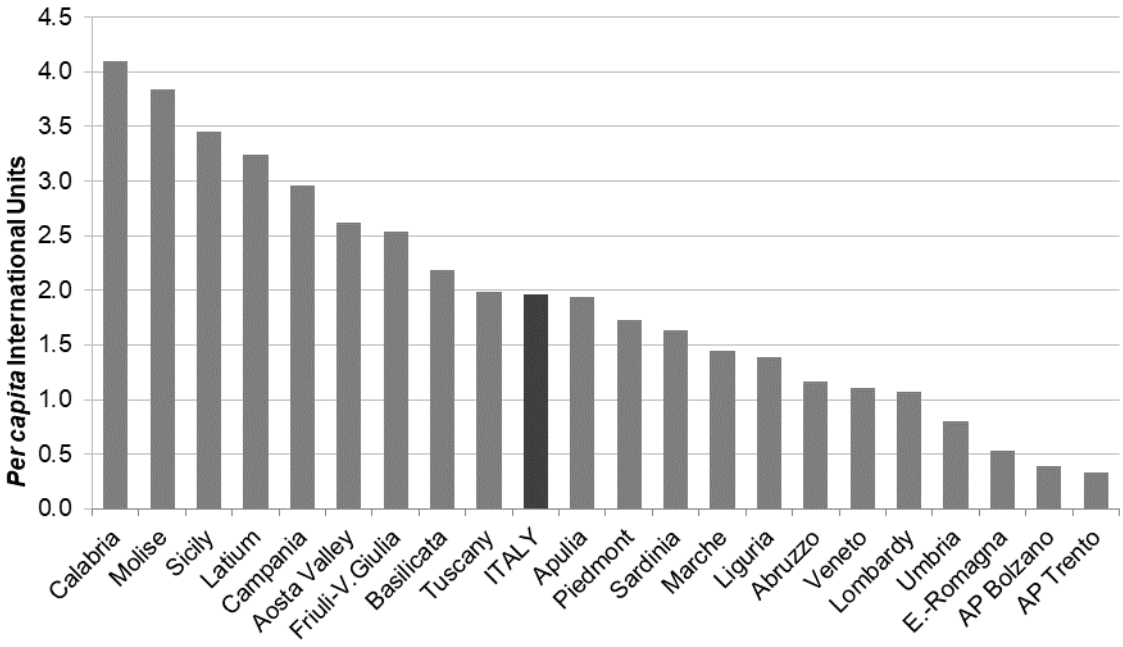

Figure 13. Total and regional demand (public and private) for antithrombin, expressed in International Units *per capita*, 2017 (adapted by the Italian National Blood Centre on data from the traceability information flow)

Figure 14 shows the difference between the regional *per capita* percentage and the national mean value for the year 2017.

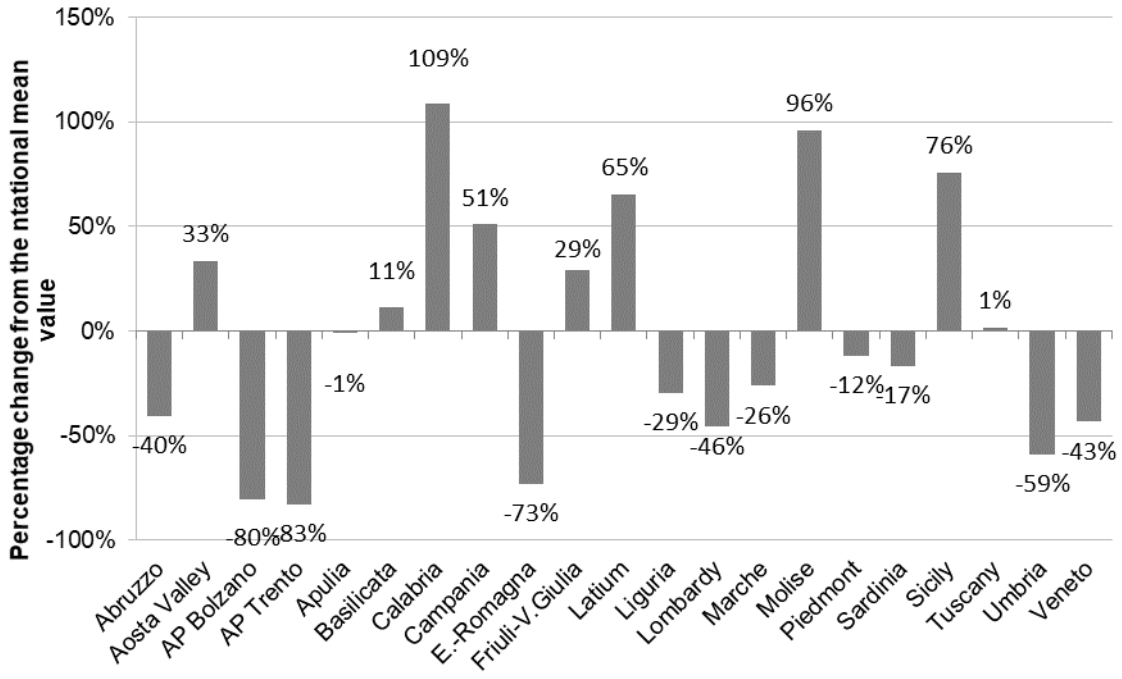

Figure 14. Percentage change from the national mean value of standardised regional demand for antithrombin in 2017 (adapted by the CNS on data from the traceability information flow)

COAGULATION FACTOR VIII (ATC B02BD02), COAGULATION FACTOR VIII AND VON WILLEBRAND FACTOR IN COMBINATION (ATC B02BD06), VON WILLEBRAND FACTOR (ATC B02BD10) AND RECOMBINANT FACTOR VIII (ATC B02BD02)

Coagulation FVIII is used in the replacement therapy of haemophilia A, a rare, haemorrhagic, hereditary, x-linked or acquired recessive disorder caused by FVIII deficiency. Depending on the level of activity of the circulating FVIII, there are severe forms of haemophilia A (FVIII <1%), moderate (between 1 and 5%) and mild (>5%) (22).

Products containing FVIII are subdivided in plasma-derived concentrates (pdFVIII) and products obtained with genetic recombination techniques (rFVIII) (23). pdFVIII concentrates are obtained from plasma pools of thousands of donors. FVIII is initially separated from the plasma by cold precipitation (cryoprecipitation) and then further purified with different techniques such as ion exchange and affinity chromatography (24). The number of FVIII units administered is expressed in IUs, according to the current international WHO standards (25) for human FVIII concentrates. One IU is equivalent to the amount of FVIII in 1 millilitre (mL) of normal human plasma. The calculation of the required dosage is based on empirical evidence that 1 IU of FVIII per kilogram of body weight increases the plasma activity of FVIII by 2.1 ± 0.4% of normal activity.

Many of the pdFVIII concentrates also contain von Willebrand factor (vWF) with a different ratio compared to the FVIII content: following clinical trials supporting their efficacy, some of these drugs were approved for both the treatment of haemophilia and of von Willebrand disease (26).

The recombinant products obtained with genetic engineering techniques became part of clinical practice in Italy in the 1990s. The recombinant protein is synthesised by inserting the regions encoding the human FVIII gene in Chinese hamster ovary cells (CHO) or in newborn hamster kidney cells (BHK) (23).

Tables 13-15 show the brand names of the preparations containing both plasma-derived and recombinant FVIII currently on the market in Italy and the relative amount of active ingredient contained expressed in IUs.

Table 13. Products containing plasma-derived coagulation factor VIII currently available on the Italian market (adapted by CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
Plasma-derived coagulation factor VIII				
038541013	HAEMOCTIN*FL 250UI+FL 5ML+SIR	250	BIOTEST PHARMA GMBH	A
038541025	HAEMOCTIN*FL 500UI+FL 10ML+SIR	500	BIOTEST PHARMA GMBH	A
038541037	HAEMOCTIN*FL 1000UI+FL 10ML+SI	1000	BIOTEST PHARMA GMBH	A
Lyophilised plasma-derived coagulation factor VIII				
033657014	BERIATE*F 250UI+SOLV+SET	250	CSL BEHRING SpA	A
023564216	EMOCLOT*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
033657026	BERIATE*F 500UI+SOLV+SET	500	CSL BEHRING SpA	A
041649017	KLOTT*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
023564228	EMOCLOT*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
033657038	BERIATE*F 1000UI+SOLV+S	1000	CSL BEHRING SpA	A
041649029	KLOTT*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
033657040	BERIATE*FL 2000UI+FL 10ML	2000	CSL BEHRING SpA	A

Table 14. Products containing plasma-derived coagulation factor VIII and von Willebrand factor in combination currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
033077088	ALPHANATE*INF 1F 250UI+SIR+AD	250	GRIFOLS ITALIA SpA	A
040112017	OCTANATE*INIET FL 250UI+FL 5ML	250	OCTAPHARMA ITALY SpA	A
042939013	VONCENTO*250UI/600UI+FL 5ML	250	CSL BEHRING SpA	C(nn)
044564019	PLITATE*INF FL 250UI+SIR SOLV+SET	250	GRIFOLS ITALIA SpA	C(nn)
023308152	EMOWIL*1F 500UI+F 10ML	500	KEDRION SpA	A
026600080	HAEMATEP*FL 500UI+FL 10ML+SET	500	CSL BEHRING SpA	A
033077090	ALPHANATE*INF 1F 500UI+SIR+AD	500	GRIFOLS ITALIA SpA	A
033866056	FANHDI*INF FL 500UI+SIR SOLV+S	500	GRIFOLS ITALIA SpA	A
039385036	WILATE*FL 500+500UI+FL 5ML+SIR	500	OCTAPHARMA ITALY SpA	A
040112029	OCTANATE*INIET FL 500UI+FL 10ML	500	OCTAPHARMA ITALY SpA	A
040112056	OCTANATE*INIET FL 5ML100UI/ML	500	OCTAPHARMA ITALY SpA	A
042939025	VONCENTO*500UI/1200UI+FL 10ML	500	CSL BEHRING SpA	C(nn)
042939037	VONCENTO*500UI/1200UI+FL 5ML	500	CSL BEHRING SpA	C(nn)
044564021	PLITATE*INF FL 500UI+SIR SOLV+SET	500	GRIFOLS ITALIA SpA	C(nn)
023308188	EMOWIL*1F 1000UI+F 10ML	1000	KEDRION SpA	A
026600078	HAEMATEP*FL 1000UI+FL 15ML+SET	1000	CSL BEHRING SpA	A
033077102	ALPHANATE*INF 1F 1000UI+SIR+AD	1000	GRIFOLS ITALIA SpA	A
033866068	FANHDI*INF FL 1000UI+SIR SOLV+S	1000	GRIFOLS ITALIA SpA	A
037148032	TALATE*1000UI/750UI+FL10ML+SIR	1000	BAXALTA ITALY Srl	A
037392014	WILFACTIN*1000UI+FL 10ML	1000	LFB	C
039385024	WILATE*FL 900+800UI+FL 10ML+SIR	1000	OCTAPHARMA ITALY SpA	A
039385048	WILATE*FL 1000+1000UI+FL 10ML+SI	1000	OCTAPHARMA ITALY SpA	A
040112031	OCTANATE*INIET FL 1000UI+FL 10ML	1000	OCTAPHARMA ITALY SpA	A
040112068	OCTANATE*INIET FL 5ML 200UI/ML	1000	OCTAPHARMA ITALY SpA	A
042939049	VONCENTO*1000UI/2400UI+FL 10ML	1000	CSL BEHRING SpA	C(nn)
044564033	PLITATE*INF FL1000UI+SIR SOLV+SET	1000	GRIFOLS ITALIA SpA	C(nn)
033077114	ALPHANATE*INF 1F 1500UI+SIR+AD	1500	GRIFOLS ITALIA SpA	A
033866070	FANHDI*INF FL1500UI+SIR SOLV+S	1500	GRIFOLS ITALIASpA	A
044564045	PLITATE*INF FL1500UI+SIR SOLV+SET	1500	GRIFOLS ITALIA SpA	C(nn)

Table 15. Products containing recombinant coagulation factor VIII factor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
028687010	RECOMBINATE*FL 250UI+FL 10ML	250	BAXALTA ITALY Srl	A
028687046	RECOMBINATE*FL 250UI+FL 5ML	250	BAXALTA ITALY Srl	A
028687073	RECOMBINATE*FL 250UI+FL 5ML	250	BAXALTA ITALY Srl	A
028687109	RECOMBINATE*FL 250UI+FL 10ML	250	BAXALTA ITALY Srl	A
034421014	REFACTOAF*IV 1FL 250UI+SIR 4ML	250	PFIZER ITALIA Srl	A
034421091	REFACTOAF*IV 1SIR PRER 250UI	250	PFIZER ITALIA Srl	A
034955017	KOGENATE BAYER*250UI+1FL+1KI	250	BAYER SpA	A
034955043	KOGENATE BAYER*FL 250UI+SIR+1KI	250	BAYER SpA	A
034955070	KOGENATE BAYER*EV 250UI+SIR	250	BAYER SpA	A
034956019	HELIXATE NEXGEN*250UI+1FL+1KIT	250	CSL BEHRING SpA	A
036160012	ADVATE*FL 250UI+FL SOLV 5ML	250	BAXTER SpA	A
036160113	ADVATE*FL 250UI+FL SOLV 5ML	250	BAXALTA ITALY Srl	A
036160176	ADVATE*FL 250UI+FL SOLV 2ML	250	BAXALTA ITALY Srl	A
043153016	NOVOEIGHT*EV FL 250UI+SIR 4ML	250	NOVO NORDISK SpA	A
043534015	NUWIQ*EV FL 250UI+SIR 2,5ML	250	KEDRION SpA	A
044563017	ELOCTA*IV 1FL 250UI+SIR PRERI	250	SOBI Srl	A
044725012	IBLIAS*FL POLV EV 250UI+FL 2,5ML	250	BAYER SpA	C(nn)
044726014	KOVALTRY*1FL POLV EV 250UI+SOLV	250	BAYER SpA	A
044726026	KOVALTRY*1FL POLV EV 250UI+SOLV	250	BAYER SpA	A
045255015	AFSTYLA 250UI+FL SOLV 2,5ML+SIR	250	CSL BEHRING GmbH	A
045273012	VIHUMA*EV 250UI+FL SOLV 2,5ML+SIR	250	OCTAPHARMA AB	C(nn)

AIC code	Brand name	IU	Manufacturer	NHS class
028687022	RECOMBINATE*FL 500UI+FL 10ML	500	BAXALTA ITALY Srl	A
028687059	RECOMBINATE*FL 500UI+FL 5ML	500	BAXALTA ITALY Srl	A
028687085	RECOMBINATE*FL 500UI+FL 5ML	500	BAXALTA ITALY Srl	A
028687111	RECOMBINATE*FL 500UI+FL 10ML	500	BAXALTA ITALY Srl	A
034421026	REFACTOAF*IV 1FL 500UI+SIR 4ML	500	PFIZER ITALIA Srl	A
034421065	REFACTOAF*IV 1SIR PRER 500UI	500	PFIZER ITALIA Srl	A
034955029	KOGENATE BAYER*500UI+1FL+1KIT	500	BAYER SpA	A
034955056	KOGENATE BAYER*FL 500UI+SIR+1KIT	500	BAYER SpA	A
034955082	KOGENATE BAYER*EV 500UI+SIR	500	BAYER SpA	A
034956021	HELIXATE NEXGEN*500UI+1FL+1KIT	500	CSL BEHRING SpA	A
036160024	ADVATE*FL 500UI+FL SOLV 5ML	500	BAXTER SpA	A
036160125	ADVATE*FL 500UI+FL SOLV 5ML	500	BAXALTA ITALY Srl	A
036160188	ADVATE*FL 500UI+FL SOLV 2ML	500	BAXALTA ITALY Srl	A
043153028	NOVOEIGHT*EV FL 500UI+SIR 4ML	500	NOVO NORDISK SpA	A
043534027	NUWIQ*EV FL 500UI+SIR 2,5ML	500	KEDRION SpA	A
044563029	ELOCTA*IV 1FL 500UI+SIR PRERI	500	SOBI Srl	A
044725024	IBLIAS*FL POLV EV 500UI+FL 2,5ML	500	BAYER SpA	C(nn)
044726038	KOVALTRY*1FL POLV EV 500UI+SOLV	500	BAYER SpA	A
044726040	KOVALTRY*1FL POLV EV 500UI+SOLV	500	BAYER SpA	A
045255027	AFSTYLA 500UI+FL SOLV 2,5ML+SIR	500	CSL BEHRING GmbH	A
045273024	VIHUMA*EV 500UI+FL SOLV 2,5ML+SIR	500	OCTAPHARMA AB	C(nn)
044563031	ELOCTA*IV 1FL 750UI+SIR PRERI	750	SOBI Srl	A
028687034	RECOMBINATE*FL 1000UI+FL 10ML	1000	BAXALTA ITALY Srl	A
028687061	RECOMBINATE*FL 1000UI+FL 5ML	1000	BAXALTA ITALY Srl	A
028687097	RECOMBINATE*FL 1000UI+FL 5ML	1000	BAXALTA ITALY Srl	A
028687123	RECOMBINATE*FL 1000UI+FL 10ML	1000	BAXALTA ITALY Srl	A
034421038	REFACTO AF*IV 1FL 1000UI+SIR 4ML	1000	PFIZER ITALIA Srl	A
034421077	REFACTO AF*IV 1SIR PRER 1000UI	1000	PFIZER ITALIA Srl	A
034955031	KOGENATE BAYER*1000UI+1FL+1KIT	1000	BAYER SpA	A
034955068	KOGENATE BAYER*FL 1000UI+SIR+1KIT	1000	BAYER SpA	A
034955094	KOGENATE BAYER*EV 1000UI+SIR	1000	BAYER SpA	A
034956033	HELIXATE NEXGEN*1000UI+1FL+KIT	1000	CSL BEHRING SpA	A
036160036	ADVATE*FL 1000UI+FL SOLV 5ML	1000	BAXTER SpA	A
036160137	ADVATE*FL 1000UI+FL SOLV 5ML	1000	BAXALTA ITALY Srl	A
036160190	ADVATE*FL 1000UI+FL SOLV 2ML	1000	BAXALTA ITALY Srl	A
043153030	NOVOEIGHT*EV FL 1000UI+SIR 4ML	1000	NOVO NORDISK SpA	A
043534039	NUWIQ*EV FL 1000UI+SIR 2,5ML	1000	KEDRION SpA	A
044563056	ELOCTA*IV 1FL 1000UI+SIR PRERI	1000	SOBI Srl	A
044725036	IBLIAS*FL POLV EV 1000UI+2,5 ML	1000	BAYER SpA	C(nn)
044726053	KOVALTRY*FL POLV EV 1000UI+SOLV	1000	BAYER SpA	A
044726065	KOVALTRY*FL POLV EV 1000UI+SOLV	1000	BAYER SpA	A
045255039	AFSTYLA 1000UI+FL SOLV 2,5ML+SIR	1000	CSL BEHRING GmbH	A
045273036	VIHUMA*EV 1000UI+FL SOLV 2,5ML+SIR	1000	OCTAPHARMA AB	C(nn)
036160048	ADVATE*FL 1500UI+FL SOLV 5ML	1500	BAXTER SpA	A
036160149	ADVATE*FL 1500UI+FL SOLV 5ML	1500	BAXALTA ITALY Srl	A
036160202	ADVATE*FL 1500UI+FL SOLV 2ML	1500	BAXALTA ITALY Srl	A
043153042	NOVOEIGHT*EV FL 1500UI+SIR 4ML	1500	NOVO NORDISK SpA	A
044563068	ELOCTA*IV 1FL 1500UI+SIR PRERI	1500	SOBI Srl	A
045255041	AFSTYLA 1500UI+FL SOLV 2,5ML+SIR	1500	CSL BEHRING GmbH	A
034421040	REFACTOAF*IV 1FL 2000UI+SIR 4ML	2000	PFIZER ITALIA Srl	A
034421089	REFACTOAF*IV 1SIR PRER 2000UI	2000	PFIZER ITALIA Srl	A
034955106	KOGENATE BAYER*EV 2000UI+SIR+DI	2000	BAYER SpA	A
034955118	KOGENATE BAYER*EV 2000UI+SIR	2000	BAYER SpA	A
034956045	HELIXATE NEXGEN*2000UI+1FL+KIT	2000	CSL BEHRING SpA	A
036160051	ADVATE*FL 2000UI+FL SOLV 5ML	2000	BAXTER SpA	A
036160152	ADVATE*FL 2000UI+FL SOLV 5ML	2000	BAXALTA ITALY Srl	A
043153055	NOVOEIGHT*EV FL 2000UI+SIR 4ML	2000	NOVO NORDISK SpA	A
043534041	NUWIQ*EV FL 2000UI+SIR 2,5ML	2000	KEDRION SpA	A
044563070	ELOCTA*IV 1FL 2000UI+SIR PRERI	2000	SOBI Srl	A

AIC code	Brand name	IU	Manufacturer	NHS class
044725048	IBLIAS*FL POLV EV 2000UI+FL 5ML	2000	BAYER SpA	C(nn)
044726077	KOVALTRY*FL POLV EV 2000UI+SOLV	2000	BAYER SpA	A
044726089	KOVALTRY*FL POLV EV 2000UI+SOLV	2000	BAYER SpA	A
045255054	AFSTYLA 2000UI+FL SOLV 2,5ML+SIR	2000	CSL BEHRING GmbH	A
045273048	VIHUMA*EV 2000UI+FL SOLV 2,5ML+SIR	2000	OCTAPHARMA AB	C(nn)
045255066	AFSTYLA 2500UI+FL SOLV 2,5ML+SIR	2500	CSL BEHRING GmbH	A
034421053	REFACTO AF*IV 1SIR PRER 3000UI	3000	PFIZER ITALIA Srl	A
034955120	KOGENATE BAYER*EV 3000UI+SIR+DI	3000	BAYER SpA	A
034955132	KOGENATE BAYER*EV 3000UI+SIR+AD	3000	BAYER SpA	A
034956058	HELIXATE NEXGEN*3000UI+1FL+KIT	3000	CSL BEHRING SpA	A
036160063	ADVATE*FL 3000UI+FL SOLV 5ML	3000	BAXTER SpA	A
036160164	ADVATE*FL 3000UI+FL SOLV 5ML	3000	BAXALTA ITALY Srl	A
043153067	NOVOEIGHT*EV FL 3000UI+SIR 4ML	3000	NOVO NORDISK SpA	A
044563082	ELOCTA*IV 1FL 3000UI+SIR PRERI	3000	SOBI Srl	A
044725051	IBLIAS*FL POLV EV 3000UI+FL 5ML	3000	BAYER SpA	C(nn)
044726091	KOVALTRY*FL POLV EV 3000UI+SOLV	3000	BAYER SpA	A
044726103	KOVALTRY*FL POLV EV 3000UI+SOLV	3000	BAYER SpA	A
045255078	AFSTYLA 3000UI+FL SOLV 2,5ML+SIR	3000	CSL BEHRING GmbH	A

Quantification and characterisation of demand

In Italy, the total demand for both plasma-derived and recombinant formulations FVIII, was equal to 589,239,500 IUs in 2017 (Table 16); of these, about a quarter (22.4 % of the total - 132,033,500 IUs) were human plasma-derived (Figure 15).

Table 16. Total demand (public and private) and total standardised demand for coagulation factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017(adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	10,167,500	7.7	11,281,000	8.5	11.3
Aosta Valley	521,000	4.1	1,044,000	8.2	101.1
AP Bolzano	3,112,500	6.0	3,638,750	6.9	16.2
AP Trento	3,230,000	6.0	2,656,000	4.9	-17.8
Apulia	46,320,000	11.4	46,748,250	11.5	1.3
Basilicata	4,389,250	7.7	4,382,000	7.7	0.4
Calabria	19,636,750	10.0	21,691,750	11.0	10.8
Campania	67,114,750	11.5	69,642,250	11.9	4.0
E.-Romagna	37,327,750	8.4	34,958,500	7.9	-6.4
Friuli-V. Giulia	10,783,500	8.8	11,053,000	9.1	2.8
Latium	83,638,000	14.2	91,786,750	15.6	9.6
Liguria	9,733,500	6.2	11,318,000	7.2	16.7
Lombardy	80,509,000	8.0	79,375,250	7.9	-1.5
Marche	11,032,500	7.1	11,258,500	7.3	2.4
Molise	2,211,000	7.1	2,943,000	9.5	33.8
Piedmont	46,229,250	10.5	49,602,000	11.3	7.6
Sardinia	12,201,500	7.4	11,681,750	7.1	-4.0
Sicily	49,891,750	9.8	54,077,750	10.7	8.8
Tuscany	27,660,500	7.4	24,302,000	6.5	-12.1
Umbria	7,120,500	8.0	7,727,000	8.7	8.8
Veneto	34,049,500	6.9	38,072,000	7.8	12.0
ITALY	566,882,016	9.3	589,239,500	9.7	4.1

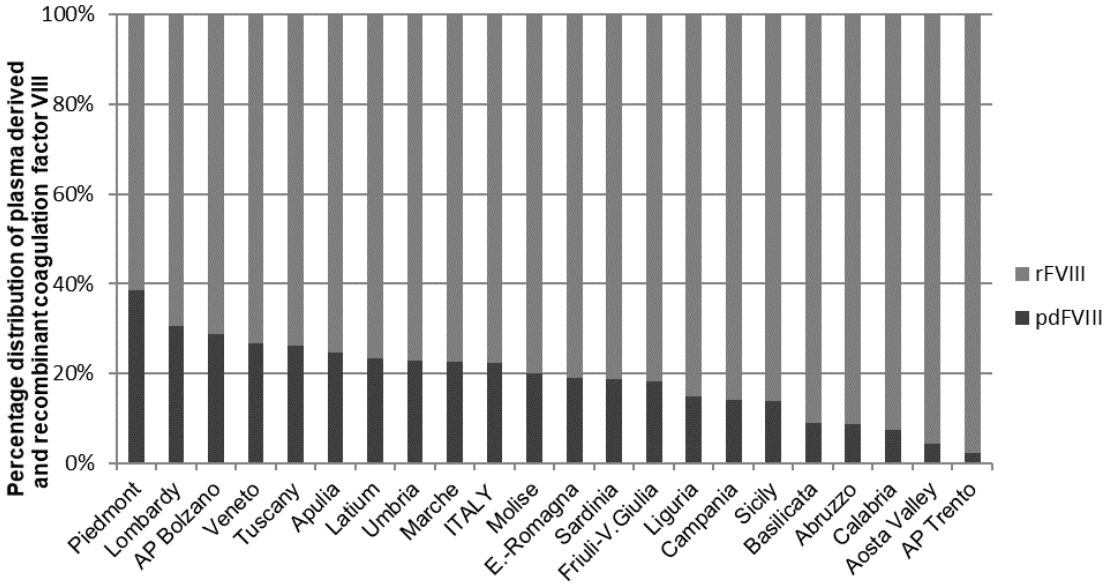

Figure 15. Percentage distribution of plasma-derived and recombinant coagulation factor VIII, per Region, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

The tendency to use pdFVIII varied significantly from one region to another ranging from 2.3% in the AP of Trento to 38.5% in Piedmont. In 2017, the total FVIII demand *per capita* (plasma-derived and recombinant) was 9.7 IUs with an increase of 4.1% compared to 2016. The regional *per capita* demand shows significant fluctuations ranging from about 4.9 IUs in the AP of Trento to about 16 IUs in Latium (Figure 16).

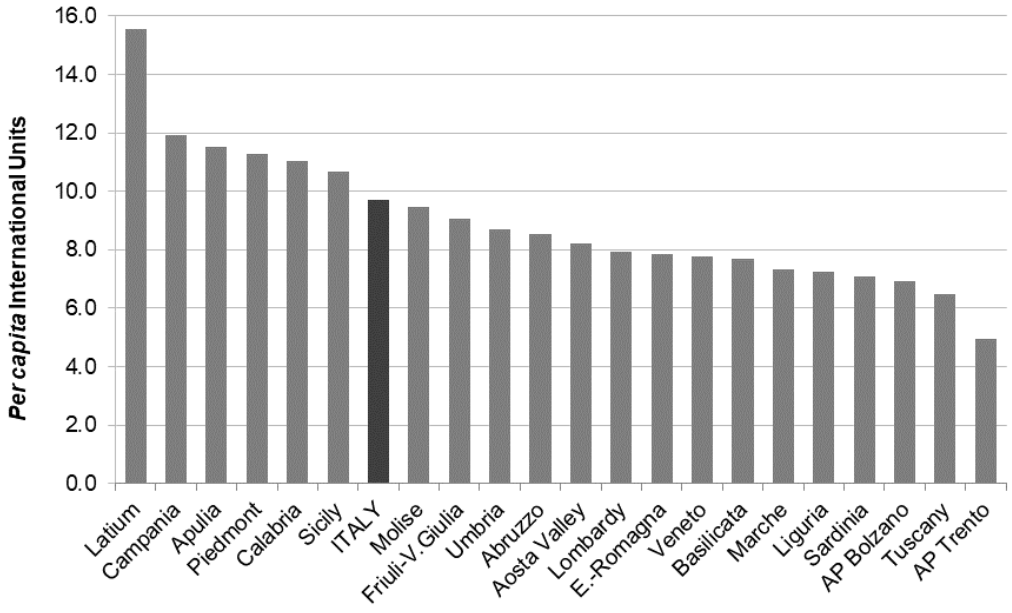

Figure 16. Total and regional demand (public and private) for coagulation factor VIII, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

The most significant increases in standardised regional demand was observed in Aosta Valley and Molise, where utilisation increased by 101% and 34%, respectively.

It is important to underline that, for FVIII, strong fluctuations can occur due to the contingent needs of a few patients (immunotolerance treatment, surgery, severe trauma, etc.). However, six regions had a greater demand compared to national average. (Figure 17).

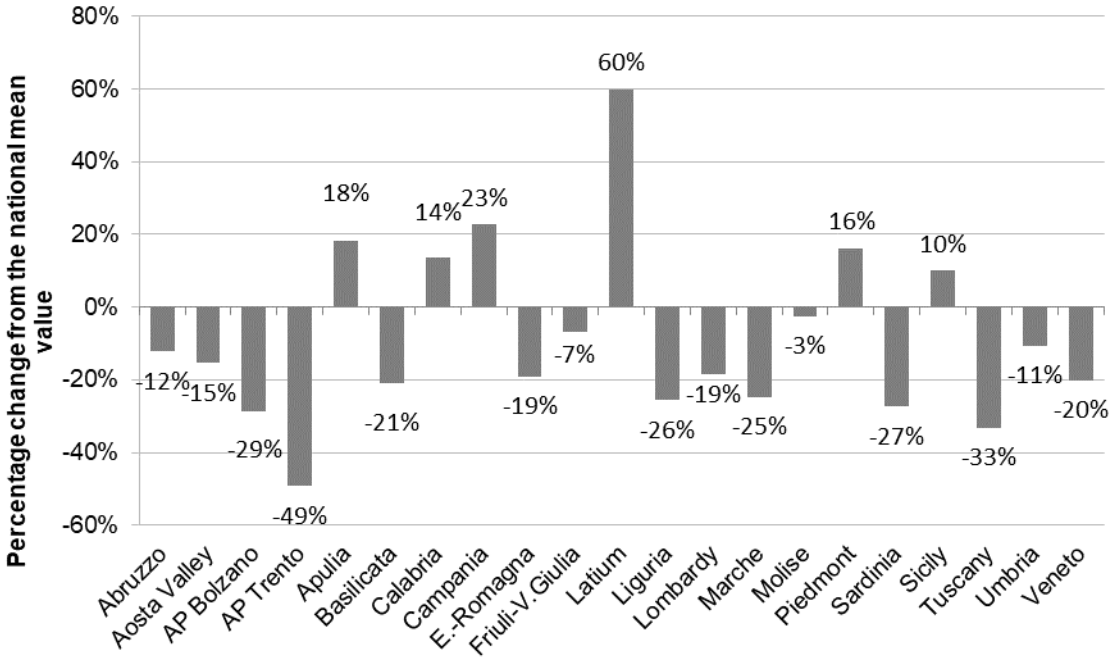

Figure 17. Percentage change from the national mean value of standardised regional demand for coagulation factor VIII in 2017 (adapted by the CNS on data from the traceability information flow)

Plasma-derived Factor VIII

In 2017, the national demand for pdFVIII was about 22% - equivalent to 132,033,500 IUs - of the total demand. There was a 1% decrease compared to 2016 and a total standardised demand of 2.2 IUs *per capita* (Table 17). Per capita demand varied significantly with the highest volumes in Piedmont (4.3 IUs *per capita*), Latium (3.7 IUs *per capita*) and Apulia (2.8 IUs *per capita*); the corresponding percentage change between the aforementioned values and the Italian mean value were of +99%, +68% and +30%, respectively. The lowest volumes (below 1 IU *per capita*) were recorded in Calabria, Basilicata, Abruzzo, Aosta Valley and the AP of Trento (Figures 18 and 19).

The national trend decreased in almost all Italian regions (from -41.5% to -0.4%), with the exception of Aosta Valley, Apulia, Basilicata, Calabria, Friuli V. Giulia, Latium, Lombardy, Molise, Sardinia, Umbria, where there were increases of between 3% and 96%.

Table 17. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,051,500	0.8	977,000	0.7	-6.8
Aosta Valley	24,000	0.2	47,000	0.4	96.5
AP Bolzano	1,063,000	2.0	1,048,000	2.0	-2.0
AP Trento	105,000	0.2	61,500	0.1	-41.5
Apulia	10,045,000	2.5	11,489,000	2.8	14.7
Basilicata	343,000	0.6	390,000	0.7	14.4
Calabria	1,332,000	0.7	1,629,500	0.8	22.7
Campania	12,789,000	2.2	9,854,000	1.7	-22.8
E.-Romagna	8,487,000	1.9	6,639,000	1.5	-21.8
Friuli-V. Giulia	1,133,000	0.9	2,024,000	1.7	79.1
Latium	20,805,000	3.5	21,569,500	3.7	3.5
Liguria	2,098,000	1.3	1,692,000	1.1	-19.1
Lombardy	23,516,500	2.3	24,329,500	2.4	3.3
Marche	2,567,000	1.7	2,547,000	1.7	-0.4
Molise	541,000	1.7	593,000	1.9	10.2
Piedmont	19,442,000	4.4	19,078,000	4.3	-1.6
Sardinia	1,693,000	1.0	2,193,000	1.3	29.9
Sicily	7,860,000	1.5	7,543,000	1.5	-3.7
Tuscany	7,018,000	1.9	6,387,000	1.7	-8.9
Umbria	1,442,500	1.6	1,775,000	2.0	23.4
Veneto	10,228,500	2.1	10,167,500	2.1	-0.4
ITALY	133,584,000	2.2	132,033,500	2.2	-1.0

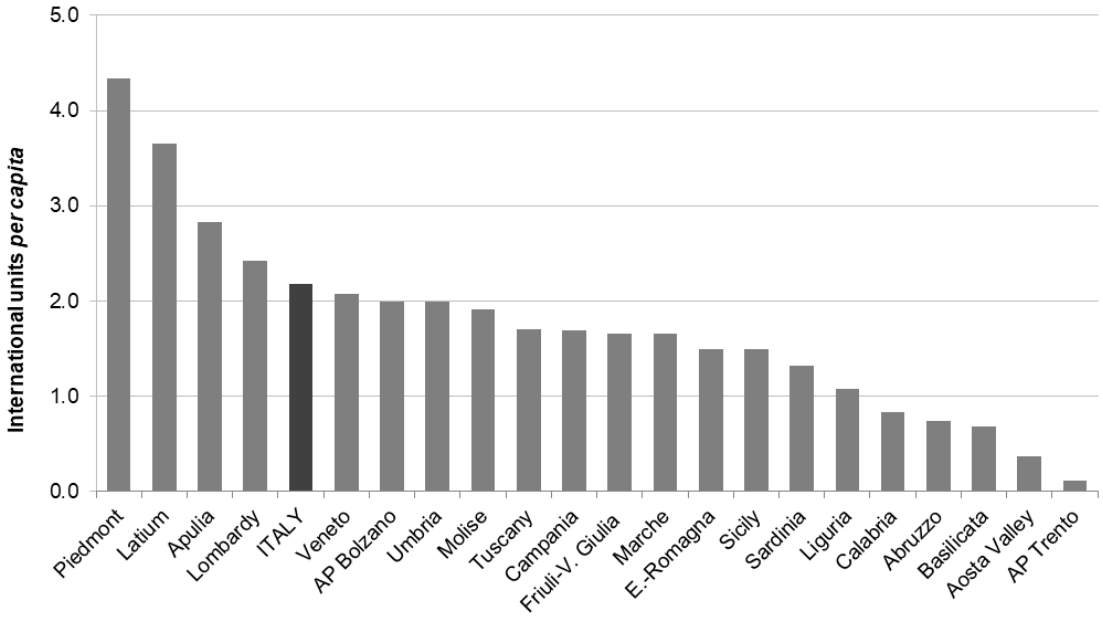

Figure 18. Total and regional demand (public and private) for plasma-derived coagulation factor VIII, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

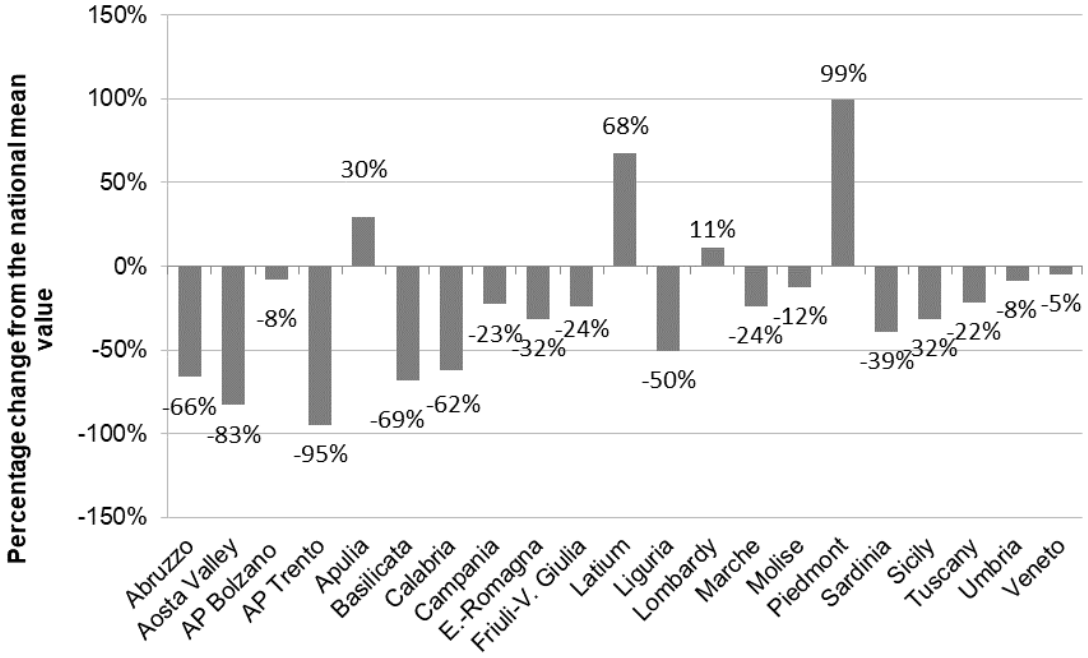

Figure 19. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation factor VIII in 2017 (adapted by the CNS on data from the traceability information flow)

Recombinant Factor VIII

In 2017, the total demand for rFVIII was 457,206,000 IUs, with a 5.7% increase compared to 2016. The mean national demand *per capita* was about 7.5 IUs, with a range between regions of 4.8 IUs and 11.9 IUs (Table 18).

Table 18. Total demand (public and private) and total standardised demand for recombinant coagulation factor VIII, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	9,116,000	6.9	10,304,000	7.8	13.4
Aosta Valley	497,000	3.9	997,000	7.9	101.3
AP Bolzano	2,049,500	3.9	2,590,750	4.9	25.6
AP Trento	3,125,000	5.8	2,594,500	4.8	-17.0
Apulia	36,275,000	8.9	35,259,250	8.7	-2.5
Basilicata	4,046,250	7.1	3,992,000	7.0	-0.8
Calabria	18,304,750	9.3	20,062,250	10.2	9.9
Campania	54,325,750	9.3	59,788,250	10.2	10.3
E.-Romagna	28,840,750	6.5	28,319,500	6.4	-1.8
Friuli-V. Giulia	9,650,500	7.9	9,029,000	7.4	-6.2

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Latium	62,833,000	10.7	70,217,250	11.9	11.6
Liguria	7,635,500	4.9	9,626,000	6.1	26.5
Lombardy	56,992,500	5.7	55,045,750	5.5	-3.5
Marche	8,465,500	5.5	8,711,500	5.7	3.3
Molise	1,670,000	5.4	2,350,000	7.6	41.4
Piedmont	26,787,250	6.1	30,524,000	6.9	14.3
Sardinia	10,508,500	6.3	9,488,750	5.7	-9.4
Sicily	42,031,750	8.3	46,534,750	9.2	11.1
Tuscany	20,642,500	5.5	17,915,000	4.8	-13.2
Umbria	5,678,000	6.4	5,952,000	6.7	5.1
Veneto	23,821,000	4.8	27,904,500	5.7	17.3
ITALY	433,298,016	7.1	457,206,000	7.5	5.7

The regions in which the highest *per capita* utilisation of rFVIII was observed were Latium (11.9 IUs), Campania and Calabria (10.2 IUs) (Figure 20), with a percentage change compared to the Italian mean value of +58%, +36 % and 35%, respectively (Figure 21). The lowest utilisation – between 4.8 and 5.7 IUs *per capita* – was observed in Tuscany, AP of Trento, AP of Bolzano, Lombardy and Marche.

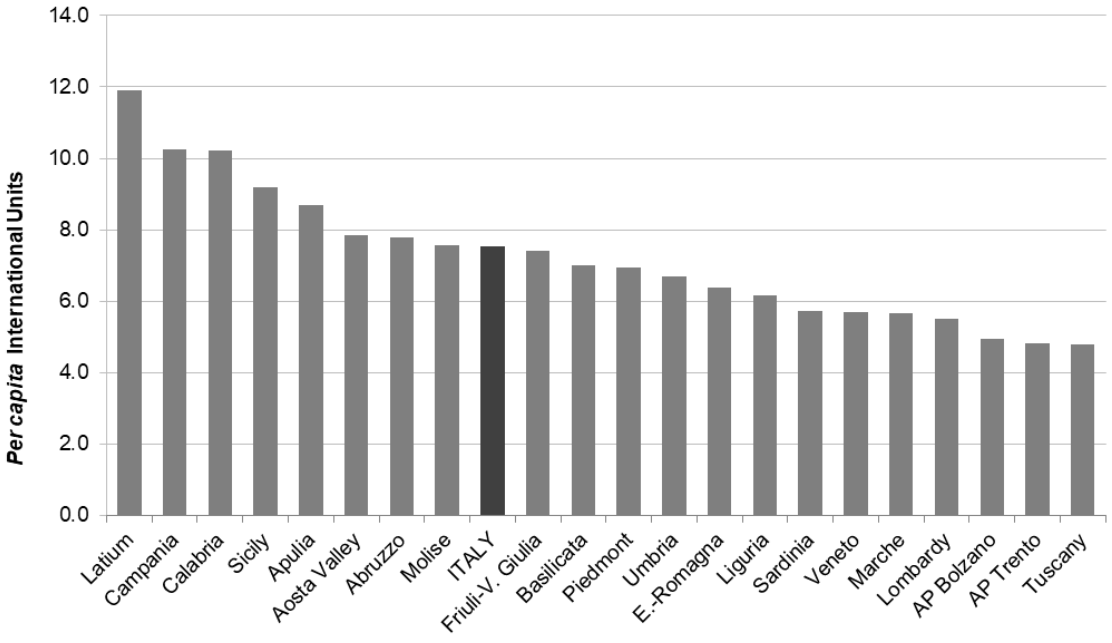

Figure 20. Total and regional demand (public and private) for recombinant coagulation factor VIII, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

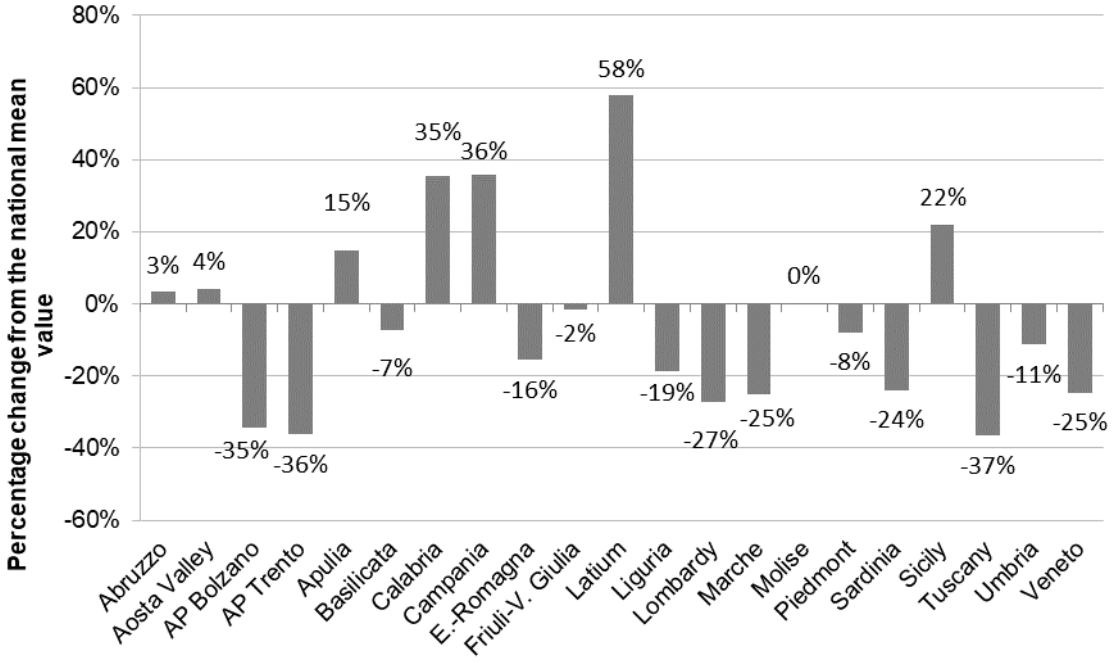

Figure 21. Percentage change from the national mean value of standardised regional demand for recombinant coagulation factor VIII in 2017 (adapted by the CNS on data from the traceability information flow)

COAGULATION FACTOR IX (ATC B02BD04), RECOMBINANT COAGULATION FACTOR IX (ATC B02BD09)

Coagulation FIX is used in the replacement therapy of haemophilia B, also called Christmas disease, a rare, haemorrhagic, hereditary, x-linked or acquired recessive disorder, with an estimated prevalence of 2-3/100,000 male subjects (27) and caused by a FIX deficiency. Depending on the level of activity of the circulating factor, there are severe forms of haemophilia B (FIX <1%), moderately severe (between 1 and 5%) and mild (> 5%) (28).

FIX coagulation concentrates are distinguished in plasma-derived concentrates and products obtained with genetic recombination techniques (28). Tables 19 and 20 show the brand names of preparations containing pdFIX and rFIX currently marketed in Italy and the related amount of active ingredient contained and expressed in IUs.

Table 19. Products containing plasma-derived coagulation factor IX currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
025841089	AIMAFIX*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
028142026	MONONINE*EV F 500UI+F 5ML+KIT	500	CSL BEHRING SpA	A
039072020	HAEMOBIONINE*1FL 500UI	500	BIOTEST ITALIA Srl	A
040092013	OCTANINE*FL 500UI+FL 5ML	500	OCTAPHARMA ITALY SPA	A
041799026	IXED*FL 500UI+FL 10ML+SET	500	KEDRION SpA	A
038324024	FIXNOVE*FL 600UI+FL 10ML	600	BAXALTA ITALY Srl	A
025841103	AIMAFIX*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
028142038	MONONINE*EV F 1000UI	1000	CSL BEHRING SpA	A
029250077	ALPHANINE “1000 UI/10 ML	1000	GRIFOLS ITALIA SpA	A
039072032	HAEMOBIONINE*1FL 1000UI	1000	BIOTEST ITALIA Srl	A
040092025	OCTANINE*FL 1000UI+FL	1000	OCTAPHARMA ITALY SPA	A
041799038	IXED*FL 1000UI+FL 10ML+SET	1000	KEDRION SpA	A
038324036	FIXNOVE*FL 1200UI+FL 10ML	1200	BAXALTA ITALY Srl	A
029250089	ALPHANINE “1500 UI/10 ML	1500	GRIFOLS ITALIA SpA	A

Table 20. Products containing recombinant coagulation factor IX currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
033535042	BENEFIX*IV 1FL 250UI+SIR 5ML+SE	250	PFIZER ITALIA Srl	A
043796010	RIXUBIS*IV 1FL 250UI 5ML	250	BAXALTA INN. GmbH	A
044888016	ALPROLIX*1FL 250UI+1SIR 5ML	250	SOBI SRL	A
044891012	IDELVION*EV FL 250UI+FL 2,5ML	250	CSL BEHRING SpA	A
033535055	BENEFIX*IV 1FL 500UI+SIR 5ML+SE	500	PFIZER ITALIA Srl	A
043796022	RIXUBIS*IV 1FL 500UI 5ML	500	BAXALTA INN. GmbH	A
044888028	ALPROLIX*1FL 500UI+1SIR 5ML	500	SOBI Srl	A
044891024	IDELVION*EV FL 500UI+FL 2,5ML	500	CSL BEHRING SpA	A
045488018	REFIXIA*EV FL 500UI+FL 4ML+SIR	500	NOVO NORDISK A/S	C(nn)
033535067	BENEFIX*IV 1FL 1000UI+SIR 5ML+S	1000	PFIZER ITALIA Srl	A
043796034	RIXUBIS*IV 1FL 1000UI 5ML	1000	BAXALTA INN. GmbH	A
044888030	ALPROLIX*1FL 1000UI+1SIR 5ML	1000	SOBI Srl	A
044891036	IDELVION*EV FL 1000UI+FL 2,5ML	1000	CSL BEHRING SpA	A
045488020	REFIXIA*EV FL 1000UI+FL 4ML+SIR	1000	NOVO NORDISK A/S	C(nn)
033535079	BENEFIX*IV 1FL 2000UI+SIR 5ML+S	2000	PFIZER ITALIA Srl	A

043796046	RIXUBIS*IV 1FL 2000UI 5ML	2000	BAXALTA INN. GmbH	A
044888042	ALPROLIX*1FL 2000UI+1SIR 5ML	2000	SOBI Srl	A
044891048	IDELVION*EV FL 2000UI+FL 2,5ML	2000	CSL BEHRING SpA	A
045488032	REFIXIA*EV FL 2000UI+FL 4ML+SIR	2000	NOVO NORDISK A/S	C(nn)
033535081	BENEFIX*IV 1FL 3000UI+SIR 5ML+S	3000	PFIZER ITALIA Srl	A
043796059	RIXUBIS*IV1FL 3000UI 5ML	3000	BAXALTA INN. GmbH	A
044888055	ALPROLIX*1FL 3000UI+1SIR 5ML	3000	SOBI Srl	A

Quantification and characterisation of the demand

Table 21 shows the total and *per capita* demand for plasma-derived and recombinant FIX for the two-year period 2016-2017, at national and regional levels. FIX formulations registered a total demand for the year 2017 of 67,525,150 IUs; about 19% of the aforementioned amount (12,638,400 IUs) was plasma-derived. There was a decreasing demand for pdFIX whereas for rFIXa slight increase was observed (-9% and +4%, respectively).

Table 21. Total demand (public and private) and total standardised demand for coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	2,533,000	1.9	2,630,000	2.0	4.2
Aosta Valley	-	NA	-	NA	NA
AP Bolzano	39,000	0.1	36,000	0.1	-8.3
AP Trento	397,500	0.7	537,500	1.0	35.1
Apulia	7,955,250	2.0	6,757,500	1.7	-14.8
Basilicata	113,000	0.2	141,750	0.2	26.2
Calabria	1,748,000	0.9	1,436,500	0.7	-17.6
Campania	8,174,500	1.4	8,228,000	1.4	0.9
E.-Romagna	3,340,500	0.8	5,128,750	1.2	53.5
Friuli-V. Giulia	1,326,000	1.1	1,193,000	1.0	-9.8
Latium	4,255,250	0.7	5,058,100	0.9	18.7
Liguria	3,110,000	2.0	2,821,000	1.8	-9.0
Lombardy	10,488,250	1.0	10,617,750	1.1	1.1
Marche	2,367,500	1.5	1,922,500	1.2	-18.5
Molise	15,000	0.0	-	NA	-100.0
Piedmont	4,549,250	1.0	3,888,750	0.9	-14.3
Sardinia	6,000	0.0	9,000	0.0	50.5
Sicily	4,873,000	1.0	4,559,000	0.9	-6.1
Tuscany	7,644,000	2.0	8,271,300	2.2	8.3
Umbria	570,500	0.6	477,000	0.5	-16.2
Veneto	3,268,000	0.7	3,811,750	0.8	16.8
ITALY	66,773,500	1.1	67,525,150	1.1	1.3

* The values inserted as “0.0” do not identify the absence of quantities distributed, but consumption that would have required an excessive number of decimals to be quantified.

In 2017, the standardised demand for plasma-derived and recombinant FIX was 1.1 IUs *per capita*, with significantly different regional trends. These ranged from a minimum - close to zero - in Sardinia and in Molise (-100% and -96% percentage change compared to the Italian mean value, respectively), to a maximum in Tuscany and Abruzzo with 2,2 IUs and 2 IUs *per capita* (+ 98%, 78% percentage change compared to the national mean value, respectively) (Figures 22 and

23). In ten regions the demand increased (percentage range: 0.9–53.5%), while it decreased in another ten regions (from -6.1 to -100%) (*see* Table 21).

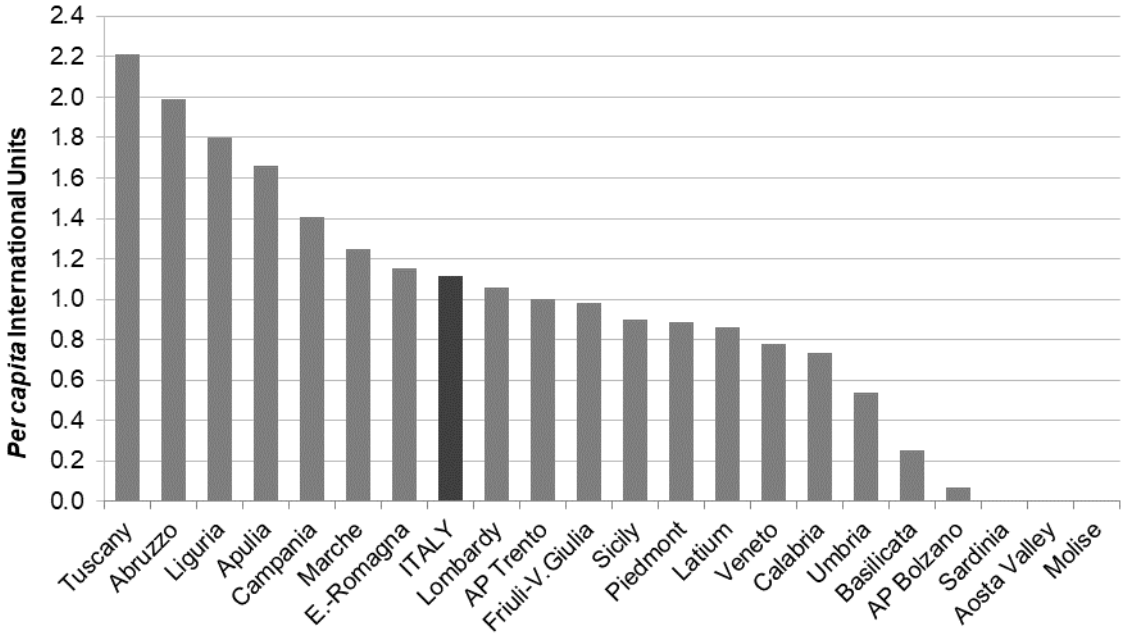

Figure 22. Total and regional demand (public and private) for coagulation factor IX, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

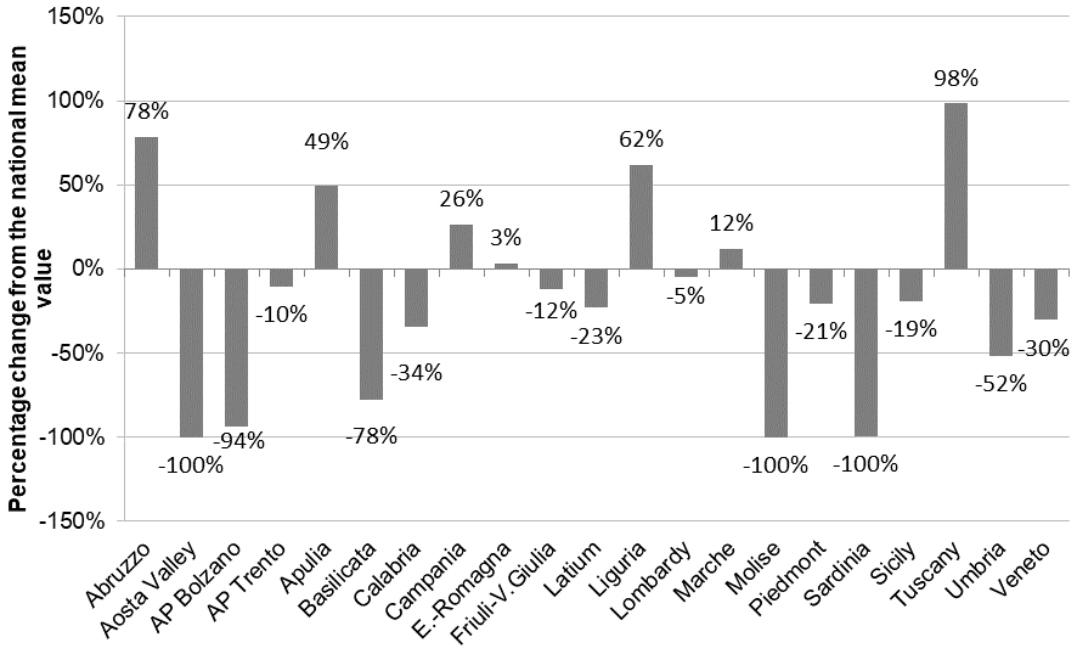

Figure 23. Percentage change from the national mean value of standardised regional demand for coagulation factor IX (International Units *per capita*) in 2017 (adapted by the CNS on data from the traceability information flow)

In Campania, Molise, AP of Trento Sardinia and Aosta Valley rFIX was used almost exclusively, while in Apulia, Liguria, Basilicata, Tuscany, Latium, Calabria and Sicily, rFIX demand reached volumes of above 80% (Figure 24).

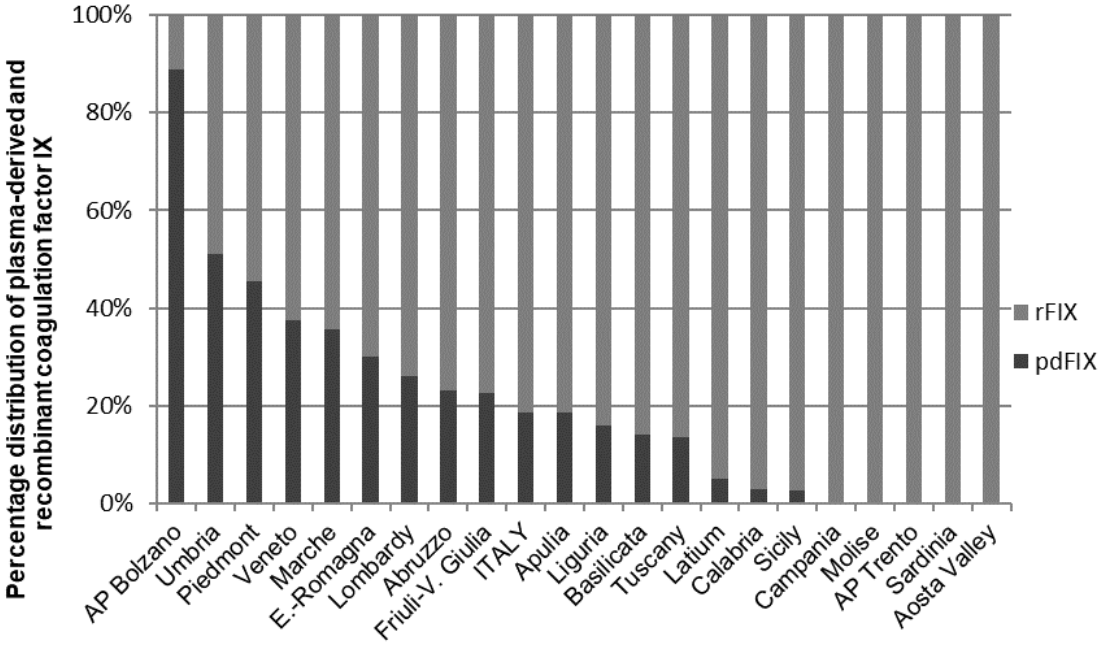

Figure 24. Distribution expressed in % of factor IX per type, by Region, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

Plasma-derived Factor IX

In 2017, the total demand for pdFIX (expressed in absolute values and *per capita* volumes), was 12,638,400 IUs, equal to 0.2 IU *per capita*, a 9.1% decrease compared to 2016 (Table 22).

Table 22. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU*per capita*	IU	IU*per capita*	
Abruzzo	699,500	0.5	609,000	0.5	-12.7
Aosta Valley	-	NA	-	NA	NA
AP Bolzano	32,000	0.1	32,000	0.1	-0.6
AP Trento	-	NA	-	NA	NA
Apulia	2,429,000	0.6	1,263,000	0.3	-47.8
Basilicata	-	NA	20,000	0.0	100
Calabria	91,000	0.0	43,000	0.0	-52.6
Campania	-	NA	5,000	0.0	100
E.-Romagna	1,251,000	0.3	1,547,000	0.3	23.6
Friuli-V.Giulia	296,000	0.2	270,000	0.2	-8.5
Latium	658,500	0.1	248,600	0.0	-62.3
Liguria	160,000	0.1	448,000	0.3	181.0
Lombardy	2,509,000	0.3	2,766,000	0.3	10.1

Marche	682,000	0.4	687,000	0.4	1.1
Molise	10,000	0.0	-	NA	-100.0
Piedmont	2,118,000	0.5	1,773,000	0.4	-16.1
Sardinia	-	NA	-	NA	NA
Sicily	266,000	0.1	124,000	0.0	-53.2
Tuscany	1,292,000	0.3	1,130,800	0.3	-12.4
Umbria	174,000	0.2	244,000	0.3	40.6
Veneto	1,250,000	0.3	1,428,000	0.3	14.4
ITALY	13,918,000	0.2	12,638,400	0.2	-9.1

* The amounts of pdFIX contained in Factor X P Behring® are not included (see Table 57).

The regions with the highest *per capita* demand for pdFIX were Abruzzo, Marche, Piedmont with 0.5 IU, and 0.4 IU for the last two, almost double the demand registered at national level; while in Basilicata, Calabria, Campania, Latium, Sicily *per capita* volumes were close to zero (Figures 25 and 26). In some Regions, there was no reported utilisation of pdFIX.

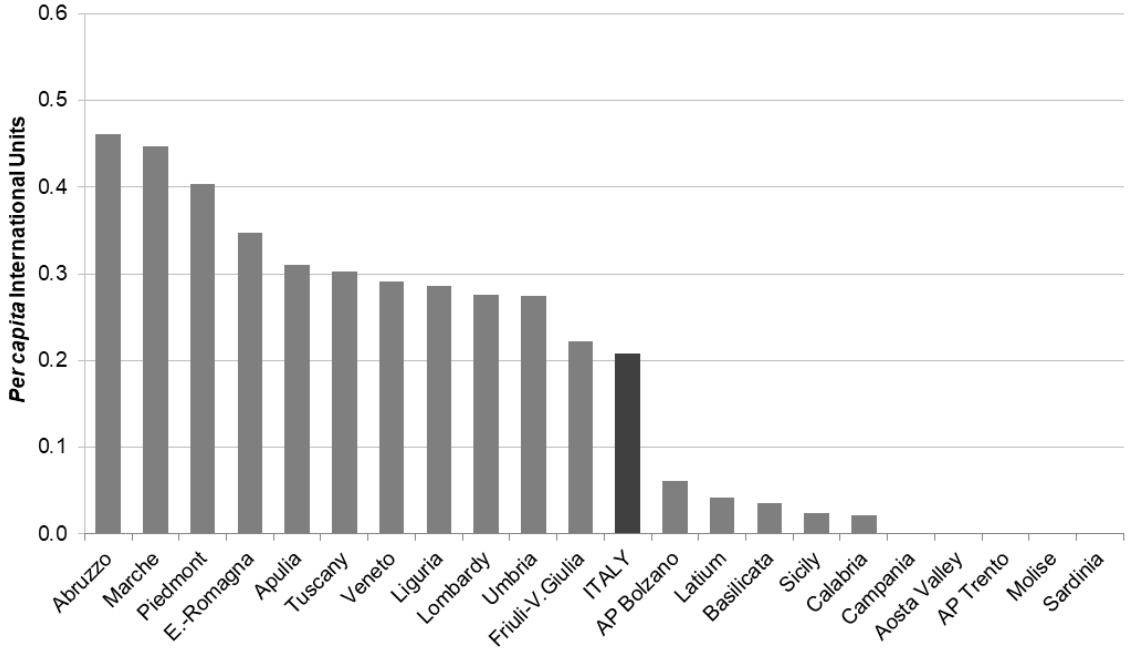

Figure 25. Total and regional demand (public and private) for plasma-derived coagulation factor IX, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

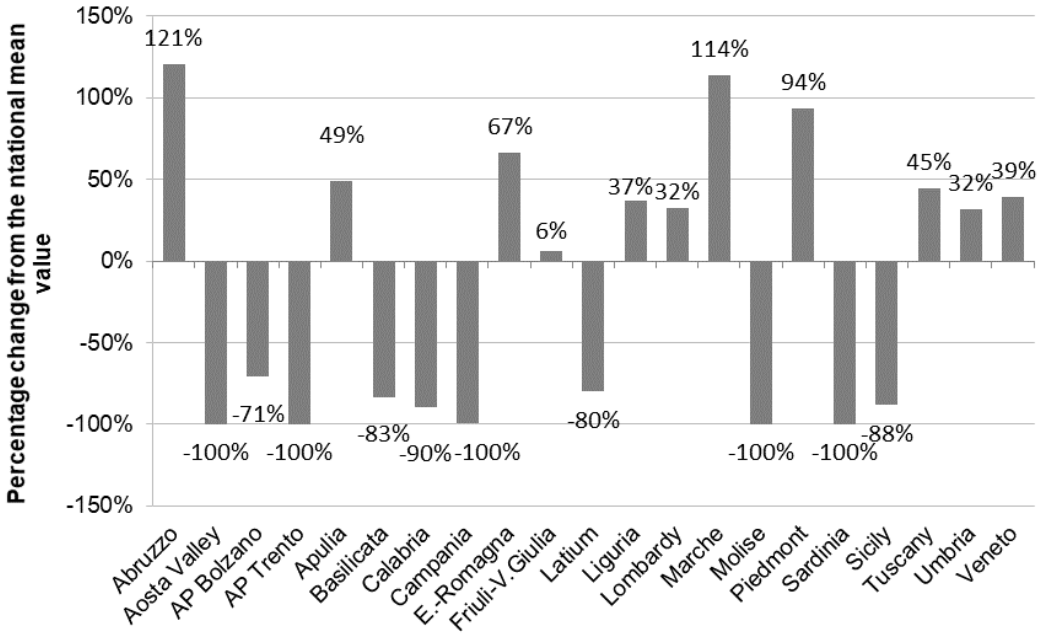

Figure 26. Percentage change from the national mean value of standardised regional demand for plasma-derived coagulation factor IX in 2017(adapted by the CNS on data from the traceability information flow)

Recombinant Factor IX

The total demand for rFIX increased by 4% in the period 2016-2017, with a volume of 54,886,750 IUs in 2017 alone, equal to 0.9 IU *per capita* (Table 23).

Table 23. Total demand (public and private) and total standardised demand for recombinant coagulation factor IX, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	1,833,500	1.4	2,021,000	1.5	10.6
Aosta Valley	-	0.0	-	-	0.0
AP Bolzano	7,000	0.0	4,000	0.0	-43.2
AP Trento	397,500	0.7	537,500	1.0	35.1
Apulia	5,526,250	1.4	5,494,500	1.4	-0.2
Basilicata	113,000	0.2	121,750	0.2	8.4
Calabria	1,657,000	0.8	1,393,500	0.7	-15.7
Campania	8,174,500	1.4	8,223,000	1.4	0.8
E.-Romagna	2,089,500	0.5	3,581,750	0.8	71.4
Friuli-V. Giulia	1,030,000	0.8	923,000	0.8	-10.1
Latium	3,596,750	0.6	4,809,500	0.8	33.5
Liguria	2,950,000	1.9	2,373,000	1.5	-19.3

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Lombardy	7,979,250	0.8	7,851,750	0.8	-1.7
Marche	1,685,500	1.1	1,235,500	0.8	-26.4
Molise	5,000	0.0	-	-	-100.0
Piedmont	2,431,250	0.6	2,115,750	0.5	-12.7
Sardinia	6,000	0.0	9,000	0.0	50.5
Sicily	4,607,000	0.9	4,435,000	0.9	-3.4
Tuscany	6,352,000	1.7	7,140,500	1.9	12.5
Umbria	396,500	0.4	233,000	0.3	-41.1
Veneto	2,018,000	0.4	2,383,750	0.5	18.3
ITALY	52,855,500	0.9	54,886,750	0.9	4.0

The regions with the highest *per capita* demand of rFIX (Figure 27) were Tuscany, Abruzzo and Liguria with 1.9 IUs; 1.5 IUs (Abruzzo and Liguria), respectively (+ 111%, +69% and +67% percentage change compared to the Italian mean value) (Figure 28). In Aosta Valley and Molise there was no reported consumption of rFIX in 2017.

In 2017, there was a stable *per capita* demand compared to 2016 in almost every region. E.-Romagna, the AP of Trento and Latium were the regions with the highest increase.

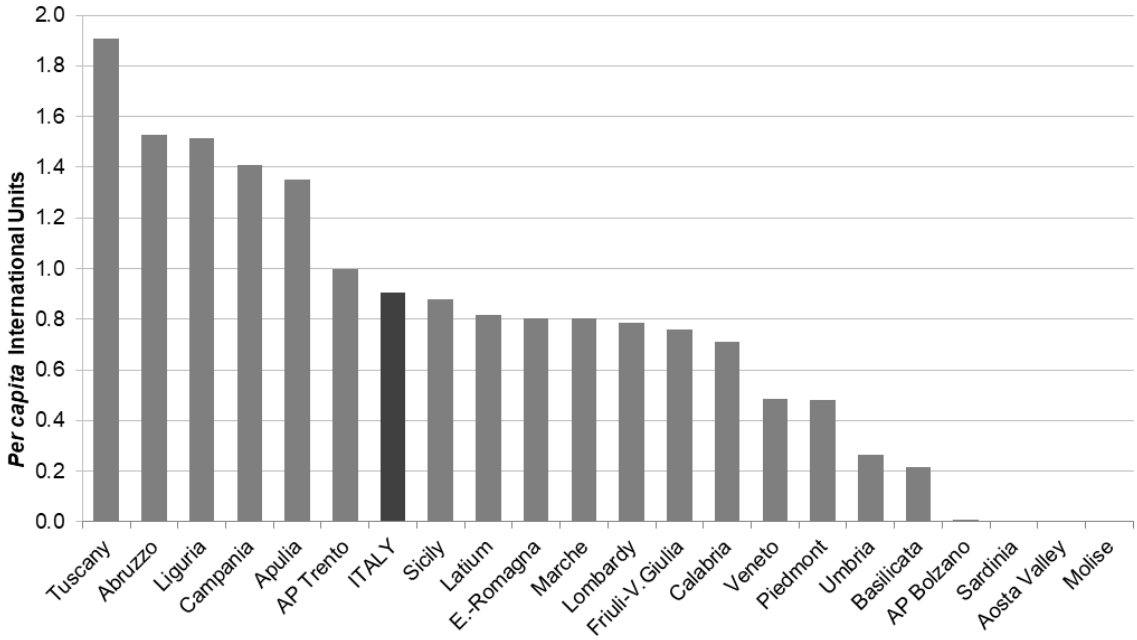

Figure 27. Total and regional demand (public and private) for recombinant coagulation factor IX, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow and Latium)

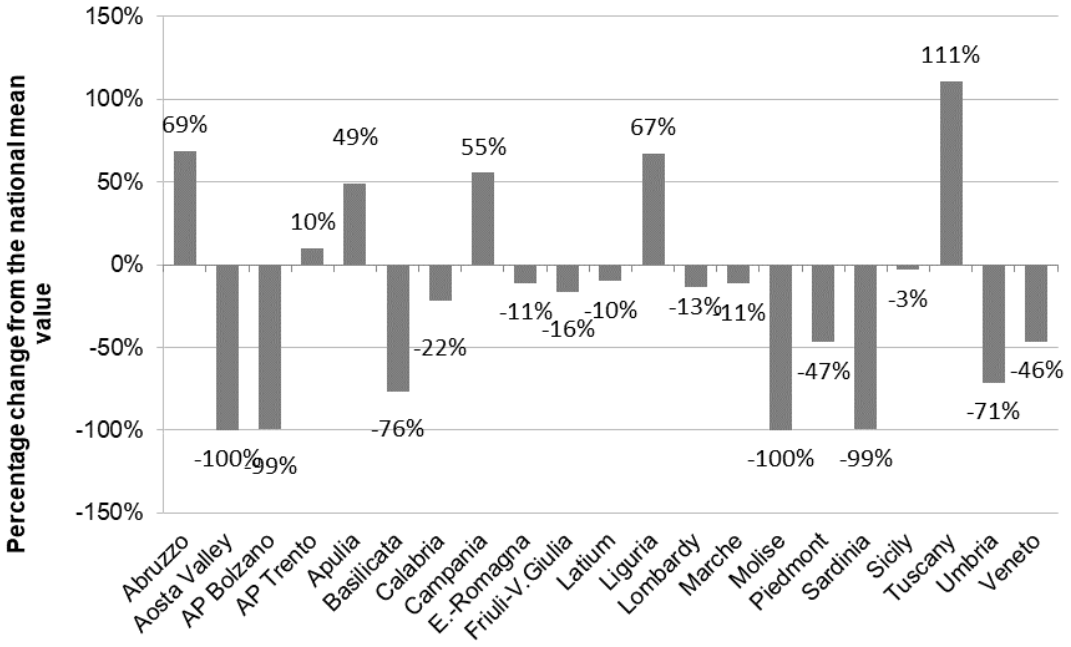

Figure 28. Percentage change from the national mean value of standardised regional demand for recombinant coagulation factor IX in 2017 (adapted by the CNS on data from the traceability information flow)

3-FACTOR PROTHROMBIN COMPLEX CONCENTRATES (ATC B02BD) AND 4-FACTOR PROTHROMBIN COMPLEX CONCENTRATES (ATC B02BD01)

Prothrombin Complex Concentrates (PCCs) are plasma-derived therapeutic drugs useful for the urgent temporary reversal of prothrombin complex factors deficiency (19).

Three or four-factor PCCs can be obtained through different production processes. 3F-PCCs contain Factor II (FII), Factor IX (FIX) and Factor X (FX), and 4F-PCCs contain FII, FVII, FIX, and FX with pro-coagulant action, as well as natural and physiological coagulation inhibitors such as protein C, protein S and traces of protein, heparin and vitronectin (29).

As with all the other PDMPs, PCCs undergo viral inactivation, which can be physical (heat), chemical (solvent-detergent use) and virus removal by nanofiltration (30).

Tables 24 and 25 show the brand names of preparations containing 3F-PCCs and 4F-PCCs currently on the market in Italy and their relative amount of active ingredient contained expressed in IUs.

Table 24. Products containing 3-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
023309103	UMANCOMPLEX D.I.*FL 500UI+F20M	500	KEDRION SpA	A
041850013	KEDCOM*FL 500UI+FL 20ML+SET	500	KEDRION SpA	H
023288032	PROTROMPLEX TIM3*F 600UI+20ML	600	BAXTER AG	A

Table 25. Products containing 4-factor prothrombin complex concentrates currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
038844015	CONFIDEX*500UI+1FL SOLV 20ML	500	CSL BEHRING GMBH	H
039240015	PRONATIV*500UI+FL SOLV 20ML	500	OCTAPHARMA ITALY	H
043304017	PROPLEX*FL 600UI/20ML+FL SOLV	600	BAXALTA ITALY Srl	H

Quantification and characterisation of the demand

Table 26 shows the total and standardised demand (expressed in IUs *per capita*) for 3F-PCCs in the two-year period 2016-2017, both nationally and regionally.

In 2017, there was a total demand comparable to that of 2016; it stood at 37,296,600 IUs, equal to 0.6 IU *per capita*. There were considerable differences in the use of 3F-PCCs from one region to another with standardised values ranging from 0.3 IU (Latium) to 1.2 IUs (Aosta Valley), with a percentage change compared to the Italian mean value of over 50% in Friuli V. Giulia, the AP of Bolzano, E.-Romagna and Aosta Valley (+52%, 59%, 66% and +92%, respectively) (Figures 29 and 30).

Table 26. Total demand (public and private) and total standardised demand for 3 factor-prothrombin complex concentrates, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	545,500	0.4	463,500	0.4	-14.8
Aosta Valley	74,000	0.6	150,000	1.2	103.4
AP Bolzano	656,000	1.3	512,000	1.0	-22.5
AP Trento	408,000	0.8	471,000	0.9	15.4
Apulia	2,515,300	0.6	1,795,000	0.4	-28.4
Basilicata	80,500	0.1	189,000	0.3	136.2
Calabria	395,800	0.2	1,094,500	0.6	177.3
Campania	2,895,100	0.5	2,289,900	0.4	-20.7
E.-Romagna	4,272,300	1.0	4,541,000	1.0	6.3
Friuli-V. Giulia	847,000	0.7	1,137,000	0.9	34.6
Latium	1,787,400	0.3	1,693,000	0.3	-5.4
Liguria	1,160,200	0.7	1,016,500	0.6	-12.1
Lombardy	5,711,000	0.6	5,854,400	0.6	2.4
Marche	1,090,500	0.7	1,358,000	0.9	25.0
Molise	193,500	0.6	211,000	0.7	9.6
Piedmont	3,041,500	0.7	2,649,000	0.6	-12.7
Sardinia	1,018,300	0.6	1,140,000	0.7	12.3
Sicily	2,950,900	0.6	3,022,800	0.6	2.8
Tuscany	2,833,700	0.8	3,205,000	0.9	13.2
Umbria	507,000	0.6	519,500	0.6	2.7
Veneto	4,114,900	0.8	3,984,500	0.8	-3.0
ITALY	37,098,400	0.6	37,296,600	0.6	0.7

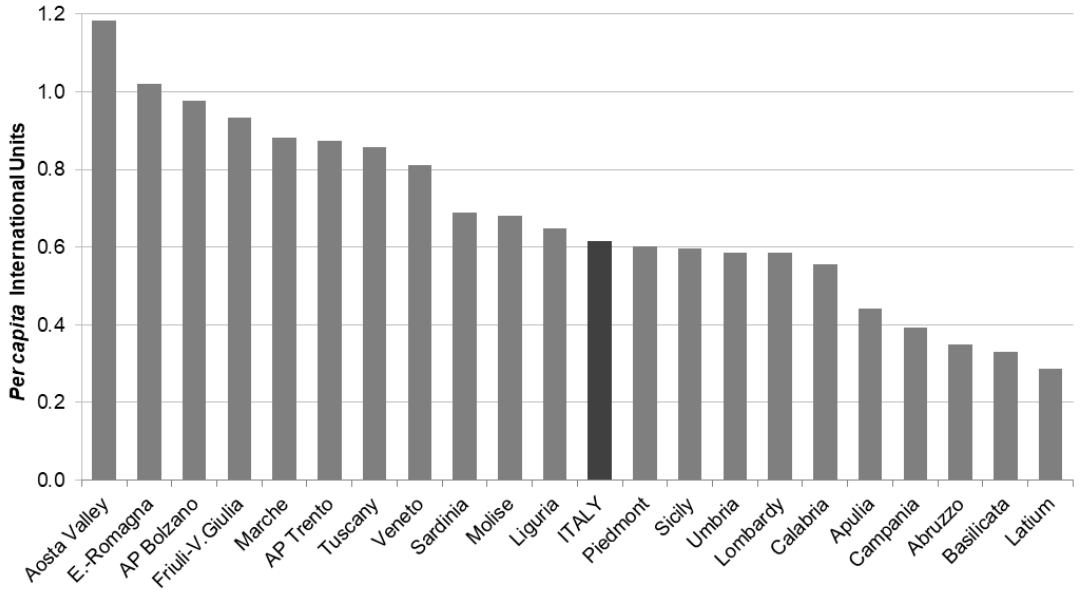

Figure 29. Total and regional demand (public and private) for 3-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow)

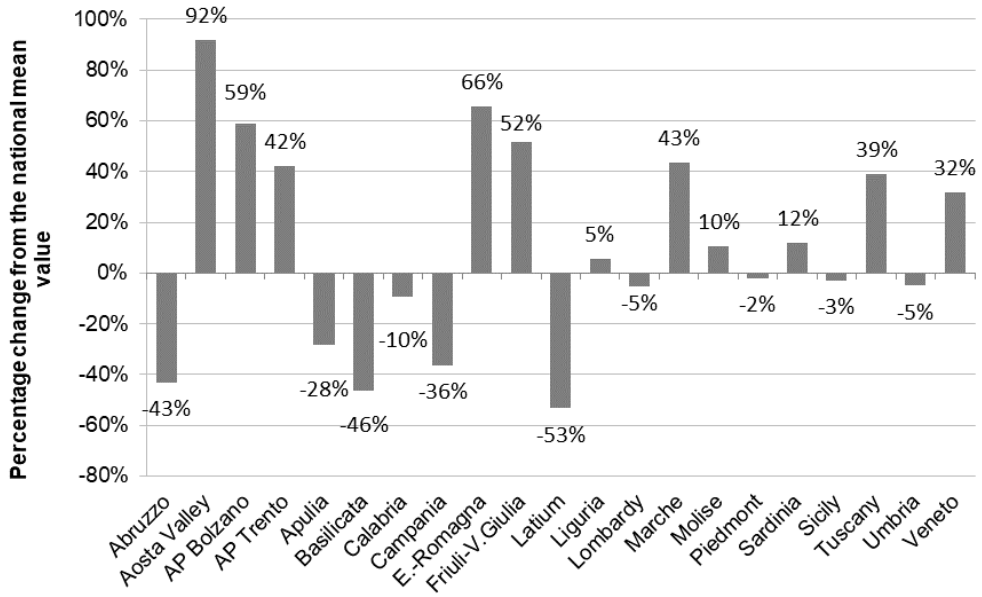

Figure 30. Percentage change from the national mean value of standardised regional demand for 3-factor prothrombin complex concentrates in 2017 (adapted by the CNS on data from the traceability information flow)

In 2017, the national demand for 4F-PCCs was 8,810,500 IUs, equal to 19% of the overall demand for PCCs, with a standardised demand of 0.1 IU *per capita* and a 34% increase compared to the previous year (Table 27). Also, for this PDMP there were considerable differences regarding utilisation from one region to another. Excluding the AP of Trento, Friuli-V. Giulia and Tuscany, all of the regions recorded significant increases in the demand.

Table 27. Total demand (public and private) and total standardised demand for 4-factor prothrombin complex concentrates, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	162,500	0.1	264,000	0.2	63.0
Aosta Valley	-	NA	-	NA	NA
AP Bolzano	466,500	0.9	607,000	1.2	29.3
AP Trento	6,500	0.0	1,500	0.0	-76.9
Apulia	68,000	0.0	246,000	0.1	262.9
Basilicata	223,500	0.4	232,000	0.4	4.4
Calabria	533,500	0.3	542,500	0.3	2.0
Campania	887,000	0.2	999,000	0.2	12.9
E.-Romagna	817,000	0.2	1,074,000	0.2	31.4
Friuli-V. Giulia	81,500	0.1	73,500	0.1	-9.6
Latium	1,048,000	0.2	1,305,500	0.2	24.4
Liguria	77,000	0.0	105,500	0.1	37.5
Lombardy	147,500	0.0	670,000	0.1	353.7
Marche	101,500	0.1	113,500	0.1	12.2
Molise	40,000	0.1	76,000	0.2	91.0
Piedmont	280,000	0.1	402,500	0.1	44.1

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Sardinia	501,500	0.3	616,500	0.4	23.3
Sicily	341,000	0.1	655,500	0.1	92.9
Tuscany	717,500	0.2	706,500	0.2	-1.5
Umbria	22,000	0.0	26,500	0.0	20.8
Veneto	61,500	0.0	93,000	0.0	51.5
ITALY	6,583,500	0.1	8,810,500	0.1	34.0

The region with the highest demand in 2017 was the AP of Bolzano with 1.2 IUs *per capita*, followed by Basilicata and Sardinia with 0.4 and then Calabria with 0.3 IU *per capita* (Figure 31).

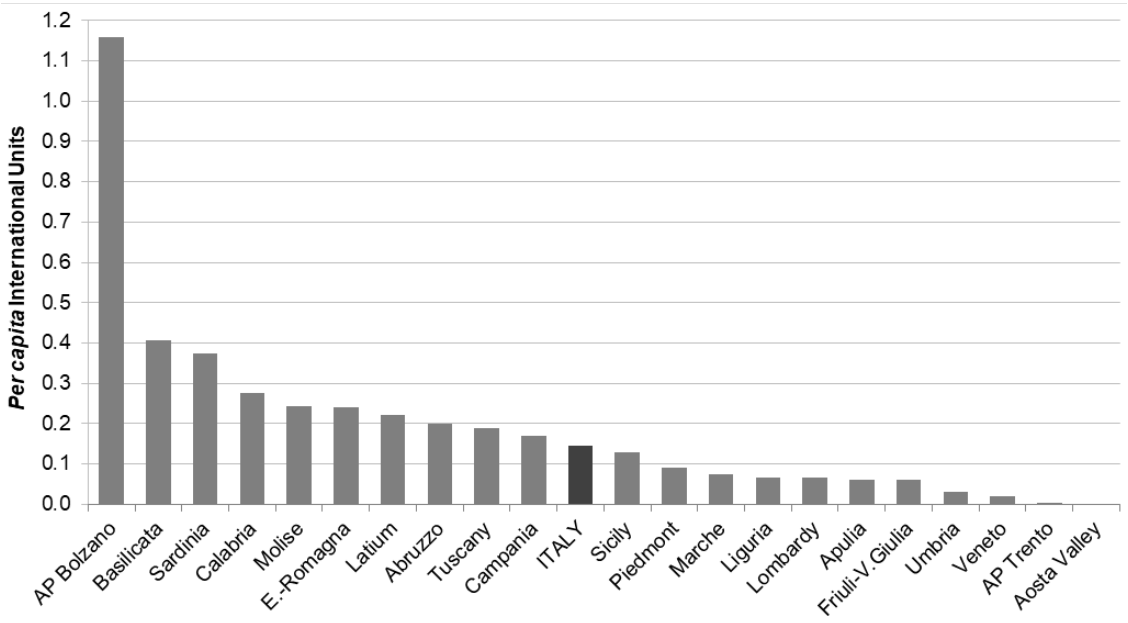

Figure 31. Total and regional demand (public and private) for 4-factor prothrombin complex concentrates, expressed in International Units *per capita*, 2017 (adapted by the CNS on data from the traceability information flow)

Figure 32 shows percentage changes compared to the Italian mean values of the standardised regional demand for 4F-PCCs as recorded by the drug traceability system in 2017.

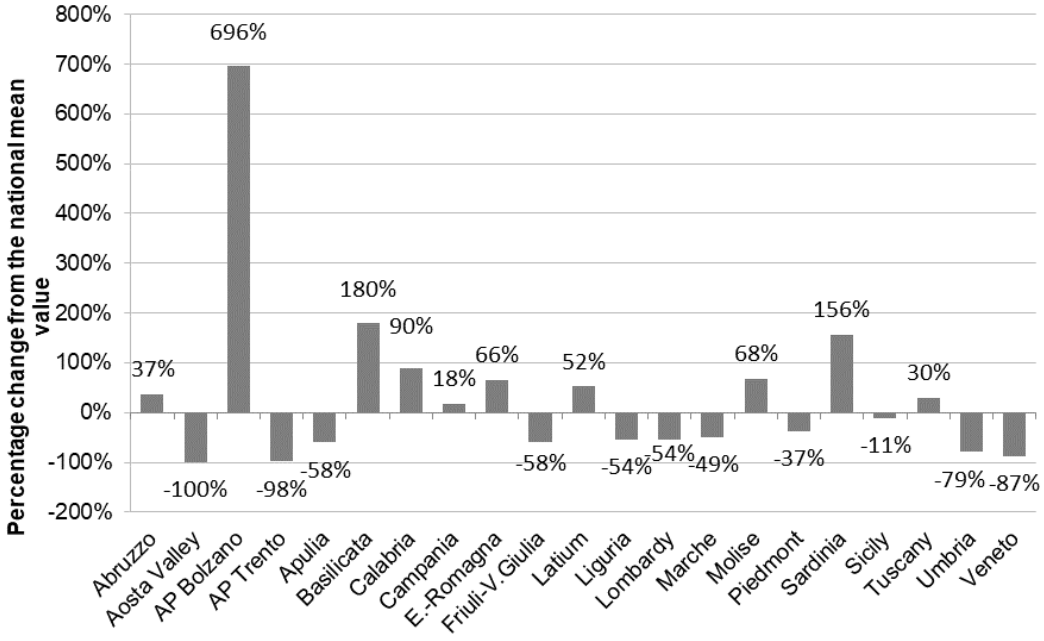

Figure 32. Percentage change from the national mean value of standardised regional demand for 4-factor prothrombin complex concentrates in 2017 (adapted by the CNS on data from the traceability information flow)

PART B
Other plasma-derived medicinal products

HEPATITIS B IMMUNOGLOBULINS FOR INTRAVENOUS AND SUBCUTANEOUS USE (ATC J06BB04)

The tables below show the brand names of medicinal products containing hepatitis B immunoglobulins for intravenous (IV) (Table 28) and subcutaneous (SC) / intramuscular (IM) use (Table 29) currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 28. Products containing hepatitis B immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
035561012	NEOHEPATECT*IV 1F 100UI 2ML	100	BIOTEST PHARMA GMBH	H
026415048	VENBIG*1F 500UI+F 10ML+SET	500	KEDRION SpA	H
035561024	NEOHEPATECT*IV 1F 500UI 10ML	500	BIOTEST PHARMA GMBH	H
038059010	KEYVENB”500UI/10ML+SET	500	KEDRION SpA	H
038059034	KEYVENB”50UI/ML” F. CON 500UI	500	KEDRION SpA	H
041985019	VEBIKED”50UI/ML” FL CON 500UI	500	KEDRION SpA	C(nn)
038445021	NIULIVA*INF 1SIR 4ML”250IU/ML	1000	INSTITUTO GRIFOLS S.A.	H
035561036	NEOHEPATECT*IV FL 2000UI 40ML	2000	BIOTEST PHARMA GMBH	H
026415051	VENBIG*F 2500UI/50ML+F 45ML+SE	2500	KEDRION SpA	H
038059022	KEYVENB”2500UI/45ML+SET	2500	KEDRION SpA	H
038059046	KEYVENB”50UI/ML” F CON 2500UI	2500	KEDRION SpA	H
041985021	VEBIKED”50UI/ML” FL CON 2500UI+SET	2500	KEDRION SpA	C(nn)
035561048	NEOHEPATECT*IV FL 5000UI 100ML	5000	BIOTEST ITALIA Srl	H
038445033	NIULIVA*INF 1FL 20ML 250IU/ML	5000	GRIFOLS ITALIA SpA	H
038445045	NIULIVA”250IU/ML” 1F. 40ML	10000	INSTITUTO GRIFOLS S.A.	H

Table 29. Products containing hepatitis B immunoglobulins for subcutaneous/intramuscular use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
023782028	UMAN BIG “180 UI/1 ML SOLUZ. INIET”	180	KEDRION SpA	A
025653015	IMMUNOHBS*IM 1F 1ML 180UI	180	KEDRION SpA	A
042002016	KEDHBS 180 UI/1 ML - 1 FL DA 1 ML	180	KEDRION SpA	A
023782016	UMANBIG*IM 1FL 3ML 540UI	540	KEDRION SpA	A
025653027	IMMUNOHBS*IM 1F 3ML 540UI	540	KEDRION SpA	A
042002028	KEDHBS 540 UI/3 - 1 FL DA 3 ML	540	KEDRION SpA	A
035320011	IGANTIBE*IM 1F 3ML 600UI/3ML	600	INSTITUTO GRIFOLS S.A.	A
025653054	IMMUNOHBS*IM 1SIR 1000UI 3ML	1000	KEDRION SpA	A
035320023	IGANTIBE*IM 1F 5ML 1000UI/5ML	1000	INSTITUTO GRIFOLS S.A.	A
042002030	KEDHBS 1000 UI/3 ML 1 SIR 3 ML	1000	KEDRION SpA	A
039644012	ZUTECTRA*SC 5SIR 1ML 500UI	2500	BIOTEST PHARMA GMBH	A

Quantification of the demand

Tables 30 and 31 show, respectively, the total demand and the total standardised demand (expressed in IUs *per capita*) of hepatitis B IG formulations for IV and for SC/IM use for the two-year period 2016-2017, at national and at regional levels.

The national demand of hepatitis B IGs for IV use, confirmed an upward trend (+3.1 %), unlike that observed in the previous years (17,31). The total demand in 2017 was around 23 million IUs (0.4 IU *per capita*) (Table 30).

Table 30. Total demand (public and private) and total standardised demand for hepatitis B immunoglobulins for intravenous use, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow).

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU *per capita*	
Abruzzo	74,000	0.1	64,000	0.0	-13.2
Aosta Valley	-	-	-	-	-
AP Bolzano	-	-	-	-	-
AP Trento	-	-	-	-	-
Apulia	2,537,000	0.6	2,760,000	0.7	9.1
Basilicata	-	-	1,000	0.0	-
Calabria	285,500	0.1	272,000	0.1	-4.5
Campania	7,411,500	1.3	7,258,000	1.2	-1.9
E.-Romagna	2,965,000	0.7	2,378,500	0.5	-19.8
Friuli-V. Giulia	5,000	0.0	310,000	0.3	>100
Latium	780,000	0.1	592,000	0.1	-24.2
Liguria	39,000	0.0	45,000	0.0	15.8
Lombardy	2,335,000	0.2	1,771,000	0.2	-24.2
Marche	465,000	0.3	737,000	0.5	59.1
Molise	20,000	0.1	20,000	0.1	0.0
Piedmont	799,000	0.2	852,500	0.2	7.0
Sardinia	1,040,500	0.6	789,000	0.5	-23.9
Sicily	332,200	0.1	296,100	0.1	-10.6
Tuscany	1,043,500	0.3	1,445,500	0.4	38.6
Umbria	-	-	-	-	-
Veneto	2,245,000	0.5	3,455,500	0.7	54.2
ITALY	22,377,200	0.4	23,047,100	0.4	3.1

Campania continued to be the Region with the highest demand (1.2 IUs *per capita*), equal to one third of the national demand, followed by Veneto, Apulia, E.-Romagna, and Sardinia.

On the other hand, the national demand for hepatitis B IGs for SC/IM use showed a downward trend (-11.3%) compared to the demand registered in 2016; total consumption in 2017 was almost 65 million IUs (1.1 IUs *per capita*) (Table 31) and accounted for 74% of the total demand for hepatitis B IGs.

Table 31. Total demand (public and private) and total standardised demand for hepatitis B immunoglobulins for subcutaneous/intramuscular use, expressed in International Units and International Units *per capita*, and variations in percentage between 2016-2017(adapted by the CNS on data from the traceability information flow).

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	IU*per capita*	
Abruzzo	643,800	0.5	549,980	0.4	-14.3
Aosta Valley	257,100	2.0	225,980	1.8	-11.8
AP Bolzano	113,200	0.2	121,860	0.2	7.0
AP Trento	170,540	0.3	171,960	0.3	0.8
Apulia	5,609,900	1.4	6,000,620	1.5	7.3
Basilicata	310,460	0.5	301,680	0.5	-2.3
Calabria	1,248,820	0.6	1,218,420	0.6	-2.2
Campania	30,928,900	5.3	18,428,040	3.2	-40.3
E.-Romagna	3,699,900	0.8	3,840,020	0.9	3.8
Friuli-V. Giulia	266,620	0.2	326,700	0.3	22.9
Latium	1,799,600	0.3	2,499,800	0.4	38.7
Liguria	1,164,060	0.7	938,780	0.6	-19.1
Lombardy	8,509,240	0.9	11,268,900	1.1	32.3
Marche	553,700	0.4	534,340	0.3	-3.1
Molise	173,760	0.6	146,060	0.5	-15.5
Piedmont	4,944,040	1.1	4,769,380	1.1	-3.3
Sardinia	3,190,980	1.9	3,282,060	2.0	3.2
Sicily	2,652,500	0.5	3,467,560	0.7	31.2
Tuscany	4,104,180	1.1	3,629,740	1.0	-11.5
Umbria	265,660	0.3	245,880	0.3	-7.2
Veneto	2,293,720	0.5	2,608,040	0.5	13.9
ITALY	72,900,680	1.2	64,575,800	1.1	-11.3

TETANUS IMMUNOGLOBULINS (ATC J06BB02)

Table 32 shows drugs containing tetanus IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 32. Products containing tetanus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
022488047	TETANUSGAMMA*IM 1SIR 250UI 2ML	250	KEDRION SpA	A
022488062	TETANUSGAMMA*IM SIR 250UI 1ML	250	KEDRION SpA	A
022635041	GAMMATET P*IM 1F 250UI 1ML	250	CSL BEHRING SpA	A
022635066	GAMMATET P*IM 1SIR 250UI 1ML	250	CSL BEHRING SpA	A
033863010	IGANTET*IM 1SIR 1ML 250UI	250	GRIFOLS ITALIA SpA	A
022488050	TETANUSGAMMA*IM 1SIR 500UI 2ML	500	KEDRION SpA	A
022635054	GAMMATET P*IM 1F 500UI 2ML	500	CSL BEHRING SpA	A
022635078	GAMMATET P*IM 1SIR 500UI 2ML	500	CSL BEHRING SpA	A
033863022	IGANTET*IM 1SIR 2ML 500UI	500	GRIFOLS ITALIA SpA	A
-*	TETAGAM P 250 IU/1 mL	250	CSL BEHRING SpA	-

*Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

In 2017, the total demand for tetanus IGs decreased by 7% compared to 2016. Total demand was 141,258,000 IUs (2.3 IUs *per capita*) (Table 33).

Table 33. Total demand (public and private) and total standardised demand, expressed in International Units and International Units *per capita*, for tetanus immunoglobulins and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2016		2017		% Var
	IU	IU *per capita*	IU	IU *per capita*	2016-2017
Abruzzo	5,252,000	4.0	6,013,250	4.5	14.86
Aosta Valley	493,000	3.9	426,250	3.4	-13.24
AP Bolzano	662,500	1.3	888,500	1.7	33.25
AP Trento	512,000	1.0	503,500	0.9	-1.73
Apulia	9,548,500	2.3	7,959,500	2.0	-16.37
Basilicata	1,645,500	2.9	1,854,000	3.3	13.33
Calabria	7,693,750	3.9	6,147,000	3.1	-19.88
Campania	29,035,750	5.0	21,153,750	3.6	-27.00
E.-Romagna	7,449,250	1.7	7,489,000	1.7	0.52
Friuli-V. Giulia	869,000	0.7	1,277,750	1.0	47.44
Latium	10,614,500	1.8	11,183,000	1.9	5.18
Liguria	5,361,750	3.4	4,905,500	3.1	-8.17
Lombardy	21,007,500	2.1	20,886,750	2.1	-0.68
Marche	4,395,750	2.8	5,417,000	3.5	23.69
Molise	962,500	3.1	1,314,500	4.2	37.27
Piedmont	6,420,000	1.5	6,748,750	1.5	5.40
Sardinia	4,163,750	2.5	3,951,250	2.4	-4.82
Sicily	14,065,250	2.8	10,822,500	2.1	-22.79
Tuscany	13,158,000	3.5	14,607,750	3.9	11.08
Umbria	2,084,250	2.3	2,062,000	2.3	-0.81
Veneto	6,144,000	1.3	5,646,500	1.2	-7.96
ITALY	151,538,500	2.5	141,258,000	2.3	-6.67

The regions with the highest demand, expressed as standardised volume for the resident population, were Abruzzo (4.5 IUs), Molise (4.2IUs) and Tuscany (3.9 IUs) *per capita*, respectively. In 2017, the demand decreased – in some cases very significantly - in almost all regions, with the exception of Abruzzo (14.9%), the AP of Bolzano (33.3%), Basilicata (13.3%), E. Romagna (0.5%), Friuli-V. Giulia (47.4%), Latium (5.2%), Marche (23.7%), Molise (37.3%), Piedmont (5.4%) and Tuscany (11.8%).

ANTI-D (RH) IMMUNOGLOBULINS (ATC J06BB01)

Table 34 shows the brand names of medicinal products containing the anti-D (Rh) IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 34. Products containing anti-D (Rh) immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
039596010	RHESONATIV*1F 1ML 625UI/ML	625	OCTAPHARMA ITALY SpA	A
022547020	IMMUNORHO*IM 1FL 200MCG+1F 2ML	1000	KEDRION SpA	A
039596022	RHESONATIV*1F 2ML 625UI/ML	1250	OCTAPHARMA ITALY SpA	A
022547018	IMMUNORHO*IM 1FL 300MCG+1F 2ML	1500	KEDRION SpA	A
022547044	IMMUNORHO*IM 1SIR 2ML 300MCG	1500	KEDRION SpA	A
033867021	IGAMAD*IM 1SIR 1500UI/2ML	1500	GRIFOLS ITALIA SpA	A
036161026	RHOPHYLAC*1SIR 300MCG/2ML	1500	CSL BEHRING GmbH	C
039596034	RHESONATIV*10F 2ML 625UI/ML	12500	OCTAPHARMA ITALY SPA	A

Quantification of the demand

The national anti-D (Rh) IGs demand decreased by 4% between 2016 and 2017 and its volume was 122,330,125 IUs in 2017 (2.0 IUs *per capita*), with a maximum in the AP of Bolzano and a minimum in Sardinia (3.9 and 0.8 IUs *per capita*, respectively) (Table 35).

Table 35. Total demand (public and private) and total standardised demand for anti-D (Rh) immunoglobulins, expressed in International Units and in International Units *per capita* and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU *per capita*	IU	UI *per capita*	
Abruzzo	2,756,500	2.1	2,533,500	1.9	-7.8
Aosta Valley	340,500	2.7	304,500	2.4	-10.3
AP Bolzano	2,218,500	4.3	2,052,000	3.9	-8.1
AP Trento	1,902,250	3.5	1,945,000	3.6	2.2
Apulia	6,652,500	1.6	5,854,500	1.4	-11.7
Basilicata	976,500	1.7	888,000	1.6	-8.5
Calabria	2,578,500	1.3	2,188,500	1.1	-14.9
Campania	11,117,000	1.9	10,202,000	1.7	-8.0
E.-Romagna	11,954,500	2.7	10,664,375	2.4	-10.8
Friuli-V. Giulia	3,040,500	2.5	2,791,500	2.3	-7.9
Latium	12,053,500	2.0	11,648,750	2.0	-3.5
Liguria	3,156,000	2.0	2,763,000	1.8	-12.1
Lombardy	25,734,000	2.6	23,775,000	2.4	-7.7
Marche	3,249,000	2.1	2,767,500	1.8	-14.5
Molise	473,500	1.5	404,750	1.3	-14.1
Piedmont	9,481,000	2.2	9,108,875	2.1	-3.7
Sardinia	1,428,250	0.9	1,257,000	0.8	-11.7
Sicily	8,005,500	1.6	8,428,500	1.7	5.7
Tuscany	7,486,625	2.0	9,591,875	2.6	28.2
Umbria	1,842,000	2.1	1,555,500	1.7	-15.3
Veneto	11,173,500	2.3	11,605,500	2.4	4.0
ITALY	127,620,125	2.1	122,330,125	2.0	-4.0

CYTOMEGALOVIRUS IMMUNOGLOBULINS (ATC J06BB09)

Table 36 shows the brand names of medicinal products containing cytomegalovirus immunoglobulins (anti-CMV IGs) currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 36. Products containing cytomegalovirus immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
026167015	CYTOTECT BIOTEST*EV 10ML 500UI	500	BIOTEST PHARMA GmbH	H
026167027	CYTOTECT BIOTEST*EV 20ML 1000U	1000	BIOTEST PHARMA GmbH	H
026167041	CYTOTECT BIOTEST*EV 10ML1000UI	1000	BIOTEST ITALIA Srl	C
026167039	CYTOTECT BIOTEST*EV 50ML 2500U	2500	BIOTEST PHARMA GmbH	H
026167054	CYTOTECT BIOTEST*EV 50ML5000UI	5000	BIOTEST ITALIA Srl	C

Quantification of the demand

Table 37 shows the total and the total standardised demand (IU *per capita*) for CMV IGs for the two-year period 2016-2017, at national and regional levels.

Table 37. Total demand (public and private) and total standardised demand for cytomegalovirus immunoglobulins products, expressed in International Units and in International Units *per capita*, and variations in percentages between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU*per capita*	IU	IU *per capita*	
Abruzzo	202,000	0.2	294,000	0.2	46.0
Aosta Valley	-	0.0	-	-	
AP Bolzano	27,000	0.1	86,000	0.2	216.5
AP Trento	-	0.0	5,000	0.0	
Apulia	246,000	0.1	293,000	0.1	19.5
Basilicata	104,000	0.2	101,000	0.2	-2.3
Calabria	25,000	0.0	10,000	0.0	-59.9
Campania	280,000	0.0	529,000	0.1	89.3
E.-Romagna	2,458,000	0.6	3,069,000	0.7	24.8
Friuli-V. Giulia	516,000	0.4	685,000	0.6	33.1
Latium	791,000	0.1	845,000	0.1	6.7
Liguria	24,000	0.0	-	-	-100.0
Lombardy	555,000	0.1	1,664,000	0.2	199.5
Marche	143,000	0.1	214,000	0.1	50.2
Molise	-	0.0	-	-	
Piedmont	1,719,000	0.4	2,835,000	0.6	65.4
Sardinia	36,000	0.0	-	-	-100.0
Sicily	180,000	0.0	956,000	0.2	433.0
Tuscany	180,000	0.0	293,000	0.1	62.9
Umbria	51,000	0.1	49,000	0.1	-3.7
Veneto	4,590,000	0.9	3,853,000	0.8	-15.9
ITALY	12,127,000	0.2	15,781,000	0.3	30.3

During the period under examination, the CMV IGs national demand increased by 30% to a volume of 15,781,000 IUs. However, the national average displayed strong fluctuations and trends varied from one region to another; Veneto was confirmed as the largest user (0.8 IU *per capita*), followed by Emilia-Romagna (0.7 IU *per capita*), Friuli-Venezia Giulia and Piedmont (0.6 IU *per capita*).

VARICELLA/ZOSTER IMMUNOGLOBULINS FOR INTRAVENOUS USE (ATC J06BB03)

Human immunoglobulins with specific anti-human herpesvirus 3 antibodies (varicella-zoster virus 1) (Var IGs) are used in post-exposure prophylaxis of varicella zoster and in therapy in severe varicella-zoster infections or complications, in immunocompromised patients or infants at risk. These human immunoglobulins are obtained from selected plasma donors with high titers of anti-varicella antibodies (32,33,34).

Table 38 shows the brand names of medicinal products containing Var IGs currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 38. Products containing specific varicella/zoster immunoglobulins for intravenous use currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
026978027*	VARITECT 25 UI/mL 1F 5mL	125	BIOTEST PHARMA GmbH	H
026978015*	VARITECT 25 UI/mL 1F 20mL	500	BIOTEST PHARMA GmbH	H

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

Table 39 shows the total demand and the total standardised demand (IUs per 1,000 population) of Var IGs in the two-year period 2016-2017, at national and regional levels. The national demand for Var IGs showed a slight increase (+6%). Total demand in 2017 was 195,750 IUs (3.2 IUs per 1,000 population units).

Table 39. Total demand (public and private) and total standardised demand for products containing varicella/zoster immunoglobulins for intravenous use, expressed in International Units and International Units per 1,000 population and variations in percentage between 2016 and 2017 (adapted by the CNS on data from Product Quality and Pharmacrime Office - AIFA)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	1,000	0.8	2,125	1.6	113
Aosta Valley	-	NA	-	NA	NA
AP Bolzano	250	0.5	-	NA	-100
AP Trento	3,375	6.3	14,125	26.2	318
Apulia	2,500	0.6	1,500	0.4	-40
Basilicata	-	NA	500	0.9	NA
Calabria	375	0.2	-	NA	-100
Campania	3,750	0.6	2,875	0.5	-23
Emilia-Romagna	54,500	12.3	26,625	6.0	-51
Friuli-V. Giulia	19,625	16.1	18,500	15.2	-5
Latium	9,250	1.6	8,125	1.4	-12
Liguria	3,125	2.0	8,625	5.5	177
Lombardy	33,000	3.3	64,250	6.4	94

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Marche	23,500	15.2	22,125	14.4	-6
Molise	-	NA	250	0.8	NA
Piedmont	125	0.0	1,125	0.3	802
Sardinia	-	NA	-	NA	NA
Sicily	-	NA	1,000	0.2	100
Tuscany	4,625	1.2	3,875	1.0	-16
Umbria	4,125	4.6	5,750	6.5	40
Veneto	21,875	4.5	14,375	2.9	-34
ITALY	185,000	3.0	195,750	3.2	6

RABIES IMMUNOGLOBULINS (ATC J06BB05)

Human immunoglobulins with rabies-specific antibodies (rabies IGs) are used for post-exposure prophylaxis in cases of scratches, bites or other injuries caused by rabid or potentially rabid animals. They are obtained from selected plasma donors with high titers of anti-rabies antibodies (35). Table 40 shows the brand names of drugs containing rabies IGs currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 40. Products containing rabies immunoglobulins currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
- *	BERIRAB P 150UI/mL 2ml	300	CSL BEHRING GmbH	-
- *	BERIRAB P 150UI/mL 5ml	750	CSL BEHRING GmbH	-

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

In 2017, the total demand for rabies IGs, registered in eight regions, showed a significant decrease compared to 2016(-20.5%). The total demand amounted to 84,000 IUs (1.4 IUs per 1,000 population) (Table 41).

Table 41. Total demand (public and private) and total standardised demand for rabies immunoglobulin, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from Product Quality and Pharmacrime Office – AIFA)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1.000 pop.	IU	IU per 1.000 pop.	
Abruzzo	-	-	-	-	NA
Aosta Valley	3,000	23.6	1,500	11.8	-49.8
AP Bolzano	9,300	17.9	10,500	20.0	12.2
AP Trento	3,000	5.6	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	7,650	1.7	9,000	2.0	17.6
Friuli-V. Giulia	18,150	14.9	10,500	8.6	-42.0
Latium	3,000	0.5	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	15,000	1.5	12,000	1.2	-20.1
Marche	-	-	3,750	2.4	NA
Molise	-	-	-	-	NA
Piedmont	-	-	-	-	NA
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	4,650	1.2	10,200	2.7	119.5
Umbria	-	0.0	-	0.0	NA
Veneto	42,000	8.5	26,550	5.4	-36.7
ITALY	105,750	1.7	84,000	1.4	-20.5

LOCAL HAEMOSTATICS AGENTS- COMBINATIONS (ATC B02BC - ATC B02BC30)

Table 42 shows the brand names of drugs containing local haemostatics - combinations currently on the market in Italy and the amount of active ingredient expressed in mL and in the number of gelatin sponges they contain.

Table 42. Products containing local haemostatics - combinations currently available on the Italian market (adapted by the Italian National Blood Centre on data from Farmadati, 31/12/2017)

AIC code	Brand name	mL	Manufacturer	NHS class
035941018	BERIPLAST P*FL POLV 0,5ML+FL	0.5	CSL BEHRING GmbH	C
035941020	BERIPLAST P*FL POLV 1ML+FL+SET	1	CSL BEHRING GmbH	C
035941032	BERIPLAST P*FL POLV 3ML+FL+SET	3	CSL BEHRING GmbH	C
039546015	ARTISS SOL. ADESIVO TISSUTALE	1	BAXTER SpA	H
025243179	TISSEEL 2ml ADESIVO TISSUTALE	2	BAXTER SpA	H
039546027	ARTISS SOL. ADESIVO TISSUTALE	2	BAXTER SpA	H
039591019	EVICEL*2FL 1ml 90MG/mL+1200UI	2	OMRIX BIOPHARMA	H
042046019	SILKETAL 2,5ml ADESIVO TISSUTALE	2.5	KEDRION SpA	C
044152015	KOLFIB*FL POLV SOLV 2,5ML	2.5	KEDRION SpA	C(nn)
025243181	TISSEEL 4ML ADESIVO TISSUTALE	4	BAXTER SpA	H
039591021	EVICEL*2FL 2ML 90MG/ML+1200UI	4	OMRIX BIOPHARMA	H
039546039	ARTISS SOL. ADESIVO TISSUTALE	5	BAXTER SpA	H
042046021	SILKETAL 5ml ADESIVO TISSUTALE	5	KEDRION SpA	C
044152027	KOLFIB*FL POLV SOLV 5ML	5	KEDRION SpA	C(nn)
025243193	TISSEEL 10ml ADESIVO TISSUTALE	10	BAXTER SpA	H
039591033	EVICEL*2FL 5ml 90MG/ML+1200UI	10	OMRIX BIOPHARMA	H
042046033	SILKETAL 10ml ADESIVO TISSUTALE	10	KEDRION SpA	C
044152039	KOLFIB*FL POLV SOLV 10ML	10	KEDRION SpA	C(nn)
AIC code	**Brand name**	**sponges**	**Manufacturer**	**NHS class**
036557015	TACHOSIL*1SPUGNA 9,5CMx4,8CM	1	TAKEDA ITALY SpA	C
036557054	TACHOSIL*1MATRICE 4,8CMx4,8CM	1	TAKEDA ITALY SpA	C
043011016	EVARREST*1BUST 8,1MG+40UI/CM2	1	OMRIX BIOPHARMA	C
036557027	TACHOSIL*2SPUGNE 4,8CMx4,8CM	2	TAKEDA ITALY SpA	C
043011028	EVARREST*2BUST 8,1MG+40UI/CM2	2	OMRIX BIOPHARMA	C

Quantification of demand

The various products with an ATC code related to local haemostatics – combinations do not always have the same composition, but as they are considered equivalent, the active ingredient is expressed in mL and mL per 1,000 population (Table 43). For the products in the form of "medicated gelatin sponges" that cannot be expressed in mL no standardisation is performed and demand is calculated according to the number of packs sold (Table 44).

In 2017, the total demand for local haemostatics - combinations reached a volume of about 75,660 mL (1.2 mL per 1,000 population), showing a slight decrease (-68%) compared to the volume of 2016 (Table 43).

Table 43. Total demand (public and private) and total standardised demand for local haemostatics - combinations, expressed in millilitres and in millilitres per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	8,994	6.8	2,029	1.5	-77.4
Aosta Valley	1,130	8.9	250	2.0	-77.8
AP Bolzano	1,982	3.8	532	1.0	-73.3
AP Trento	3,184	5.9	836	1.6	-73.8
Apulia	16,698	4.1	5,800	1.4	-65.2
Basilicata	3,964	6.9	1,057	1.9	-73.2
Calabria	4,262	2.2	1,360	0.7	-68.0
Campania	31,438	5.4	7,698	1.3	-75.5
Emilia-Romagna	12,016	2.7	5,266	1.2	-56.2
Friuli-V. Giulia	3,494	2.9	1,042	0.9	-70.1
Latium	29,160	5.0	8,010	1.4	-72.6
Liguria	4,803	3.1	1,382	0.9	-71.1
Lombardy	48,216	4.8	18,917	1.9	-60.8
Marche	4,274	2.8	1,174	0.8	-72.4
Molise	1,682	5.4	416	1.3	-75.1
Piedmont	15,615	3.5	3,734	0.9	-76.0
Sardinia	5,870	3.5	948	0.6	-83.8
Sicily	16,377	3.2	3,952	0.8	-75.8
Tuscany	12,891	3.4	4,283	1.1	-66.8
Umbria	4,518	5.1	1,196	1.3	-73.5
Veneto	2,251	0.5	5,778	1.2	157.1
ITALY	232,819	3.8	75,660	1.2	-67.5

Table 44. Total demand (public and private) and total standardised demand for local haemostatics - combinations, expressed in number of gelatin sponges, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016	2017	% Var 2016-2017
	sponges	sponges	
Abruzzo	962	935	-2.5
Aosta Valley	184	182	-0.7
AP Bolzano	347	472	35.1
AP Trento	102	146	43.0
Apulia	1,981	2,393	21.2
Basilicata	1,041	917	-11.4
Calabria	2,037	2,158	6.2
Campania	4,360	4,247	-2.4
Emilia-Romagna	762	940	23.3
Friuli-Venezia Giulia	1,044	1,305	25.3
Latium	2,523	2,505	-0.9
Liguria	489	429	-11.9
Lombardy	6,625	6,785	2.3
Marche	897	1,049	17.4
Molise	23	7	-69.4
Piedmont	3,044	2,844	-6.3
Sardinia	858	673	-21.3
Sicily	2,504	3,167	26.9
Tuscany	2,404	2,651	10.3
Umbria	741	1,127	52.5
Veneto	2,429	2,574	6.1
ITALY	35,357	37,506	6.2

COAGULATION FACTOR VII (ATC B02BD05)

Table 45 shows the brand names of medicinal products containing FVII currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 45. Products containing Factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
024748042	PROVERTINUM TIM3*IV FL 600UI	600	BAXTER AG	A

Quantification of the demand

In 2017, the total demand and the total standardised national demand for FVII was approximately 6 million IUs and showed an increase, compared to 2016, equal to 43% (Table 46). This increase was generalised with the exception of Liguria, Lombardy, Marche. In 2017, there was no utilisation of FVII in several Regions.

Table 46. Total demand (public and private demand) and total standardised demand for Factor VII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow and Latium region)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	94,800	71.5	101,400	76.7	7.3
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	142,200	34.9	495,000	121.8	249.2
Basilicata	-	-	7,200	12.6	100
Calabria	-	-	9,000	4.6	100
Campania	-	-	54,000	9.2	100
E.-Romagna	144,600	32.5	196,800	44.2	36.1
Friuli-V. Giulia	-	-	-	-	NA
Latium	1,687,800	286.6	2,750,400	466.3	62.7
Liguria	45,000	28.6	14,400	9.2	-67.9
Lombardy	1,638,600	163.7	1,420,200	141.7	-13.4
Marche	3,000	1.9	-	-	-100.0
Molise	228,000	730.7	630,000	2,029.3	177.7
Piedmont	174,600	39.6	213,600	48.6	22.7
Sardinia	-	-	-	-	NA
Sicily	7,800	1.5	51,000	10.1	556.1
Tuscany	-	-	4,200	1.1	100
Umbria	-	-	2,400	2.7	100
Veneto	15,000	3.1	36,600	7.5	144.4
ITALY	4,181,400	68.9	5,982,000	98.7	43.2

RECOMBINANT ACTIVATED FACTOR VII (EPTACOG ALFA ACTIVATED) (ATC B02BD08)

Table 47 shows the brand names of medicinal products containing recombinant activated factor VII (rFVIIa) currently available on the Italian market and the amount of active ingredient they contain expressed in milligrams (mg).

Table 47. Products containing recombinant activated factor VII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	mg	Manufacturer	NHS class
029447048	NOVOSEVEN*IV 1MG(50KUI)+1,1ML	1	NOVO NORDISK SpA	H
029447087	NOVOSEVEN*IV 1MG(50KUI)+1ML	1	NOVO NORDISK SpA	H
029447012	NOVOSEVEN*IV 1,2MG(60KUI)+2,2ML	1.2	NOVO NORDISK SpA	H
029447051	NOVOSEVEN*IV 2MG(100KUI)+2,1ML	2	NOVO NORDISK SpA	H
029447099	NOVOSEVEN*IV 2MG(100KUI)+2ML	2	NOVO NORDISK SpA	H
029447063	NOVOSEVEN*IV 5MG(250KUI)+5,2ML	5	NOVO NORDISK SpA	H
029447101	NOVOSEVEN*IV 5MG(250KUI)+5ML	5	NOVO NORDISK SpA	H
029447113	NOVOSEVEN*IV 8MG(400KUI)+8ML	8	NOVO NORDISK SpA	H

Quantification of the demand

Table 48 shows the total demand (mg) and the total standardised demand (mg per 1,000 population) of rFVIIa over the two-year period 2016-2017, at national and regional levels. The total demand for rFVIIa registered in 2017 was 98,963 mg (1.6 mg per 1,000 population), +23.2% compared to 2016.

Table 48. Total demand (public and private) and total standardised demand for recombinant activated factor VII expressed in milligrams and in milligrams per 1,000 population and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Abruzzo	730	0.6	1,315	1.0	80.7
Aosta Valley	28	0.2	13	0.1	-53.4
AP Bolzano	129	0.2	38	0.1	-70.7
AP Trento	21	0.0	1	0.0	-95.2
Apulia	11,101	2.7	11,441	2.8	3.4
Basilicata	288	0.5	152	0.3	-46.9
Calabria	6,585	3.3	7,652	3.9	16.5
Campania	8,720	1.5	10,828	1.9	24.4
E.-Romagna	3,199	0.7	3,895	0.9	21.7
Friuli-V. Giulia	12,072	9.9	14,292	11.7	18.7
Latium	3,808	0.6	4,604	0.8	20.7
Liguria	303	0.2	499	0.3	65.3
Lombardy	6,698	0.7	9,302	0.9	38.7
Marche	1,888	1.2	2,685	1.7	42.7

Region	2016		2017		% Var 2016-2017
	mg	mg per 1,000 pop	mg	mg per 1,000 pop	
Molise	279	0.9	76	0.2	-72.6
Piedmont	5,392	1.2	10,361	2.4	92.7
Sardinia	667	0.4	1,089	0.7	63.8
Sicily	6,799	1.3	5,894	1.2	-13.0
Tuscany	6,139	1.6	5,979	1.6	-2.6
Umbria	366	0.4	828	0.9	126.8
Veneto	5,214	1.1	8,019	1.6	54.0
ITALY	80,426	1.3	98,963	1.6	23.2

FACTOR VIII INHIBITOR BYPASSING ACTIVITY (ATC B02BD03)

Table 49 shows the brand names of medicinal products containing factor VIII inhibitor bypassing activity currently available on the Italian market and the amount of active ingredient they contain expressed in FEIBA Units (FUs).

Table 49. Products containing factor VIII inhibitor bypassing activity currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	FU	Manufacturer	NHS class
024744043	FEIBA*IV FL 500UI+F 20ML	500	BAXALTA ITALY Srl	A
024744068	FEIBA*FL 500UF+BAXJECT II HF	500	BAXALTA ITALY Srl	A
024744056	FEIBA TIM3*IV FL 1000UI+F 20ML	1000	BAXALTA ITALY Srl	A
024744070	FEIBA*FL 1000UF+BAXJECT II HF	1000	BAXALTA ITALY Srl	A

Quantification of the demand

Table 50 shows the total and the total standardised demand (FUs *per capita*) of factor VIII inhibitor bypassing activity over the two-year period 2016-2017 at regional and at national levels.

Table 50. Total demand (public and private) and total standardised demand for factor VIII inhibitor bypassing activity, expressed in FEIBA Units and FEIBA Units *per capita*, and variations in percentage 2016-2017 (adapted by the CNS on data from the traceability information flow and Latium region)

Region	2016		2017		% Var 2016-2017
	FU	FU *per capita*	FU	FU *per capita*	
Abruzzo	739,000	0.6	1,769,000	1.3	140.1
Aosta Valley	-	0.0	-	-	NA
AP Bolzano	149,000	0.3	50,000	0.1	-66.7
AP Trento	20,000	0.0	25,000	0.0	24.9
Apulia	317,000	0.1	514,000	0.1	62.7
Basilicata	-	0.0	-	-	NA
Calabria	1,971,000	1.0	1,804,000	0.9	-8.2
Campania	5,678,000	1.0	5,977,000	1.0	5.5
E.-Romagna	3,079,000	0.7	3,774,000	0.8	22.6
Friuli-V. Giulia	1,171,000	1.0	926,000	0.8	-20.7
Latium	2,125,000	0.4	1,458,000	0.2	-31.5
Liguria	370,000	0.2	-	-	-100.0
Lombardy	2,196,000	0.2	1,770,000	0.2	-19.5
Marche	-	0.0	120,000	0.1	NA
Molise	-	0.0	-	-	NA
Piedmont	1,395,000	0.3	1,456,000	0.3	4.7
Sardinia	684,000	0.4	522,000	0.3	-23.5
Sicily	3,088,000	0.6	1,299,000	0.3	-57.8
Tuscany	1,439,000	0.4	2,228,000	0.6	54.9
Umbria	10,000	0.0	10,000	0.0	0.3
Veneto	630,000	0.1	751,000	0.2	19.4
ITALY	25,061,000	0.4	24,453,000	0.4	-2.3

In 2017, the national demand for factor VIII inhibitor bypassing activity showed a slight decrease (-2.3%) compared to 2016, with wide variations at regional level. Its volume was 24,453,000 FUs, or 0.4 FU *per capita*.

FIBRINOGEN (ATC B02BB01)

Fibrinogen is one of the most abundant coagulation factors in plasma, in which it has a mean concentration of about 2-4 g/L. It is converted into fibrin by thrombin and is the main component of the coagulation phase. Fibrin, therefore, can be considered both a structural protein and a coagulation factor.

In order to provide adequate structural support, the plasma concentration of fibrinogen must be relatively high. A deficiency of fibrinogen therefore implies a lower capacity of the blood to coagulate, with a consequent increase in the tendency to bleeding (36).

The utilisation of Fibrinogen is indicated in the following clinical conditions: i) hypofibrinogenaemia or congenital afibrinogenaemia; ii) congenital dysfibrinogenaemia with a tendency to haemorrhage; iii) occasionally in acquired hypofibrinogenaemia, but only after carefully evaluating other therapeutic options (37) (fresh frozen plasma and cryoprecipitate).

Table 51 shows the brand names of medicinal products containing fibrinogen currently available on the Italian market and the amount of active ingredient they contain expressed in grams (g).

Table 51. Products containing fibrinogen currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	g	Manufacturer	NHS class
*E00178010	HAEMOCOMPLETTAN P 1F 1G	1	CSL BEHRING SpA	H
040170019	RIASTAP FL POLV 1G 20MG/ML	1	CSL BEHRING SpA	C(nn)
044380018	FIBRICLOTTE*FL POLV 1,5G 100ML	1.5	LFB	C(nn)

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Quantification of the demand

Table 52 shows the total demand and the total standardised demand (g per 1,000 population) for fibrinogen over the two-year period 2016-2017 at regional and national level.

In 2017, total fibrinogen demand showed a significant increase (+ 17%) compared to the previous year, confirming the rapidly up-warding trend and its volume was 33,144 g, with a standardised demand of 0.5 g per 1,000 population. The increase was mainly linked to the imported product.

All Regions, with the exception of Molise and Piedmont, contributed in a different measure to this growth.

Table 52. Total demand (public and private) and total standardised demand for fibrinogen, expressed in grams and grams per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow and Product Quality and Pharmacrime Office - AIFA)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	1,109	0.8	1,174	0.9	6.2
Aosta Valley	13	0.1	35	0.3	170.2
AP Bolzano	626	1.2	862	1.6	36.8
AP Trento	203	0.4	243	0.5	19.6
Apulia	1,637	0.4	1,848	0.5	13.3
Basilicata	147	0.3	196	0.3	34.1
Calabria	1,338	0.7	1,601	0.8	20.0
Campania	3,054	0.5	3,442	0.6	12.9
E.-Romagna	2,439	0.5	3,324	0.7	36.3
Friuli-V. Giulia	382	0.3	612	0.5	60.6
Latium	3,146	0.5	3,429	0.6	8.8
Liguria	312	0.2	383	0.2	23.2
Lombardy	3,254	0.3	3,772	0.4	15.8
Marche	474	0.3	593	0.4	25.6
Molise	72	0.2	48	0.2	-33.0
Piedmont	971	0.2	895	0.2	-7.6
Sardinia	1,422	0.9	1,578	1.0	11.3
Sicily	1,408	0.3	1,668	0.3	18.9
Tuscany	1,525	0.4	2,203	0.6	44.5
Umbria	796	0.9	1,063	1.2	33.9
Veneto	4,001	0.8	4,175	0.9	4.5
ITALY	28,329	0.5	33,144	0.5	17.1

ALPHA-1-PROTEINASE INHIBITOR (ATC B02AB02)

The alpha-1-proteinase inhibitor (also known as alpha-1-antitrypsin or alpha-1-antiproteinase) is normally present in human plasma at concentrations that range from 0.7 to 2.3 g/L. The alpha-1-proteinase inhibitor is also present in some extravascular spaces, in particular the pulmonary alveoli, where it carries out its main function. In fact, it modulates the action of enzymes produced by neutrophils (elastase) thus avoiding damage to lung tissue. Alpha-1-antitrypsin is indicated for replacement therapy in subjects with inherited deficiency (38). Table 53 shows the brand names of medicinal products containing alpha-1-proteinase inhibitor currently available on the Italian market and the relative quantity of active ingredient they contain expressed in milligrams (mg).

Table 53. Products containing alpha-1-proteinase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC Code	Brand name	mg	Manufacturer	NHS class
037709019	PROLASTIN*EV 1F 1G/40ML+F40ML	1000	GRIFOLS ITALIA SpA	H
044479018	RESPREEZA*EV 1FL 20ML+SOL 1G	1000	CSL BEHRING GmbH	C(nn)

Quantification of the demand

In 2017, the total demand for alpha-1-antitrypsin was 32,317 g (0.5 g per 1,000 population) showing a significant upward trend compared to the previous year (+20.2%) (Table 54).

Table 54. Total demand (public and private) and total standardised demand for alpha-1-proteinase inhibitor, expressed in grams and grams per 1,000 population, and variations in percentage between 2016-2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	g	g per 1,000 pop	g	g per 1,000 pop	
Abruzzo	634	0.5	777	0.6	23.0
Aosta Valley	975	7.7	1,001	7.9	3.0
AP Bolzano	2,895	5.6	3,096	5.9	6.3
AP Trento	750	1.4	640	1.2	-14.7
Apulia	817	0.2	965	0.2	18.5
Basilicata	-	0.0	-	-	0.0
Calabria	250	0.1	220	0.1	-11.8
Campania	944	0.2	1,602	0.3	70.0
E.-Romagna	1,330	0.3	2,169	0.5	63.1
Friuli-V. Giulia	2,040	1.7	2,157	1.8	6.0
Latium	668	0.1	1,182	0.2	76.7
Liguria	870	0.6	739	0.5	-14.7
Lombardy	6,132	0.6	7,256	0.7	18.2
Marche	100	0.1	251	0.2	151.9
Molise	39	0.1	108	0.3	178.3
Piedmont	2,539	0.6	2,642	0.6	4.3
Sardinia	1,219	0.7	1,466	0.9	20.6
Sicily	928	0.2	1,318	0.3	42.5
Tuscany	1,738	0.5	1,404	0.4	-19.2
Umbria	128	0.1	207	0.2	62.1
Veneto	1,913	0.4	3,117	0.6	63.2
ITALY	26,909	0.4	32,317	0.5	20.2

Demand increased in every region with the exception of Calabria, the AP of Trento, Liguria and Tuscany. Particularly, demand more than doubled compared to 2016in Molise and Marche (+178%, +152%, respectively). The regions with the highest standardised regional demand were Aosta Valley and AP of Bolzano (7.9 and 5.9 grams per 1,000 population, respectively).

PLASMA-DERIVED C1-INHIBITOR (ATC B06AC01)

Human C1 esterase inhibitor is a heat-labile plasma protein that inhibits the uncontrolled activation of the classical complement pathway (in particular that of C1 esterase) the deficiency of which is responsible for hereditary angio-oedema. The mean concentration of the C1 inhibitor in plasma is approximately 0.2 g/L (39).

Table 55 shows the brand names of medicinal products containing human C1 esterase inhibitor currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 55. Products containing human C1 esterase inhibitor currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
039056015	BERINERT*IV FL 500U+FL 10ML	500	CSL BEHRING SpA	A
042017018	CINRYZE*EV 2FL 500U+2FL	1000	SHIRE ITALIA SpA	A
039056027	BERINERT*IV FL 1500U+FL 10ML	1500	CSL BEHRING SpA	C

Quantification of the demand

In 2017, the total demand for C1 esterase inhibitor was 12,143,500 IUs (200 IUs per 1,000 population), an increase of 27% (Table 56) compared to 2016.

Table 56. Total demand (public and private) and total standardised demand for C1 esterase inhibitor, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	239,000	180.2	316,500	239.4	32.9
Aosta Valley	63,000	494.8	68,000	535.9	8.3
AP Bolzano	2,500	4.8	2,000	3.8	-20.5
AP Trento	7,000	13.0	13,000	24.1	85.6
Apulia	883,000	216.6	1,113,500	274.0	26.5
Basilicata	90,000	156.9	45,000	78.9	-49.7
Calabria	249,500	126.6	339,000	172.5	36.2
Campania	1,351,000	230.9	1,637,500	280.4	21.5
E.-Romagna	394,500	88.7	460,000	103.4	16.6
Friuli-V. Giulia	28,000	22.9	7,500	6.2	-73.1
Latium	1,053,000	178.8	1,306,000	221.4	23.8
Liguria	47,000	29.9	168,500	107.6	259.8
Lombardy	1,309,500	130.8	1,789,500	178.6	36.5
Marche	198,000	128.3	280,500	182.4	42.2
Molise	6,000	19.2	5,500	17.7	-7.9
Piedmont	531,500	120.7	585,000	133.2	10.4
Sardinia	491,500	296.4	626,000	378.7	27.8
Sicily	1,275,000	251.3	1,698,500	335.9	33.7
Tuscany	397,000	106.0	367,000	98.1	-7.5
Umbria	96,000	107.7	231,000	259.9	141.2
Veneto	867,000	176.4	1,084,000	220.9	25.2
ITALY	9,579,000	157.9	12,143,500	200.4	26.9

A high variability in standardised regional demands was observed, with maximum volumes in Aosta Valley, Sardinia and Sicily (536, 379 and 336 IUs per 1,000 population, respectively) and minimum volumes in the APs, Friuli-V. Giulia and Molise (range: 4-24 IUs per 1,000 population). The demand increased in almost all regions, with the exception of the AP of Bolzano, Basilicata, Friuli-V. Giulia, Molise and Tuscany.

COAGULATION FACTOR X (ATC B02BD13)

Congenital Factor X deficiency (or Stuart-Prower factor deficiency) is an inherited haemorrhagic disorder characterised by the decreased activity of the Factor X (FX) antigen, which causes severe or moderate bleeding. The prevalence of homozygous forms is estimated at 1/1,000,000. No gender differences were reported. Haemorrhagic episodes are usually treated with 3F-PCCs or fresh frozen plasma (40).

Table 57 shows the brand names of drugs containing FXpd currently on the market in Italy and the amount of active ingredient they contain expressed in IUs.

Table 57. Products containing coagulation Factor X currently available on the Italian market (adapted by the CNS on data from Farmadati and Product Quality and Pharmacrime Crime Office- AIFA, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
*	FACTOR X P BEHRING 1FL	600-1200§	CSL BEHRING SpA	-
044840015	COAGADEX 100 UI/ML- IV 2,5 mL	250	BIO PRODUCTS LAB. LTD	C(nn)
044840027*	COAGADEX 100 UI/ML- IV 5 mL	500	BIO PRODUCTS LAB. LTD	C(nn)

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

§ The average quantity of active ingredient contained was used in the definition of the demand.

Quantification of the demand

Products containing FX concentrates are used exclusively in Lombardy, where in 2017 the demand was for48,000 IUs (4.8 IUs per 1,000 population) (Table 58).

Table 58. Total demand (public and private) and total standardised demand for coagulation Factor X expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from Product Quality and Pharmacrime Office-AIFA)

Region	2016		2017		Var % 2016-2017
	IU	IU per 1,000 pop	UI	IU per 1,000 pop	
Lombardy	63,850	6.4	48,000	4.8	-24.9
ITALY	63,850	1.1	48,000	0.8	-24.7

COAGULATION FACTOR XIII (ATC B02BD07)

Plasma-derived coagulation Factor XIII (FXIIIpd), also called fibrin stabilising factor, plasma protransglutaminase or Laki-Lorand factor, plays a fundamental role in coagulation processes and is used in the replacement therapy for congenital FXIII deficiency, an autosomal-recessive disorder, whose prevalence is estimated at around 1/2,000,000 (41).

Depending on the level of FXIII activity, severe forms (FXIII<1%), moderate (between 1 and 4%) and mild (FXIII>5%) are distinguished. Where products containing FXIIIpd are not available, fresh frozen plasma is used as an alternative (41).

Since 2014, products obtained with recombinant genetic techniques (rFXIII) have been available (42,43) of which, starting from 2016, utilisation has been recorded only in certain regions.

Table 59 and Table 60 show the brand names of drugs containing FXIIIpd and rFXIII, respectively, currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 59. Products containing plasma-derived coagulation factor XIII distributed in ITALY (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
042605016	CLUVIAT FL 250UI	250	CSL BEHRING SpA	H
042605028	CLUVIAT FL 1250UI	1250	CSL BEHRING SpA	H
024644015*	FIBROGAMMIN 1FL 250UI	250	CSL BEHRING GmbH	H
024644027*	FIBROGAMMIN 1FL 1250UI	1250	CSL BEHRING GmbH	H

* Medicinal products imported under the provisions of DM of 11 February 1997 (8) and DM of 11 May 2001 (10).

Table 60. Products containing recombinant coagulation factor XIII currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
043034014	NOVOTHIRTEEN*EV FL 2500UI	2500	NOVO NORDISK SpA	H

Quantification of the demand

In 2017, the total demand for FXIII was 664,000 IUs (11.0 IUs per 1,000 population) and less than half, equal to 286,500 IUs (4.7 IUs per 1,000 population), was for pdFXIII. The latter registered a decrease of 2.5 % compared to 2016 (Table 61). In 2017, there was no utilisation of FXIII in some regions. The demand was highest in Basilicata and lowest in Liguria (69.5 and 0.5 IU per 1,000 population, respectively). In Abruzzo, Basilicata, Calabria and Lombardy, only rFXIII was used (Table 62).

Table 61. Total demand (public and private) and total standardised demand for plasma-derived coagulation factor XIII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by CNS on data from the traceability information flow and Product Quality and Pharmacrime Office-AIFA)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	6,250	11.6	9,000	16.7	43.9
Apulia	-	-	-	-	NA
Basilicata	-	-	-	-	NA
Calabria	-	-	-	-	NA
Campania	-	-	-	-	NA
E.-Romagna	110,500	24.8	97,250	21.9	-12.0
Friuli-V. Giulia	-	-	-	-	NA
Latium	52,000	8.8	51,750	8.8	-0.6
Liguria	13,250	8.4	750	0.5	-94.3
Lombardy	47,000	4.7	37,500	3.7	-20.3
Marche	1,250	0.8	5,250	3.4	321.6
Molise	-	-	-	-	NA
Piedmont	12,000	2.7	18,750	4.3	56.7
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	17,750	4.7	18,500	4.9	4.3
Umbria	-	-	-	-	NA
Veneto	40,500	8.2	47,750	9.7	18.1
ITALY	294,250	4.9	286,500	4.7	-2.5

Table 62. Total demand (public and private) and total standardised demand for recombinant coagulation factor XIII expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow and Product Quality and Pharmacrime office, AIFA)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	55,000	41.5	65,000	49.2	18.6
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	-	-	-	-	NA
Basilicata	40,000	69.7	37,500	65.7	-5.7
Calabria	70,000	35.5	107,500	54.7	54.0
Campania	20,000	3.4	-	-	-100
E.-Romagna	-	-	-	-	NA
Friuli-V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	40,000	25.5	45,000	28.7	12.9
Lombardy	50,000	5.0	62,500	6.2	24.9
Marche	-	-	-	-	NA
Molise	-	-	-	-	NA
Piedmont	-	-	45,000	10.2	100
Sardinia	-	-	-	-	NA
Sicily	-	-	-	-	NA
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	10,000	2.0	15,000	3.1	50.2
ITALY	285,000	4.7	377,500	6.2	32.6

PROTEIN C (ATC B01AD12)

Protein C is one of the most important factors of the anticoagulant system together with AT and protein S. It is a vitamin K-dependent serine-protease produced by the liver, which is indicated in purpura fulminans and in patients with severe congenital deficiencies. The mean concentration of protein C in plasma is approximately 3-5 μg / mL (44).

Table 63 shows the brand names of drugs containing protein C currently available on the Italian market and the amount of active ingredient they contain expressed in IUs.

Table 63. Products containing protein C currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	IU	Manufacturer	NHS class
035389016	CEPROTIN*IV 500UI	500	BAXTER SpA	H
035389028	CEPROTIN*IV 1000UI	1000	BAXTER SpA	H

Quantification of the demand

In 2017, the national demand for protein C stood at a volume of 800,000 IUs (13.2 IUs per 1,000 population) with a decrease of around a quarter compared to 2016 (Table 64).

Table 64. Total demand (public and private) and total standardised demand for protein C, expressed in International Units and International Units per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	IU	IU per 1,000 pop	IU	IU per 1,000 pop	
Abruzzo	47,500	35.8	16,500	12.5	-65.2
Aosta Valley	-	-	-	-	NA
AP Bolzano	6,000	11.5	3,000	5.7	-50.3
AP Trento	-	-	-	-	NA
Apulia	130,500	32.0	36,000	8.9	-72.3
Basilicata	-	-	-	-	NA
Calabria	10,000	5.1	22,000	11.2	120.6
Campania	356,500	60.9	250,000	42.8	-29.7
E.-Romagna	22,500	5.1	14,000	3.1	-37.8
Friuli-V. Giulia	-	-	-	-	NA
Latium	54,500	9.3	70,000	11.9	28.2
Liguria	45,000	28.6	24,000	15.3	-46.5
Lombardy	173,000	17.3	149,000	14.9	-14.0
Marche	21,000	13.6	-	-	-100.0
Molise	-	-	-	-	NA
Piedmont	2,500	0.6	66,000	15.0	2547.0
Sardinia	4,000	2.4	-	-	-100.0
Sicily	119,000	23.5	87,500	17.3	-26.2
Tuscany	49,000	13.1	5,000	1.3	-89.8
Umbria	1,000	1.1	4,000	4.5	301.0
Veneto	40,500	8.2	53,000	10.8	31.1
ITALY	1,082,500	17.8	800,000	13.2	-26.0

The maximum regional demand was in Campania, Sicily and Liguria, with 43, 17 and 15 IUs per 1,000 population, respectively; the minimum regional demand was in Tuscany, E.-Romagna and Umbria, with volumes between 1.3 and 4.5 IUs per 1,000 population.

OTHER PLASMA PROTEIN FRACTIONS (ATC B05AA02)

Other plasma protein fractions include products with different compositions and therapeutic indications and include solvent/detergent-treated plasma (Plasmasafe™, Plasmagrade™ and Octaplas™) and products with an albumin content of between 85 and 90% (Umanserum™).

Solvent/detergent-treated plasma is a product obtained from a pool of hundreds of donors of the same group (1) and has the following characteristics:

- high lot-to-lot standardisation;
- declaration of the concentration/activity of biologically active proteins;
- reduction of immunological risks due to the presence of antibodies, cells (or their fragments);
- inactivation of potentially transmissible pathogens.

Solvent/detergent-treated plasma has the same therapeutic indications as fresh frozen plasma.

Table 65 shows the brand names of the drugs containing other plasma protein fractions currently available on the Italian market and the amount of active ingredient they contain expressed in mL.

Table 65. Products containing other plasma protein fractions currently available on the Italian market (adapted by the CNS on data from Farmadati, 31/12/2017)

AIC code	Brand name	mL	Manufacturer	NHS class
033369012	PLASMASAFE*INFUS SACCA 200ML	200	KEDRION SpA	H
034540017	OCTAPLAS*INFUS SACCA 200ML	200	OCTAPHARMA PHARM.	H
041868011	PLASMAGRADE*INFUS SACCA 200ML	200	KEDRION SpA	H
021112040	UMANSERUM*INFUS 250ML 5%	250	KEDRION SpA	C

Quantification of the demand

As regards the different composition and different clinical use, the demands of these two sub-groups of medicinal products have been quantified distinctly.

Table 66 shows the utilisation of Plasmasafe™ and Octaplas™, while Table 67 shows the data related to Umanserum™, the demand for which, in 2017, registered an increase of 38% compared to 2016, and a total volume of 6,368,750mL.

The national demand for solvent/detergent-treated plasma in 2017decreased by1.5% compared to 2016, with a regional upward trend only in Basilicata (8%), Calabria (8%), E.-Romagna (20%), Piedmont (28%), Sardinia (75.5%), Sicily (3.4%), Tuscany (12.7%) and Veneto (7.3%).

Table 66. Total demand (public and private) and total standardised demand for solvent/detergent-treated plasma (excluding Umanserum®), expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2016 and 2017(adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	344,000	259.3	172,000	130.1	-49.8
Aosta Valley	-	NA	-	NA	NA
AP Bolzano	-	NA	-	NA	NA
AP Trento	-	NA	-	NA	NA
Apulia	4,158,400	1,019.9	3,250,000	799.7	-21.6
Basilicata	702,000	1,223.6	754,000	1,322.0	8.0
Calabria	932,000	473.0	1,004,000	510.9	8.0
Campania	4,746,000	811.2	4,389,200	751.7	-7.3
E.-Romagna	233,200	52.4	280,000	62.9	20.0
Friuli-V. Giulia	14,000	11.5	-	NA	-100
Latium	4,769,200	809.9	4,488,000	760.9	-6.1
Liguria	873,600	556.1	650,000	415.3	-25.3
Lombardy	693,200	69.3	608,000	60.7	-12.4
Marche	2,016,400	1,306.2	1,913,000	1,243.8	-4.8
Molise	420,000	1,346.0	384,000	1,236.9	-8.1
Piedmont	3,256,000	739.3	4,152,000	945.2	27.9
Sardinia	8,000	4.8	14,000	8.5	75.5
Sicily	4,270,600	841.6	4,401,800	870.5	3.4
Tuscany	1,530,200	408.7	1,724,000	460.7	12.7
Umbria	-	NA	-	-	NA
Veneto	3,688,200	750.4	3,952,000	805.3	7.3
ITALY	32,655,000	538.3	32,136,000	530.4	-1.5

Table 67. Total demand (public and private) and total standardised demand for Umanserum™ expressed in millilitres and millilitres per 1,000 population, and variations in percentage between 2016 and 2017 (adapted by the CNS on data from the traceability information flow)

Region	2016		2017		% Var 2016-2017
	mL	mL per 1,000 pop	mL	mL per 1,000 pop	
Abruzzo	-	-	-	-	NA
Aosta Valley	-	-	-	-	NA
AP Bolzano	-	-	-	-	NA
AP Trento	-	-	-	-	NA
Apulia	2,028,750	497.6	3,136,250	771.7	55.1
Basilicata	26,250	45.8	-	-	-100
Calabria	160,000	81.2	293,750	149.5	84.1
Campania	-	-	-	-	NA
E.-Romagna	-	-	-	-	NA
Friuli-V. Giulia	-	-	-	-	NA
Latium	-	-	-	-	NA
Liguria	-	-	-	-	NA
Lombardy	-	-	-	-	NA
Marche	-	-	-	-	NA
Molise	2,500	8.0	2,500	8.1	0.5
Piedmont	150,000	34.1	-	-	-100
Sardinia	-	-	-	-	NA
Sicily	2,258,750	445.1	2,936,250	580.7	30.4
Tuscany	-	-	-	-	NA
Umbria	-	-	-	-	NA
Veneto	-	-	-	-	NA
ITALY	4,626,250	76.3	6,368,750	105.1	37.8

PART C
National self-sufficiency in toll-fractionated plasma derived medicinal products

SELF-SUFFICIENCY

According to Italian legislation, the term PDMP self-sufficiency refers to the capacity of regional health systems (through agreements signed by several or by single Regions) to satisfy their needs for PDMPs. This is achieved by utilising products obtained from the processing of plasma collected by BEs and sent to companies to be toll fractionated, which also reduces the quantity of PDMPs supplied via the pharmaceutical market. However, PDMP self-sufficiency must take into account the levels of appropriateness of clinical use and the management of available resources.

Self-sufficiency in PDMPs and blood components was one of the objectives of Law 219/2005:

- aimed at guaranteeing the same quality and safety as regards transfusion therapy to all citizens. It is a supra-regional supra-industrial non-divisible national interest for which the Regions and the Health Authorities have to compete through public tenders;
- to this end, the law establishes some principles of regional health planning (Art. 11) and entrusts all coordination activities to the CNS (Art. 12). It also recognizes the annual programme of national self-sufficiency (Art. 14);
- as the instrument to determine every aspect of national self-sufficiency, such as historical consumption, real needs, production levels required, resources, the criteria for financing the system, the methods of compensation between the Regions and the levels of import and export if necessary.

Furthermore, Article 26 of the Legislative Decree of 20 December 2007, n. 261 (45) provides for the definition of a programme by the MoH through a special decree. The objective of said decree is to develop the collection of plasma in BEs and BCUs, and promote the rational and appropriate use of PDMPs while, with the DM of 2 December 2016, the first national plasma and PDMP programme for the five-year period 2016-2020 was published (46).

Toll fractionation system

The plasma collected in Italy comes from voluntary, periodic, responsible, anonymous and non-remunerated donations. The Regions, individually or in association, send the plasma collected by the BEs, belonging to their territory, to the authorised and affiliated company for it to be industrially transformed into PDMPs. The contract with companies, which operate as service providers, is considered a "toll fractionation process" and constitutes a contract agreement for the production of PDMPs. The acquisition of toll fractionation processes is carried out through a tender procedure in compliance with current legislation. For this purpose, during 2015 and 2016, which had already been implemented, three new inter-regional agreements were signed:

- the New Interregional Agreement for Plasma-Derived Medicinal Products (*Nuovo Accordo Interregionale per la Plasmaderivazione*, NAIP), which includes Abruzzo, Basilicata, Friuli-Venezia Giulia, Liguria, the AP of Bolzano, the AP of Trento, Umbria, Veneto (Leading Region), and Aosta Valley;
- the Plasma/Plasma-Derived Interregional Grouping (*Raggruppamento Interregionale Plasma e Plasmaderivati*, RIPP) to which Calabria, Emilia-Romagna (Leading Region), Apulia and Sicily belong;
- the Plasma Network (PlaNet) which includes Campania, Latium (including the General Inspectorate of Military Health), Marche, Molise and Tuscany (Leading Region).

Under the terms of this type of agreement, as set down in the DM of 12 April 2012 (47), the production of PDMPs is defined by a qualitative-quantitative production plan. The Company accepts to produce the quantity and to guarantee the quality of the PDMPs requested by the Regions respecting both the scheduled times and specified procedures; the contracting Regions, in turn, undertake to make the necessary plasma available according to agreed quantities and quality specifications. The Regions have the right to full ownership of the plasma sent for industrial processing, of all the pharmaceutical specialties derived from it, as well as of the residual material. Consequently, the supplier of the industrial processing service cannot use the plasma, the intermediate fractions or the finished products nor the residual raw material for purposes other than those provided for under the agreement, without a prior agreement with the Regions. The DM of 5 December 2014 identifies the following companies as the only ones authorized to fractionate national plasma: Baxter Manufacturing, Csl Behring S.p.A., Grifols Italia, Kedrion, Octapharma Italy (48).

In 2016, the tender for the supply of toll fractionation services for the signatory Regions of the NAIP was won by CSL Behring S.p.A. The resultant contract provided for the supply of albumin, IV IGs, SC/IM IGs, pdFVIII, FVIII / vWF in combination and fibrinogen. The first shipment of plasma took place in May 2017. No products were supplied to NAIP Regions by the end of 2017.

The agreements with the toll fractionation company Kedrion remained in place for all the remaining Regions, whose contract involved the production of albumin, IV IGs, pdFVIII, pdFIX, 3F-PCCs, AT and solvent detergent virus-inactivated plasma.

Plasma for fractionation

From 2000 to 2017, the quantity of plasma collected on a national scale (Figure 33) steadily increased, from a total of 462,805 kilograms sent to the fractionation industry in 2000 to 836,375 kilograms in 2017, with an increase of 81% in the period under examination.

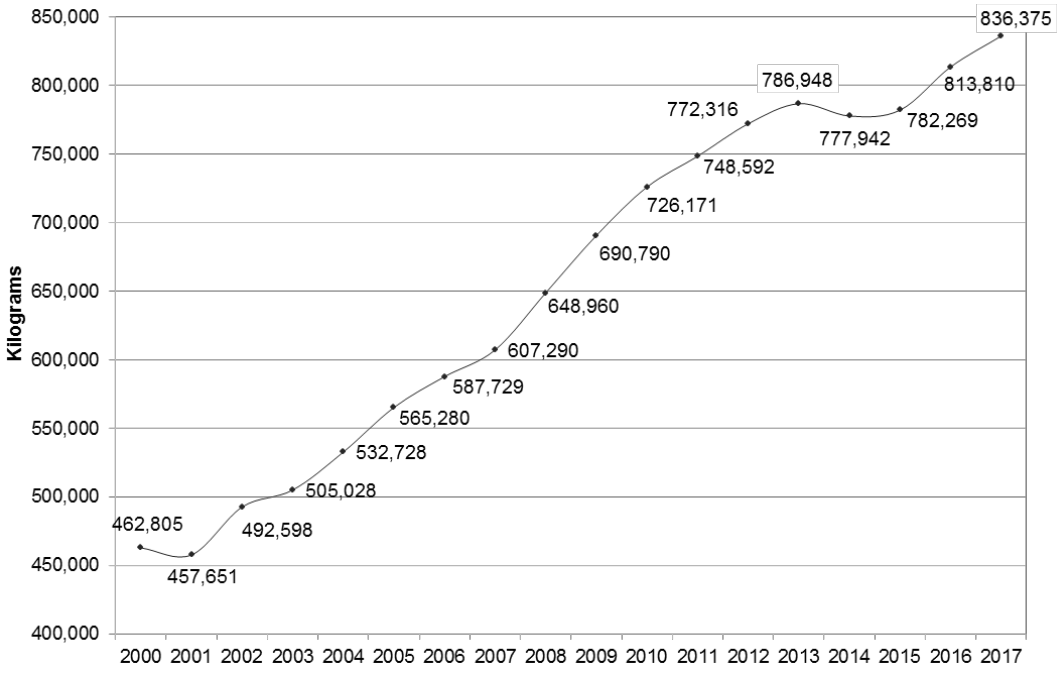

Figure 33. Plasma sent for fractionation sent, 2000-2017 (adapted by the CNS on Kedrion and CSL Behring data, December 2017)

The mean annual rate of change over the period considered was 3.6% with two peak growth periods – between 2004-2006 and 2008-2010. From the year 2008 there was a steady decline in the annual rate of change (Figure 34) which, in 2014, reached the lowest value for the entire period considered (-1.1%). The variation in percentage between 2016and 2017 was 2.8%.

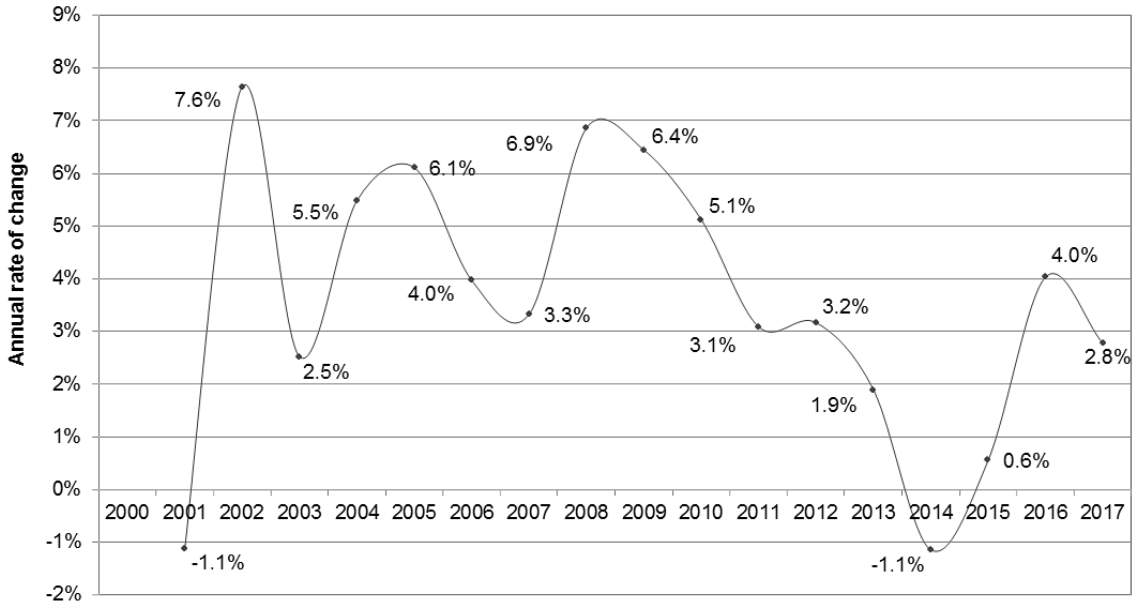

Figure 34. Annual rate of change in the amount of plasma for fractionation, from 2001 to 2017 (adapted by the CNS on Kedrion and CSL Behring data, December 2017)

The amount of plasma sent for industrial fractionation by the individual Regions, however, varied greatly in both quantitative and qualitative terms.

In 2017, the Regions participating in the LPS agreement collected about one third of the plasma sent for fractionation for a total of 245,912 kilograms. The RIPP Regions sent 211,235 kilograms, the NAIP Regions 195,910 kilograms and the Planet Regions 183,319 kilograms, corresponding respectively to 25, 23 and 22% of the total (Figure 35).

As regards the amount of plasma sent for fractionation in 2017, for the resident population, the NAIP Regions sent 16.9 kilograms (almost comparable to the 2016 volume for the same Regions), the LPS Regions sent 15.3 kilograms, the RIPP Regions sent 13.6 kilograms and the Planet Regions sent 10.6 kilograms. All volumes are expressed per 1,000 population (Figure 36).

In 2017, although the national volume stood at 13.8 kilograms per thousand population (+0.4% compared to 2016), the volumes of each single region differed greatly. In fact, the highest volumes were 22.2 kilograms per thousand population in Friuli-Venezia Giulia, 21.9 in Marche and 20.1 in Emilia-Romagna, while the lowest volumes – although higher compared to 2016 - were recorded in Calabria, Latium and Campania with 9.1, 6.9 and 5.4 kilograms per thousand population, respectively (Figure 37).

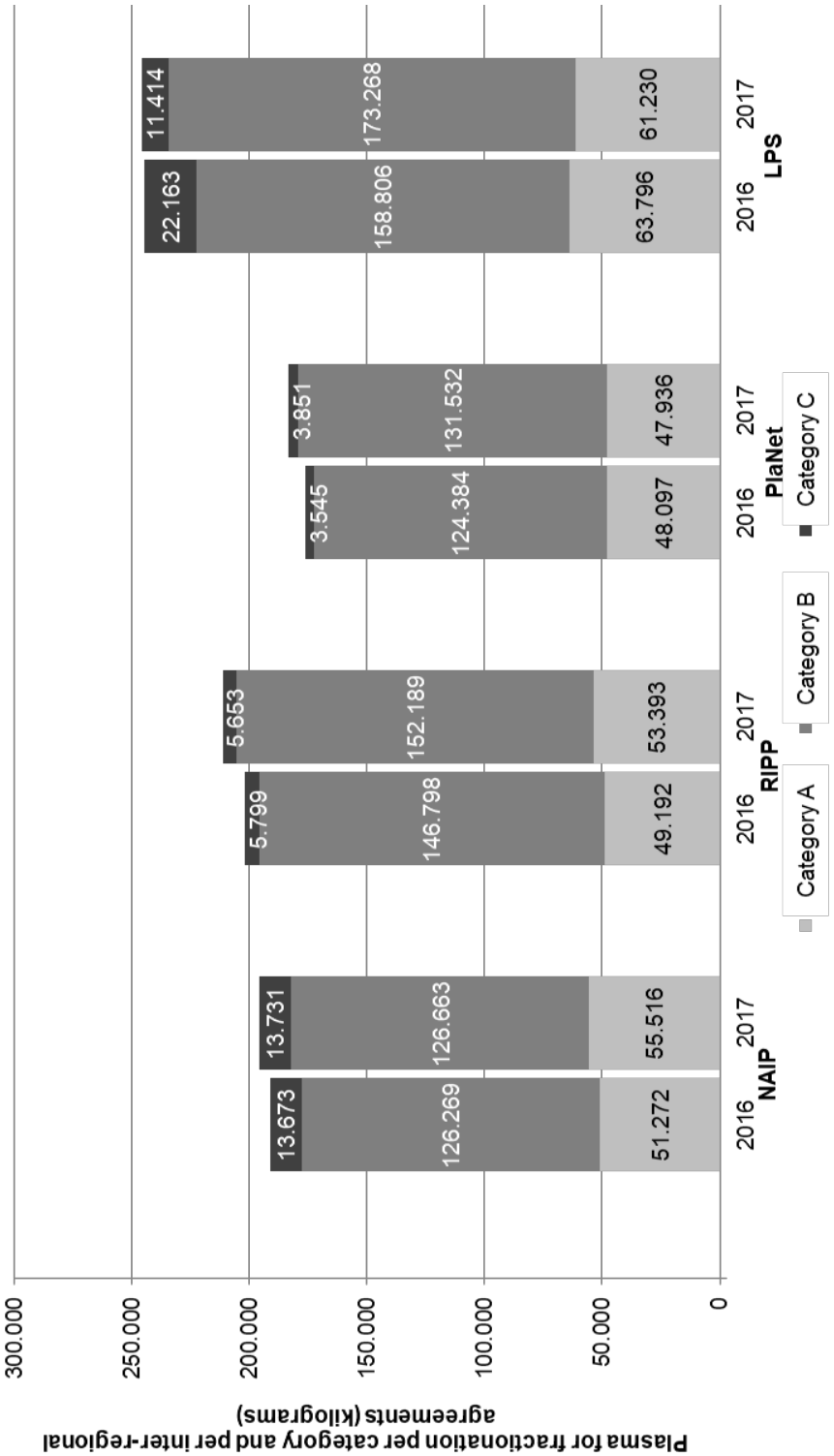

Figure 35. Total amount of plasma for fractionation by category under interregional agreements (kilograms), 2016-2017 (adapted by the CNS on data provided by Kedrion and CSL Behring, December 2017)

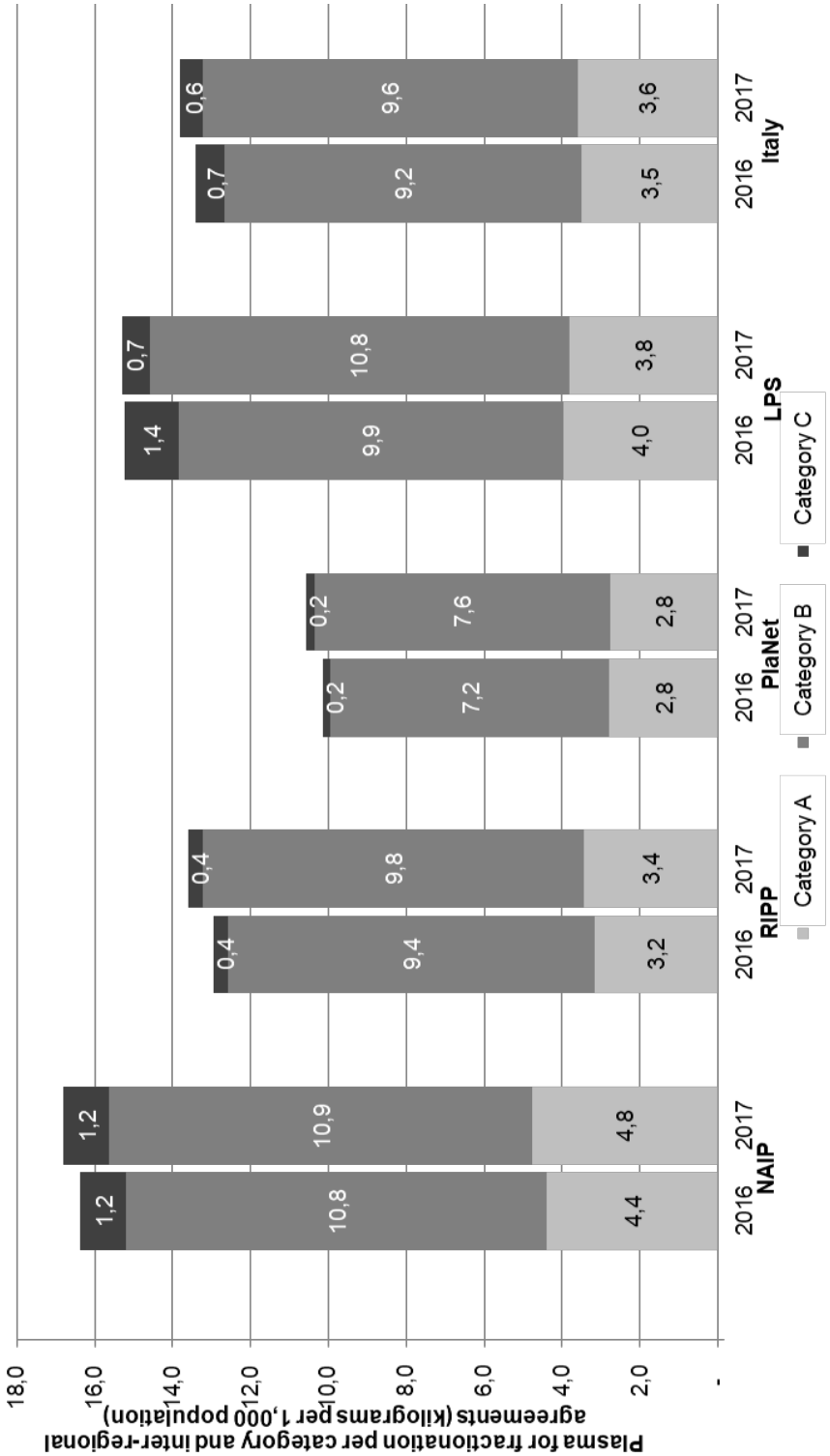

Figure 36. Total amount of plasma for fractionation by category under interregional agreements (kilograms per 1,000 population), 2016-2017 (adapted by the CNS on data provided by Kedrion and CSL Behring, December 2017)

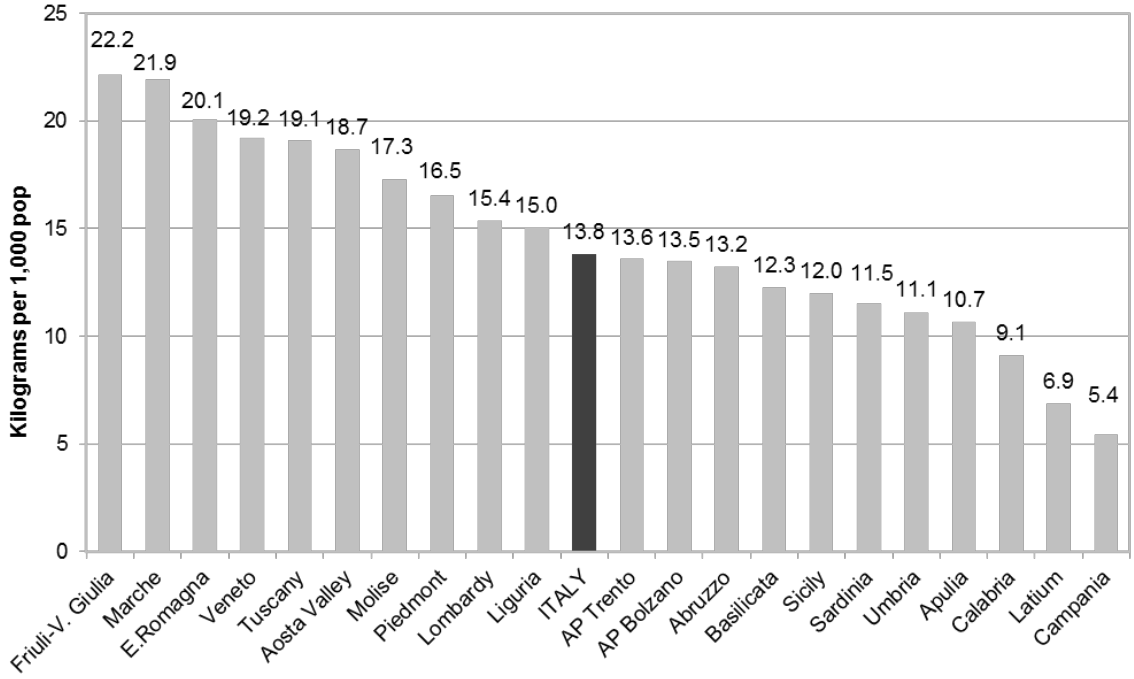

Figure 37. Total amount of plasma (kilograms per 1,000 population) for fractionation by region, year 2017 (adapted by the CNS on data provided by Kedrion and CSL Behring, December 2017)

Supply of PDMPs from toll fractionation

The total quantity of plasma sent for fractionation in 2017 by the Italian Regions was 836,375kilograms (Table 68); of these, 26% (218,074 kilograms) was apheresis plasma (category A), 70% (583,653 kilograms) separated plasma (category B) and the remaining 4% (34,649 kilograms) separated plasma (category C). In 2017, no production of hepatitis B plasma was recorded. The percentages of all three categories of plasma sent for fractionation varied from one regional area to another; in particular, the Regions that sent the highest percentages of apheresis plasma compared to the total amount of plasma sent were Tuscany, Friuli-Venezia Giulia and Marche, with values close to 42%. The Regions which sent low levels of type A plasma were Apulia, Sardinia, Calabria and Campania (<4%). As regards category B plasma, the highest percentages out of the regional total were recorded in Calabria, Campania, the AP of Trento and Umbria which accounted for over 90% of the total, while the lowest percentage share was recorded in Friuli-Venezia Giulia (57%) (Table 68). Tables 69-70 show respectively the amount of PDMPs potentially obtainable from the industrial fractionation of the total amount of plasma sent and usable in 2017 (from July 2016 to June 2017). These figures are based on the contractual yields between the fractionation companies and the Regions (potential supply or production capacity) and the quantities, in grams and IUs, of the six PDMPs distributed to the individual Regions in 2017 in accordance with the specified production and distribution programmes (effective supply or toll fractionation) (Table 71).

It is worth underlining that CSL Behring started to collect plasma in May 2017. Therefore, there was not enough time to return any PDMPs to NAIP Regions. As a result, self-sufficiency in NAIP Regions is estimated only on the basis of the PDMPs made available by Kedrion according to their expiring contract. In Table 71 only the effective supply of Kedrion products are reported.

Table 68. Total quantity, expressed in kilograms, quantity per 1,000 population and variation in percentage for the years 2016-2017 classified by Region and plasma category (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	A	%	B	%	C	%	Tot. Fract.	Total per 1,000 pop
Abruzzo	4,820	27.5	12,566	71.7	129	0.7	17,516	13.2
Aosta Valley	848	35.8	1,522	64.2	-	-	2,370	18.7
AP Bolzano	1,193	16.9	5,868	83.1	-	-	7,061	13.5
AP Trento	691	9.4	6,622	90.6	-	-	7,313	13.6
Basilicata	1,629	23.3	4,490	64.2	873	12.5	6,992	12.3
Friuli-V. Giulia	11,353	42.1	15,245	56.5	390	1.4	26,987	22.2
Liguria	5,338	22.7	18,160	77.1	42	0.2	23,540	15
Umbria	960	9.7	8,896	90.3	-	-	9,856	11.1
Veneto	28,685	30.4	53,294	56.5	12,296	13	94,275	19.2
NAIP	**55,516**	**28.3**	**126,663**	**64.7**	**13,731**	**7**	**195,910**	**16.8**
Apulia	5,158	11.9	35,609	82.1	2,606	6	43,373	10.7
Calabria	706	3.9	17,164	95.9	30	0.2	17,900	9.1
Emilia-Romagna	33,581	37.6	52,807	59.1	2,943	3.3	89,330	20.1
Sicily	13,947	23	46,609	76.9	74	0.1	60,630	12
RIPP	**53,393**	**25.3**	**152,189**	**72**	**5,653**	**2.7**	**211,233**	**13.6**
Campania	151	0.5	29,544	92.9	2,092	6.6	31,787	5.4
Latium	4,200	10.3	34,907	86	1,494	3.7	40,601	6.9
Marche	13,213	39.2	20,514	60.8	-	-	33,727	21.9
Molise	1,222	22.8	4,142	77.2	-	-	5,364	17.3
Tuscany	29,151	40.8	42,291	59.2	-	-	71,442	19.1
Ministry of Defence	-	-	133	33.4	265	66.6	398	NA
PlaNet	**47,936**	**26.1**	**131,532**	**71.8**	**3,851**	**2.1**	**183,319**	**10.6**
Lombardy	41,135	26.7	107,610	69.8	5,441	3.5	154,187	15.4
Piedmont	19,302	26.6	50,366	69.3	3,010	4.1	72,678	16.5
Sardinia	793	4.2	15,292	80.3	2,963	15.6	19,048	11.5
LPS	61,230	24.9	173,268	70.5	11,414	4.6	245,913	15.3
ITALY	**218,074**	**26.1**	**583,653**	**69.8**	**34,649**	**4.1**	**836,375**	**13.8**

Table 69. Potential supply of toll fractionated PDMPs based on the amount of plasma sent for fractionation from July 2016 to June 2017 and the yields provided by the fractionation industry – Year 2017 (adapted by the CNS on data provided by Kedrion and CSL Behring)

Region	2nd semester 2016	1st semester 2017	TOTAL	Albumin	Human Immunoglobulin intravenous use	Factor VIII	Factor IX / 3-factor prothrombin complex	Antithrombin	Factor VIII / vW Factor	Fibrinogen
	kg	kg	kg	g	g	IU	IU	IU	IU	g
Abruzzo	8,873	8,884	17,757	456,062	70,306	2,212,762	2,216,785	2,080,134	79,112	102
Aosta Valley	1,082	1,162	2,244	57,733	8,745	285,306	298,573	280,168	6,114	8
AP Bolzano	3,416	3,526	6,942	178,236	27,568	867,680	855,759	803,006	33,221	43
AP Trento	3,550	3,654	7,204	184,978	28,583	901,138	891,338	836,393	33,780	44
Apulia	18,038	20,730	38,768	1,000,220	147,319	4,706,928	5,660,158	5,311,244	-	-
Basilicata	3,646	3,451	7,097	182,453	27,844	784,643	919,651	862,961	24,521	32
Calabria	7,555	8,678	16,233	418,808	61,685	2,110,272	2,369,998	2,223,902	-	-
Campania	14,037	15,790	29,827	769,525	113,341	3,690,063	4,354,676	4,086,237	-	-
E.-Romagna	45,577	45,421	90,998	2,347,759	345,794	11,378,337	13,285,769	12,466,783	-	-
Friuli-V. Giulia	13,726	13,485	27,211	698,719	107,956	3,355,531	3,367,966	3,160,351	127,356	164
Latium	19,339	20,362	39,700	1,024,260	150,860	4,905,047	5,796,202	5,438,902	-	-
Liguria	11,806	11,367	23,173	594,825	92,224	2,867,444	2,829,960	2,655,510	116,506	150
Lombardy	76,150	79,982	156,132	4,028,204	593,301	19,368,299	22,795,261	21,390,073	-	-
Marche	17,191	16,797	33,989	876,905	129,157	4,418,512	4,962,329	4,656,432	-	-
Molise	2,713	2,564	5,277	136,145	20,052	686,003	770,434	722,942	-	-
Piedmont	36,892	37,362	74,254	1,915,741	282,163	8,960,106	10,841,013	10,172,731	-	-
Sardinia	8,433	8,933	17,367	448,063	65,994	1,870,266	2,535,548	2,379,247	-	-
Sicily	30,481	28,689	59,170	1,526,587	224,846	7,677,796	8,638,827	8,106,297	-	-
Tuscany	36,025	36,542	72,566	1,872,208	275,752	9,433,608	10,594,667	9,941,571	-	-
Umbria	5,219	5,215	10,434	268,050	41,223	1,310,350	1,314,350	1,233,328	44,012	57
Veneto	175	198	372	9,608	1,415	14,536	54,373	51,022	-	-
M. of Defence	45,134	47,575	92,709	2,381,088	367,159	10,212,618	11,562,693	10,849,924	415,449	536
ITALY	409,055	420,367	829,422	21,376,177	3,183,289	102,017,245	116,916,330	109,709,159	880,071	1,136

Table 70. Potential supply of solvent/detergent-treated plasma based on the amount of plasma sentfor fractionation from July 2016 to June 2017 and the yields provided by the industry – Year 2017 (adapted by the CNS ondata provided by Kedrion)

Region	2nd semester 2016	1st semester 2017	TOTAL	Solvent/detergent-treated plasma
	kg	kg	kg	mL
Abruzzo	-	-	-	-
Aosta Valley	-	-	-	-
AP Bolzano	-	-	-	-
AP Trento	-	-	-	-
Apulia	2,008	953	2,961	2,727,081
Basilicata	-	-	-	-
Calabria	-	-	-	-
Campania	4,258	4,013	8,271	7,617,843
E.-Romagna	-	-	-	-
Friuli-V. Giulia	-	-	-	-
Latium	1,420	1,837	3,257	2,999,697
Liguria	94	-	94	86,574
Lombardy	-	-	-	-
Marche	1,384	1,254	2,638	2,429,598
Molise	-	24	24	22,104
Piedmont	2,138	2,541	4,679	4,308,936
Sardinia	-	-	-	-
Sicily	740	1,742	2,482	2,285,922
Tuscany	-	-	-	-
Umbria	-	-	-	-
Veneto	2,277	217	2,494	2,296,974
Ministry of Defence	-	-	-	-
ITALY	14,319	12,581	26,900	24,774,730

Table 71. Effective supply (expressed in grams and International Units) of toll fractionated PDMPs classified by region for the year 2017) (adapted by theCNS on data provided by Kedrion)

Region	Total	Albumin	Human immunoglobulin intravenous use	Factor VIII	Factor IX	3-factor prothrombin complex	Antithrombin	Solvent/detergent-treated plasma
	kg	g	g	IU	IU	IU	IU	mL
Abruzzo	17,757	430,000	62,500	17,000	30,000	428,000	1,488,000	-
Aosta Valley	2,244	70,600	15,000	47,000	-	150,000	332,000	-
AP Bolzano	6,942	131,750	24,740	318,000	32,000	512,000	202,000	-
AP Trento	7,204	167,020	27,135	12,000	-	471,000	180,000	-
Apulia	38,768	1,137,800	131,395	4,151,000	948,000	1,183,500	6,209,000	2,054,400
Basilicata	7,097	250,500	19,210	33,000	20,000	189,000	990,000	-
Calabria	16,233	547,300	61,970	896,000	43,000	1,057,000	6,153,000	-
Campania	29,827	487,500	101,600	4,994,000	-	1,002,000	3,152,000	3,703,200
E.-Romagna	90,998	1,974,500	318,185	3,692,000	1,198,000	4,208,000	1,912,000	-
Friuli-V. Giulia	27,211	372,500	100,000	1,153,000	270,000	962,000	2,980,000	-
Latium	39,700	914,250	147,305	9,088,000	71,000	1,569,500	7,135,000	2,440,000
Liguria	23,173	582,740	84,300	1,152,000	448,000	880,000	1,984,000	88,000
Lombardy	156,132	4,171,200	554,965	17,298,000	2,605,000	5,450,000	4,440,500	546,000
Marche	33,989	594,500	131,310	2,039,000	687,000	1,358,000	2,227,000	1,913,000
Molise	5,277	61,400	8,960	288,000	-	192,000	1,108,000	384,000
Piedmont	74,254	1,018,200	302,080	11,305,000	1,542,000	2,432,500	7,390,500	4,152,000
Sardinia	17,367	1,129,500	55,600	634,000	-	1,138,500	2,365,000	-
Sicily	59,170	2,091,000	223,900	1,918,000	104,000	2,794,000	15,745,000	1,918,800
Tuscany	72,566	1,434,940	262,663	4,353,000	1,102,000	3,201,000	7,361,000	-
Umbria	10,434	507,200	44,770	724,000	13,000	519,500	714,000	-
Veneto	92,709	2,132,500	309,560	7,204,000	1,272,000	3,980,000	5,416,000	3,872,000
Ministry of Defence	372	NA	NA	NA	NA	NA	NA	NA
Italy	829,422	20,206,900	2,987,148	71,316,000	10,385,000	33,677,500	79,484,000	21,071,400

ANALYSIS OF SELF-SUFFICIENCY

Albumin

In 2017, the Italian NHS demand for albumin accounted for 82% of the total. The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, was 74% (+1% compared to 2016) while the effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was equal to the previous year i.e. 70% (Table 72).

The Regions that in 2017 achieved effective self-sufficiency – more than 90% – were Aosta Valley, Friuli-Venezia Giulia, Marche, Umbria, Emilia-Romagna, Veneto, AP of Trento and Liguria.

Table 72. Estimates of regional and national self-sufficiency of albumin, 2017

Region	Total demand	NHS demand	Supply Potential	Supply Effective	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	791,568	693,673	456,062	430,000	66	62
Aosta Valley	73,750	73,120	57,733	70,600	79	97
AP Bolzano	148,960	148,000	178,236	131,750	120	89
AP Trento	183,425	172,650	184,978	167,020	107	97
Apulia	2,088,145	1,740,838	1,000,220	1,137,800	57	65
Basilicata	334,825	326,680	182,453	250,500	56	77
Calabria	1,085,958	1,013,298	418,808	547,300	41	54
Campania	5,552,418	4,454,275	769,525	487,500	17	11
E.-Romagna	2,437,620	2,137,228	2,347,759	1,974,500	110	92
Friuli-V. Giulia	378,478	375,660	698,719	372,500	186	99
Latium	3,150,310	1,725,143	1,024,260	914,250	59	53
Liguria	672,413	633,120	594,825	582,740	94	92
Lombardy	6,896,345	5,075,250	4,028,204	4,171,200	79	82
Marche	717,305	612,035	876,905	594,500	143	97
Molise	144,963	91,118	136,145	61,400	149	67
Piedmont	1,449,118	1,141,833	1,915,741	1,018,200	168	89
Sardinia	1,553,920	1,521,663	448,063	1,129,500	29	74
Sicily	3,043,375	2,580,865	1,526,587	2,091,000	59	81
Tuscany	1,811,433	1,655,275	1,872,208	1,434,940	113	87
Umbria	516,325	515,745	268,050	507,200	52	98
Veneto	2,308,243	2,168,963	2,381,088	2,132,500	110	98
Italy	35,338,893	28,856,428	21,376,177	20,206,900	74	70

The Regions that mainly benefited from interregional compensation in 2017 were Umbria (98% effective self-sufficiency compared to the potential 52%) and Basilicata (77% compared to 56%) for NAIP Regions, Sardinia (74% compared to 29%) for the LPS, as well as Apulia (effective self-sufficiency 65% compared to the potential 57%) and Sicily (effective self-sufficiency 81% compared to the potential 59%).

The Regions farthest from the objective of effective self-sufficiency were Campania, Latium and Calabria, with percentages ranging between 11 and 54% of the NHS demand satisfied by the toll fractionation supply.

Normal human immunoglobulins for intravenous use

In 2017, the NHS demand for IV IGs accounted for 92% of the total demand (Table 73), a percentage similar to that recorded in the previous year.

The national potential self-sufficiency, estimated on the basis of the relationship between potential supply and NHS demand, in 2017 was 77%, against 76% recorded in 2016, showing a confirming upward trend compared to that observed in previous years. The effective self-sufficiency, understood as the ratio of the actual supply of toll fractionation to NHS demand, was 73%, against 76% in2016.

The Regions that in 2017achieved effective self-sufficiency of more than 90% were the AP of Trento, Calabria, Molise and Sicily, immediately followed by Marche, and Veneto. Apulia, Campania and Tuscany were the Regions with an effective self-sufficiency of less than or equal to 50%.

Table 73. Estimates of regional and national self-sufficiency of human immunoglobulin for intravenous use, 2017

Region	Total demand	NHS demand	Supply Potential	Supply Effective	Potential self-sufficiency	Effective self-sufficiency
	g	g	g	g	%	%
Abruzzo	77,335	76,885	70,306	62,500	91	81
Aosta Valley	20,370	20,370	8,745	15,000	43	74
AP Bolzano	37,184	37,184	27,568	24,740	74	67
AP Trento	29,788	29,788	28,583	27,135	96	91
Apulia	290,911	263,179	147,319	131,395	56	50
Basilicata	24,500	24,500	27,844	19,210	114	78
Calabria	65,700	65,420	61,685	61,970	94	95
Campania	283,254	267,361	113,341	101,600	42	38
E.-Romagna	345,136	344,356	345,794	318,185	100	92
Friuli-V. Giulia	111,770	111,650	107,956	100,000	97	90
Latium	386,649	248,116	150,860	147,305	61	59
Liguria	144,816	144,488	92,224	84,300	64	58
Lombardy	772,367	660,737	593,301	554,965	90	84
Marche	153,875	152,695	129,157	131,310	85	86
Molise	13,970	8,960	20,052	8,960	224	100
Piedmont	372,539	371,779	282,163	302,080	76	81
Sardinia	66,698	66,698	65,994	55,600	99	83
Sicily	248,354	242,096	224,846	223,900	93	92
Tuscany	603,902	559,652	275,752	262,663	49	47
Umbria	59,481	59,481	41,223	44,770	69	75
Veneto	361,188	355,468	367,159	309,560	103	87
Italy	4,469,785	4,110,861	3,183,289	2,987,148	77	73

Antithrombin

NHS demand for AT compared to national total demand dropped from 94% in 2011 to 88% in 2016. Effective self-sufficiency recorded an average value of 67% between 2011 and 2016 and 76% in 2017, significantly lower than the potential self-sufficiency (105%) (Table 74).

Table 74. Estimates of regional and national self-sufficiency of antithrombin, 2017

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective Self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	1,545,500	1,488,000	2,080,134	1,488,000	140	100
Aosta Valley	332,000	332,000	280,168	332,000	84	100
AP Bolzano	202,000	202,000	803,006	202,000	398	100
AP Trento	181,000	180,000	836,393	180,000	465	100
Apulia	7,901,500	6,860,500	5,311,244	6,209,000	77	91
Basilicata	1,247,000	1,247,000	862,961	990,000	69	79
Calabria	8,056,500	6,972,500	2,223,902	6,153,000	32	88
Campania	17,307,500	16,172,000	4,086,237	3,152,000	25	19
E.-Romagna	2,351,000	1,946,500	12,466,783	1,912,000	640	98
Friuli-V. Giulia	3,095,000	3,080,000	3,160,351	2,980,000	103	97
Latium	19,128,000	13,942,000	5,438,902	7,135,000	39	51
Liguria	2,170,500	2,074,000	2,655,510	1,984,000	128	96
Lombardy	10,721,500	6,931,000	21,390,073	4,440,500	309	64
Marche	2,227,000	2,227,000	4,656,432	2,227,000	209	100
Molise	1,194,000	1,108,000	722,942	1,108,000	65	100
Piedmont	7,597,500	7,390,500	10,172,731	7,390,500	138	100
Sardinia	2,700,500	2,698,000	2,379,247	2,365,000	88	88
Sicily	17,434,000	16,317,000	8,106,297	15,745,000	50	96
Tuscany	7,454,000	7,449,000	9,941,571	7,361,000	133	99
Umbria	714,000	714,000	1,233,328	714,000	173	100
Veneto	5,459,500	5,416,000	10,849,924	5,416,000	200	100
Italy	119,019,500	104,747,000	109,709,159	79,484,000	105	76

The Regions that achieved effective self-sufficiency of more than 90% of the total NHS demand in 2017 were Apulia, Emilia-Romagna, Friuli-Venezia Giulia, Liguria, Sicily, Tuscany, Abruzzo, Aosta Valley, the AP of Trento and AP of Bolzano, Marche, Molise, Piedmont, Umbria and Veneto. Of these, the last nine fully satisfied their NHS demand through the PDMPs produced by toll fractionation. The Regions that mainly took advantage from interregional compensation in 2017 were Calabria (88% effective self-sufficiency compared to the potential self-sufficiency of 32%), Campania (25% compared to 19%), Latium (51% compared to 39%), Apulia (77% compared to 91%) and Sicily (96% compared to 50%). The Regions farthest from the objective of effective self-sufficiency were Campania (19%) and Latium (51%).

Factor VIII

In 2017, the effective self-sufficiency of pdFVIII at national level was 55%. However, this value was considerably lower than the potential self-sufficiency (78% of the NHS demand) (Table 75).

Table 75. Estimates of regional and national self-sufficiency of plasma-derived factor VIII, 2017

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	977,000	977,000	2,212,762	17,000	226	2
Aosta Valley	47,000	47,000	285,306	47,000	607	100
AP Bolzano	1,048,000	1,048,000	867,680	318,000	83	30
AP Trento	61,500	61,500	901,138	12,000	1,465	20
Apulia	11,489,000	11,465,000	4,706,928	4,151,000	41	36
Basilicata	390,000	390,000	784,643	33,000	201	8
Calabria	1,629,500	1,291,000	2,110,272	896,000	163	69
Campania	9,854,000	9,854,000	3,690,063	4,994,000	37	51
E.-Romagna	6,639,000	6,639,000	11,378,337	3,692,000	171	56
Friuli-V. Giulia	2,024,000	2,024,000	3,355,531	1,153,000	166	57
Latium	21,569,500	21,093,500	4,905,047	9,088,000	23	43
Liguria	1,692,000	1,631,000	2,867,444	1,152,000	176	71
Lombardy	24,329,500	24,329,000	19,368,299	17,298,000	80	71
Marche	2,547,000	2,532,000	4,418,512	2,039,000	175	81
Molise	593,000	466,000	686,003	288,000	147	62
Piedmont	19,078,000	19,066,000	8,960,106	11,305,000	47	59
Sardinia	2,193,000	2,193,000	1,870,266	634,000	85	29
Sicily	7,543,000	7,393,000	7,677,796	1,918,000	104	26
Tuscany	6,387,000	6,387,000	9,433,608	4,353,000	148	68
Umbria	1,775,000	1,775,000	1,310,350	724,000	74	41
Veneto	10,167,500	10,161,500	10,212,618	7,204,000	101	71
Italy	132,033,500	130,823,500	102,017,245	71,316,000	78	55

In 2017, only Marche and Aosta Valley achieved an effective self-sufficiency of more than 80%. In the same year, the Regions farthest from the objective of real self-sufficiency were Basilicata and Abruzzo, with percentages of NHS demand covered by toll fractionation of less than 10%. In the analysis of demand and supply for pdFVIII, it must be taken into account that the choice of the pharmaceutical specialty for the treatment of haemophilia A was based on considerations matured within the therapeutic alliance between doctor and patient, which must be safeguarded and that did not necessarily allow the substitution of the prescribed medicine. Therefore, the overall demand for pdFVIII was not fully satisfied in 2017 by the only product made available by toll fractionation, i.e. Klott produced by Kedrion, while the specific demand for Klott® (formerly Emoclot®) was entirely covered by toll fractionation supplies. The potential supply of Klott® from toll fractionation reached quantities that not only satisfied the specific demand but also produced surpluses. In fact, the company was required to process all forms of intermediate products into an end product, in accordance with the agreements in force.

Factor IX and 3-Factor Prothrombin Complex Concentrates

The industrial production of pdFIX and 3F-PCCs is strictly alternative and therefore self-sufficiency for these two PDMPs were analysed together. Although the national self-sufficiency of pdFIX and 3F-PCCs was substantially reached (93% of the NHS demand), the regional self-sufficiency showed significant differences (range: 44% - 100%) confirming the criticalities already detected in previous years in the mechanisms of the inter-regional exchange and compensation programmes (Table 76).

Table 76. Estimates of regional and national self- sufficiency of plasma-derived factor IX and 3-factor prothrombin complex concentrates, 2017

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	IU	IU	IU	IU	%	%
Abruzzo	1,072,500	1,041,000	2,216,785	458,000	213	44
Aosta Valley	150,000	150,000	298,573	150,000	199	100
AP Bolzano	544,000	544,000	855,759	544,000	157	100
AP Trento	471,000	471,000	891,338	471,000	189	100
Apulia	3,058,000	2,449,000	5,660,158	2,131,500	231	87
Basilicata	209,000	209,000	919,651	209,000	440	100
Calabria	1,137,500	1,129,400	2,369,998	1,100,000	210	97
Campania	2,294,900	1,981,000	4,354,676	1,002,000	220	51
E.-Romagna	6,088,000	5,749,000	13,285,769	5,406,000	231	94
Friuli-V. Giulia	1,407,000	1,407,000	3,367,966	1,232,000	239	88
Latium	1,941,600	1,869,000	5,796,202	1,640,500	310	88
Liguria	1,464,500	1,328,000	2,829,960	1,328,000	213	100
Lombardy	8,620,400	8,216,000	22,795,261	8,055,000	277	98
Marche	2,045,000	2,045,000	4,962,329	2,045,000	243	100
Molise	211,000	202,000	770,434	192,000	381	95
Piedmont	4,422,000	4,205,500	10,841,013	3,974,500	258	95
Sardinia	1,140,000	1,140,000	2,535,548	1,138,500	222	100
Sicily	3,146,800	2,929,000	8,638,827	2,898,000	295	99
Tuscany	4,335,800	4,334,800	10,594,667	4,303,000	244	99
Umbria	763,500	763,500	1,314,350	532,500	172	70
Veneto	5,412,500	5,408,000	11,562,693	5,252,000	214	97
Italy	49,935,000	47,571,200	116,916,330	44,062,500	246	93

Solvent/detergent virus-inactivated plasma

Differently from the main PDMPs that were included in the agreements between the Regions and the fractionation company regarding the toll fractionation process, the production of solvent/detergent virus-inactivated plasma (S/D plasma) from national plasma was determined by the production planning of the individual Regions (and in some cases of Local Health Centres). Therefore, not all the Regions contributed to the determination of national self-sufficiency.

For S/D plasma, the same therapeutic indications as those for fresh-frozen plasma are provided; there is no sufficient evidence to justify the priority or preferential use of S/D plasma rather than fresh frozen plasma (49).

In 2017, the NHS demand for S/D plasma was almost equal to the total demand. For the same year, effective national self-sufficiency was 66% (Table 77).

For the Regions that used S/D plasma produced by toll fractionation, the effective regional self-sufficiency varied from 14% in Liguria to 100% in Marche, Molise, Piedmont and Veneto.

Table 77. Estimates of regional and national self-sufficiency of solvent/detergent virus-inactivated plasma, 2017

Region	Total demand	NHS demand	Potential supply	Effective supply	Potential self-sufficiency	Effective self-sufficiency
	mL	mL	mL	mL	%	%
Abruzzo	172,000	172,000	-	-	-	-
Aosta Valley	-	-	-	-	-	-
AP Bolzano	-	-	-	-	-	-
AP Trento	-	-	-	-	-	-
Apulia	3,250,000	3,186,000	2,727,081	2,054,400	86	64
Basilicata	754,000	754,000	-	-	-	-
Calabria	1,004,000	1,004,000	-	-	-	-
Campania	4,389,200	4,363,200	7,617,843	3,703,200	175	85
E.-Romagna	280,000	280,000		-	-	-
Friuli-V. Giulia	-	-	-	-		
Latium	4,488,000	4,320,000	2,999,697	2,440,000	69	56
Liguria	650,000	650,000	86,574	88,000	13	14
Lombardy	608,000	608,000	-	546,000	-	90
Marche	1,913,000	1,913,000	2,429,598	1,913,000	127	100
Molise	384,000	384,000	22,104	384,000	6	100
Piedmont	4,152,000	4,152,000	4,308,936	4,152,000	104	100
Sardinia	14,000	14,000	-	-	-	-
Sicily	4,401,800	4,401,800	2,285,922	1,918,800	52	44
Tuscany	1,724,000	1,724,000	-	-	-	-
Umbria	-	-	-	-	-	-
Veneto	3,952,000	3,872,000	2,296,974	3,872,000	59	100
Italy	32,136,000	31,798,000	24,774,730	21,071,400	78	66

PART D
Expenditure for the purchase of plasma-derived and recombinant medicinal products

EXPENDITURE FOR PLASMA-DERIVED AND RECOMBINANT MEDICINAL PRODUCTS

This chapter describes the pharmaceutical expenditure incurred by the NHS for the purchase of the following medicinal products on the commercial market:

1. PDMPs included in the agreements between the Regions and the toll fractionation companies purchased in 2017 for the quota of the demand not covered by toll fractionation (albumin, IV IGs, pdFVIII, pdFIX, 3F-PCC and AT);
2. Recombinant medicinal products used in the treatment of congenital coagulation disorders (rFVIIa, rFVIII, rFIX and rFXIII);
3. SC/IM polyvalent immunoglobulins and specific immunoglobulins, not provided by toll fractionation yet;
4. Other PDMPs.

With regard to the medicinal products distributed through public health facilities, the aggregate purchase cost was quantified based on information taken from the drug traceability system. For the distribution through accredited pharmacies, on the other hand, the quantities of PDMPs provided by AIFA were valued based on the price in force on 31/12/2017, applying the discounts envisaged by law for pharmaceutical expenditure.

Table 78 shows the total expenditure and the total *per capita* expenditure incurred by Regions and sustained by the NHS for the purchase of the medicinal products specified in point one. In 2017, expenditure for the purchase of the aforementioned PDMPs was approximately 107.9 million euro (1.78 euro *per capita*) with an increase compared to 2016 of around 6.4 million euro (+6%) showing an upward trend compared to previous years (17,31). The analysis of trends in the total *per capita* expenditure classified by active ingredient confirms the upward trend for 3F-PCCs (+17%), IV IGs (+15%), Albumin (+3%) and pdFVIII (+2.2%); while there was a significant drop for pdFIX(-25%) and AT (-16%). For the same group of PDMPs, the most significant changes in Regional expenditure were recorded in Aosta Valley, Umbria and Apulia, with percentages between +99% and +44% approximately, due to the increase of the expenditure for purchasing IV IGs.

Table 79 shows the total and the total *per capita* expenditure for the purchase of recombinant medicinal products (rFVIIa, rFVIII, rFIX and rFXIII). Overall, the expenditure for recombinant factors in the two-year period, showed a slight upward trend (+7.5%); in particular, an increased expenditure was recorded for rFVIII (+2.6%), rFIX (+28.22%) and rFVIIa (+18.66%).

In 2017, the total expenditure for recombinant coagulation factors was around 421 million euros (6.95 euros *per capita*); the Regions with the highest *per capita* expenditure were Latium, Campania, Basilicata, with 12.51,10.61and 9.22 euros respectively.

In 2017, as regards other PDMPs (Tables 80-83), the total expenditure was approximately 179 million euros, equivalent to around 3euros*per capita*, of which 89 million euros for purchasing both polyvalent and specific immunoglobulins (Table 80). SC/IM IGs showed the greatest increase with a 22% rise in *per capita* expenditure (0.77 euro *per capita* in 2017 for a total of 46.7 million euros). With regard to all other specific IGs, a constant *per capita* expenditure was observed (Table 81). The remaining PDMPs (Table 82) recorded an increase in the *per capita* expenditure (+1.6%) particularly, for the purchase of products containing FVII (+39%), Plasma-derived C1-inhibitor (+22%), PCCs4 (+21%) alpha-1 proteinase inhibitor (19%), fibrinogen (+17%). Instead, a drop in the expenditure for the purchase of products containing protein C (-26%), Factor X (-25%), Factor XIII (-18%) and local haemostatics (-31%) was observed (Table 83).

Table 78. Estimate of total expenditure and total *per capita* expenditure incurred by the National Health Service for the purchase on the market of plasma-derived medicinal products included in toll fractionation contracts in 2017

Region	Albumin		Human Immunoglobulin intravenous use		Factor VIII		Factor IX		3-factor prothrombin complex		Antithrombin		TOTAL	
	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*
Abruzzo	645,378	0.49	606,614	0.46	534,917	0.40	236,642	0.18	968	0.00	-	-	2,024,519	1.53
Aosta Valley	6,396	0.05	189,112	1.49	-	-	-	-	-	-	-	-	195,508	1.54
AP Bolzano	37,136	0.07	450,278	0.86	398,664	0.76	-	-	-	-	-	-	886,079	1.69
AP Trento	21,816	0.04	160,699	0.30	27,005	0.05	-	-	-	-	-	-	209,519	0.39
Apulia	1,992,123	0.49	5,912,537	1.45	3,762,937	0.93	107,352	0.03	743	0.00	116,879	0.03	11,892,571	2.93
Basilicata	233,020	0.41	297,651	0.52	200,277	0.35	-	-	-	-	33,641	0.06	764,590	1.34
Calabria	1,612,040	0.82	163,741	0.08	216,558	0.11	-	-	-	-	112,634	0.06	2,104,973	1.07
Campania	9,832,747	1.68	6,771,330	1.16	2,475,577	0.42	-	-	8,580	0.00	1,432,203	0.25	20,520,437	3.51
E.-Romagna	443,249	0.10	1,477,606	0.33	1,602,457	0.36	168,840	0.04	227,020	0.05	9,262	0.00	3,928,434	0.88
Friuli-V. Giulia	12,405	0.01	711,557	0.58	453,955	0.37	-	-	-	-	11,880	0.01	1,189,797	0.98
Latium	2,440,469	0.41	4,420,626	0.75	6,241,632	1.06	46,162	0.01	37,538	0.01	1,050,829	0.18	14,237,255	2.41
Liguria	169,990	0.11	1,955,962	1.25	255,752	0.16	-	-	33,159	0.02	11,039	0.01	2,425,901	1.55
Lombardy	2,572,758	0.26	4,263,241	0.43	5,051,291	0.50	83,375	0.01	-	-	394,330	0.04	12,364,994	1.23
Marche	41,624	0.03	1,089,184	0.71	254,370	0.17	-	-	-	-	-	-	1,385,179	0.90
Molise	105,879	0.34	-	-	98,296	0.32	-	-	2,420	0.01	-	-	206,595	0.67
Piedmont	231,844	0.05	2,593,971	0.59	4,060,748	0.92	-	-	-	-	-	-	6,886,563	1.57
Sardinia	1,034,819	0.63	435,490	0.26	901,363	0.55	142,956	0.09	312	0.00	47,451	0.03	2,562,391	1.55
Sicily	1,496,780	0.30	1,330,612	0.26	3,168,659	0.63	9,000	0.00	3,101	0.00	94,657	0.02	6,102,810	1.21
Tuscany	466,347	0.12	11,061,899	2.96	1,089,428	0.29	15,441	0.00	693	0.00	11,766	0.00	12,645,575	3.38
Umbria	30,786	0.03	591,284	0.67	550,956	0.62	106,722	0.12	-	-	-	-	1,279,747	1.44
Veneto	141,814	0.03	1,814,858	0.37	2,122,797	0.43	76,770	0.02	-	-	-	-	4,156,239	0.85
ITALY	23,569,419	0.39	46,298,254	0.76	33,467,639	0.55	993,260	0.02	314,534	0.01	3,326,569	0.05	107,969,675	1.78

Table 79. Estimate of the total expenditure and the total *per capita* expenditure for recombinant factors VII, VIII, IX and XIII in 2017

Region	rFVIIa		rFVIII		rFIX		rFXIII		Total	
	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*	€	€ *per capita*
Abruzzo	851,202	0.64	7,160,355	5.42	1,551,227	1.17	403,629	0.31	9,966,413	7.54
Aosta V.	535,965	0.60	3,478,623	3.91	284,527	0.32	-	-	4,299,115	4.84
AP BZ	8,415	0.07	707,858	5.58	-	-	-	-	716,273	5.65
AP Trento	24,598	0.05	1,592,906	3.04	3,034	0.01	-	-	1,620,537	3.09
Apulia	647	0.00	1,747,649	3.24	407,653	0.76	-	-	2,155,949	4.00
Basilicata	7,142,978	1.76	24,292,486	5.98	6,029,888	1.48	-	-	37,465,352	9.22
Calabria	98,390	0.17	2,820,234	4.94	99,263	0.17	232,863	0.41	3,250,749	5.70
Campania	4,949,913	2.52	13,919,882	7.08	1,306,484	0.66	667,541	0.34	20,843,819	10.61
ER	6,976,616	1.19	40,823,834	6.99	6,275,719	1.07	-	-	54,076,169	9.26
FVG	2,521,240	0.57	18,550,296	4.17	3,890,364	0.87	-	-	24,961,900	5.61
Latium	9,251,236	7.60	5,052,823	4.15	927,152	0.76	-	-	15,231,211	12.51
Liguria	1,780,730	0.30	45,524,090	7.72	3,993,315	0.68	-	-	51,298,135	8.70
Lombardy	308,982	0.20	5,700,627	3.64	2,562,178	1.64	263,911	0.17	8,835,698	5.64
Marche	4,693,844	0.47	36,447,524	3.64	7,990,026	0.80	357,057	0.04	49,488,451	4.94
Molise	1,736,718	1.13	6,006,667	3.91	1,200,465	0.78	-	-	8,943,849	5.82
Piedmont	38,191	0.12	1,441,482	4.64	-	-	-	-	1,479,673	4.77
Sardinia	6,724,180	1.53	21,398,031	4.87	2,144,324	0.49	279,436	0.06	30,545,970	6.95
Sicily	704,911	0.43	6,621,329	4.01	6,826	0.00	-	-	7,333,066	4.44
Tuscany	3,807,695	0.75	32,126,643	6.35	4,125,910	0.82	-	-	40,060,248	7.92
Umbria	3,870,217	1.03	12,341,451	3.30	6,209,012	1.66	-	-	22,420,680	5.99
Veneto	5,187,050	1.06	18,150,484	3.70	2,380,950	0.49	93,145	0.02	25,811,629	5.26
ITALY	61,213,719	1.01	305,905,268	5.05	51,388,316	0.85	2,297,582	0.04	420,804,885	6.95

Table 80. Estimate of total expenditure and total *per capita* expenditure incurred by the National Health Service for the purchase on the market of subcutaneous/intramuscular polyvalent immunoglobulins and of specific immunoglobulins in 2017

Region	SC/IM IGs	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs	Rabies IGs	TOTAL
Abruzzo	1,441,537	282,875	11,898	184,825	49,426	56,110	1,376	-	2,028,047
Aosta Valley	95,386	68,474	-	11,827	5,586	-	-	980	182,252
AP Bolzano	117,640	33,842	-	28,628	35,587	17,733	433	6,860	240,722
AP Trento	142,822	75,323	-	16,255	27,757	954	8,846	-	271,957
Apulia	4,716,732	2,681,442	610,030	251,278	73,410	689,024	967	-	9,022,884
Basilicata	422,957	146,133	253	54,119	15,510	21,892	322	-	661,186
Calabria	1,433,983	675,074	92,475	212,125	42,106	1,908	-	-	2,457,672
Campania	3,961,499	9,111,664	1,038,700	730,378	84,678	101,030	1,895	-	15,029,844
E.-Romagna	3,898,931	1,019,232	313,320	214,071	190,971	623,434	17,241	5,880	6,283,081
Friuli-V. Giulia	262,120	138,222	50,820	26,085	39,668	135,248	12,045	6,860	671,067
Latium	5,238,182	1,075,357	119,318	299,754	169,018	81,283	5,387	-	6,988,298
Liguria	1,205,208	268,441	8,382	147,138	51,171	-	4,868	-	1,685,207
Lombardy	3,737,953	5,470,409	396,428	462,258	317,728	267,216	41,642	7,840	10,701,475
Marche	1,178,861	268,326	208,893	156,691	55,959	43,532	14,268	2,450	1,928,981
Molise	197,610	77,830	6,380	31,716	8,696	-	173	-	322,405
Piedmont	3,842,030	2,192,735	140,724	183,295	198,978	-	755	-	6,558,517
Sardinia	352,844	1,579,304	126,849	118,622	21,227	-	-	-	2,198,845
Sicily	3,182,689	1,765,240	2,763	384,324	126,739	177,133	495	-	5,639,383
Tuscany	5,795,478	1,032,740	202,338	447,975	162,800	63,120	2,659	6,664	7,713,775
Umbria	1,255,431	134,051	-	61,335	29,227	10,548	3,982	-	1,494,574
Veneto	4,306,016	1,074,897	637,299	120,136	168,872	720,511	9,284	17,346	7,054,361
ITALY	46,785,908	29,171,612	3,966,870	4,142,835	1,875,113	3,010,677	126,639	54,880	89,134,534

Table 81. Estimate of standardised expenditure (euro *per capita* and euro per 1,000 population) incurred by the National Health Service for the purchase on the market of polyvalent immunoglobulins for subcutaneous/intramuscular use and specific immunoglobulins in 2017

Region	SC/IM IGs	Hepatitis B IGs	Hepatitis B IGs for IV use	Tetanus IGs	Anti-D IGs	CMV IGs	Varicella IGs*	Rabies IGs	TOTAL
Abruzzo	1.09	0.21	0.01	0.14	0.04	0.04	1.04	-	1.53
Aosta Valley	0.75	0.54	-	0.09	0.04	-	-	7.72	1.44
AP Bolzano	0.22	0.06	-	0.05	0.07	0.03	0.83	13.09	0.46
AP Trento	0.27	0.14	-	0.03	0.05	0.00	16.42	-	0.50
Apulia	1.16	0.66	0.15	0.06	0.02	0.17	0.24	-	2.22
Basilicata	0.74	0.26	0.00	0.09	0.03	0.04	0.57	-	1.16
Calabria	0.73	0.34	0.05	0.11	0.02	0.00	-	-	1.25
Campania	0.68	1.56	0.18	0.13	0.01	0.02	0.32	-	2.57
E.-Romagna	0.88	0.23	0.07	0.05	0.04	0.14	3.88	1.32	1.41
Friuli-V. Giulia	0.22	0.11	0.04	0.02	0.03	0.11	9.89	5.63	0.55
Latium	0.89	0.18	0.02	0.05	0.03	0.01	0.91	-	1.18
Liguria	0.77	0.17	0.01	0.09	0.03	-	3.11	-	1.08
Lombardy	0.37	0.55	0.04	0.05	0.03	0.03	4.16	0.78	1.07
Marche	0.77	0.17	0.14	0.10	0.04	0.03	9.28	1.59	1.25
Molise	0.64	0.25	0.02	0.10	0.03	-	0.56	-	1.04
Piedmont	0.87	0.50	0.03	0.04	0.05	-	0.17	-	1.49
Sardinia	0.21	0.96	0.08	0.07	0.01	-	-	-	1.33
Sicily	0.63	0.35	0.00	0.08	0.03	0.04	0.10	-	1.12
Tuscany	1.55	0.28	0.05	0.12	0.04	0.02	0.71	1.78	2.06
Umbria	1.41	0.15	-	0.07	0.03	0.01	4.48	-	1.68
Veneto	0.88	0.22	0.13	0.02	0.03	0.15	1.89	3.53	1.44
ITALY	0.77	0.48	0.07	0.07	0.03	0.05	2.09	0.91	1.47

*values per 1,000 population

Table 82. Estimate of total expenditure for other PDMPs in 2017

Region	Factor VII	Factor VIII inhibitor bypassing activity	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Fibrinogen	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X	Factor XIII	Protein C	TOTAL
Abruzzo	255,295	2,165,787	382,697	65,274	94,034	516,560	205,128	385,833		-	25,174	4,095,782
Aosta Valley	-	-	61,049	-	-	15,400	264,264	78,576		-	-	419,290
AP Bolzano	-	61,215	183,570	-	173,949	379,280	806,472	2,341		-	6,567	1,613,394
AP Trento	-	30,608	56,599	-	677	106,920	174,242	11,956		15,025	-	396,026
Apulia	338,371	629,292	910,449	804,516	16,422	812,640	254,760	1,356,217		-	78,804	5,201,470
Basilicata	5,601	-	357,971	268,535	76,050	86,240	-	51,604		-	-	846,000
Calabria	6,408	2,062,662	726,208	433,032	18,150	704,440	58,080	396,946		-	46,222	4,452,148
Campania	38,575	5,956,490	1,762,067	244,368	165,224	1,514,480	421,526	1,961,760		-	432,022	12,496,511
E-Romagna	153,084	4,620,523	392,961	110,110	307,261	1,462,080	572,616	502,085		165,053	3,432	8,289,204
FVG	-	904,270	509,329	-	26,681	269,280	560,433	1,383		-	-	2,271,376
Latium	1,041,608	1,269,312	919,917	705,851	100,859	1,508,760	301,078	1,408,952		86,917	86,130	7,429,385
Liguria	8,401	-	185,832	214,733	34,544	168,520	194,618	184,764		1,172	43,560	1,036,143
Lombardy	1,089,522	1,910,867	1,709,774	22,910	68,589	1,606,520	1,847,046	2,274,929	35,228	61,272	181,028	10,807,685
Marche	-	146,917	355,793	-	54,670	260,920	66,264	325,497		8,303	-	1,218,364
Molise	261,319	-	20,877	351	-	21,120	28,512	6,574		-	-	338,753
Piedmont	166,152	1,826,656	914,756	-	172,851	393,800	697,488	709,896		30,583	105,270	5,017,450
Sardinia	-	639,089	257,572	5,005	194,104	691,120	383,567	750,015		-	-	2,920,472
Sicily	34,054	1,272,293	1,115,082	1,319,389	71,710	733,920	347,952	2,054,260		-	136,125	7,084,784
Tuscany	3,267	2,727,744	1,111,526	657,061	190,420	969,320	366,226	427,009		29,570	10,945	6,493,089
Umbria	1,867	12,243	368,910	-	8,366	467,720	54,630	278,946		-	8,756	1,201,439
Veneto	28,003	915,776	942,527	-	30,506	1,834,600	822,888	1,302,909		83,365	63,908	6,024,482
ITALY	3,431,527	27,151,742	13,245,464	4,851,134	1,805,065	14,523,640	8,427,790	14,472,452	35,228	481,260	1,227,943	89,653,246

Table 83. Estimate of standardised expenditure (euro *per capita* and euro per 1,000 population) for other PDMPs in 2017

Region	Factor VII	Factor VIII inhibitor bypassing activity	Local Haemostatic agents-combinations	Other plasma Proteins fractions	4-factor prothrombin complex concentrates	Fibrinogen	Alpha-1-proteinase inhibitor	Human C1 esterase inhibitor	Factor X*	Factor XIII *	Protein C	TOTAL
Abruzzo	0.19	1.64	0.29	0.05	0.07	0.39	0.16	0.29	-	-	0.02	3.10
Aosta Valley	-	-	0.48	-	-	0.12	2.08	0.62	-	-	-	3.30
AP Bolzano	-	0.12	0.35	-	0.33	0.72	1.54	0.00	-	-	-	3.08
AP Trento	-	0.06	0.11	-	0.00	0.20	0.32	0.02	-	27.90	-	0.74
Apulia	0.08	0.15	0.22	0.20	0.00	0.20	0.06	0.33	-	-	0.02	1.28
Basilicata	-	-	0.63	0.47	0.13	0.15	-	0.09	-	-	-	1.48
Calabria	-	1.05	0.37	0.22	0.01	0.36	0.03	0.20	-	-	0.02	2.27
Campania	-	1.02	0.30	0.04	0.03	0.26	0.07	0.34	-	-	0.07	2.14
E-Romagna	0.03	1.04	0.09	0.02	0.07	0.33	0.13	0.11	-	37.10	0.00	1.86
FVG	-	0.74	0.42	-	0.02	0.22	0.46	0.00	-	-	-	1.87
Latium	0.18	0.22	0.16	0.12	0.02	0.26	0.05	0.24	-	14.74	0.01	1.26
Liguria	0.01	-	0.12	0.14	0.02	0.11	0.12	0.12	-	0.75	0.03	0.66
Lombardy	0.11	0.19	0.17	0.00	0.01	0.16	0.18	0.23	3.52	6.12	0.02	1.08
Marche	-	0.10	0.23	-	0.04	0.17	0.04	0.21	-	5.40	-	0.79
Molise	0.84	-	0.07	0.00	-	0.07	0.09	0.02	-	-	-	1.09
Piedmont	0.04	0.42	0.21	-	0.04	0.09	0.16	0.16	-	6.96	0.02	1.14
Sardinia	-	0.39	0.16	0.00	0.12	0.42	0.23	0.45	-	-	-	1.77
Sicily	0.01	0.25	0.22	0.26	0.01	0.15	0.07	0.41	-	-	0.03	1.40
Tuscany	0.00	0.73	0.30	0.18	0.05	0.26	0.10	0.11	-	7.90	0.00	1.73
Umbria	0.00	0.01	0.42	-	0.01	0.53	0.06	0.31	-	-	0.01	1.35
Veneto	0.01	0.19	0.19	-	0.01	0.37	0.17	0.27	-	16.99	0.01	1.23
ITALY	0.06	0.45	0.22	0.08	0.03	0.24	0.14	0.24	0.58	7.94	0.02	1.48

*Values per 1,000 population.

National and Regional mean price per gram or International Unit

Tables 84-86 show the mean price per unit paid by the Regions to buy albumin, IVIGs and pdFVIII (ATC B02BD02, B02BD06).

The price varied depending on the distribution channel (NHS facilities and pharmacies open to the public).

For each PDMP, the percentage of product by distribution channel and the costs registered in the two distribution channels were reported.

The aforementioned prices include VAT. However, it should be noted that in some Regions (pdFVIII: Sardinia, Lombardy, Veneto, Liguria and Sicily; IVIGs: Emilia-Romagna, Latium, Marche, Sicily and Calabria) the mean price per unit exceeded the maximum price of transfer to public health facilities as defined by the AIFA resolution of 5 August 2006 (50).

Regarding albumin (Table 84), the national mean price per gram was 2.72 euros. The variability observed between Regions (range: 1.90-3.93 euro per gram) was affected by the different contribution of each distribution channel to the definition of costs, as well as volumes. In particular, the mean price paid by NHS facilities was subject to variability that could be linked to the different contracts awarded following a tender process, while the cost recorded through the public pharmacies was substantially similar for all Regions. In fact, the prices of the packages and the discounts applied are the same nationwide and the slight differences are probably due to the different composition of the "basket" compared to the dosages and relative prices.

Emilia-Romagna, Marche, Piedmont, the AP of Bolzano and Tuscany were the Regions in which more than 90% of the commercial demand was dispatched to NHS facilities.

In other Regions, such as Friuli-Venezia Giulia, Veneto and the AP of Trento, the commercial demand (although not significant) was mainly dispatched to the accredited pharmacies channel, showing significantly higher mean prices per gram.

The market demand for IV IGs (excluding the specific demand for products containing IVIGs with high titers of IGM - *see* Table 7) recorded an expenditure of € 39.7 million with an increase of 11% compared to 2016, in line with the increasing availability of toll fractionation products (Table 85). The mean unit price per gram at national level was 38.12 euros (range: 31.65-48.95 euros).

The purchase price of pdFVIII on the market was € 33,467,639 (€ 0.56 per IU), and almost entirely accounted for the distribution through NHS facilities (97%) with a 3% increase compared to 2016 (Table 86).

Table 84. National and Regional mean price per gram for the purchase of albumin by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2017

Region	Mean price per gram			Demand				Total expenditure			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
				g	%	g	%	g	%	g	%
Abruzzo	2.11	3.95	2.45	214,840	81%	48,833	19%	452,564	70%	192,814	30%
Aosta Valley	2.18	3.93	2.54	2,000	79%	520	21%	4,350	68%	2,046	32%
AP Bolzano	2.29	NA	2.29	16,250	100%	-	NA	37,136	100%	-	NA
AP Trento	NA	3.87	3.87	-	NA	5,630	100%	-	NA	21,816	100%
Apulia	2.27	3.92	3.30	226,525	38%	376,513	62%	514,963	26%	1,477,160	74%
Basilicata	2.35	3.94	3.06	42,225	55%	33,955	45%	99,270	43%	133,750	57%
Calabria	2.20	3.90	3.46	120,400	26%	345,598	74%	264,980	16%	1,347,060	84%
Campania	2.04	3.88	2.48	3,026,905	76%	939,870	24%	6,182,265	63%	3,650,483	37%
E.-Romagna	2.69	3.93	2.72	157,850	97%	4,878	3%	424,094	96%	19,155	4%
Friuli-V. Giulia	-	3.93	3.93	-	NA	3,160	100%	-	NA	12,405	100%
Latium	2.35	3.92	3.01	470,603	58%	340,290	42%	1,107,421	45%	1,333,048	55%
Liguria	2.25	3.93	3.37	16,750	33%	33,630	67%	37,697	22%	132,293	78%
Lombardy	2.10	3.92	2.85	533,553	59%	370,498	41%	1,121,668	44%	1,451,089	56%
Marche	2.36	3.93	2.37	17,385	99%	150	1%	41,035	99%	589	1%
Molise	2.46	3.93	3.56	7,500	25%	22,218	75%	18,480	17%	87,399	83%
Piedmont	1.79	3.93	1.88	118,638	96%	4,995	4%	212,189	92%	19,655	8%
Sardinia	1.90	3.95	2.64	250,545	64%	141,618	36%	475,983	46%	558,836	54%
Sicily	2.11	3.89	3.06	229,350	47%	260,515	53%	483,988	32%	1,012,792	68%
Tuscany	2.05	3.92	2.12	213,075	97%	7,260	3%	437,866	94%	28,481	6%
Umbria	2.09	3.91	3.60	1,438	17%	7,108	83%	3,004	10%	27,781	90%
Veneto	2.64	3.93	3.89	1,250	3%	35,213	97%	3,300	2%	138,514	98%
ITALY	2.10	3.91	2.72	5,667,080	66%	2,982,448	34%	11,922,255	51%	11,647,164	49%

Table 85. National and Regional mean price per gram for the purchase of intravenous immunoglobulins by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2017

Region	Mean price per gram NHS facilities	Total demand (g) NHS facilities	Total expenditure NHS facilities*
Abruzzo	41.59	14,195	590,360
Aosta Valley	35.22	5,370	189,112
AP Bolzano	35.21	12,204	429,643
AP Trento	42.90	1,500	64,350
Apulia	42.52	124,161	5,279,347
Basilicata	39.39	3,390	133,531
Calabria	45.22	3,265	147,664
Campania	35.55	141,484	5,029,344
Emilia-Romagna	45.71	18,036	824,398
Friuli-Venezia Giulia	42.21	6,340	267,641
Latium	43.03	98,850	4,253,065
Liguria	31.82	59,395	1,889,709
Lombardy	40.00	105,038	4,201,306
Marche	49.57	20,530	1,017,706
Molise	NA	-	-
Piedmont	35.89	67,760	2,431,871
Sardinia	39.15	11,075	433,535
Sicily	48.95	5,460	267,257
Tuscany	35.99	289,152	10,406,684
Umbria	40.13	14,690	589,528
Veneto	31.65	38,470	1,217,627
ITALY	38.12	1,040,366	39,663,678

* The value does not include *Pentaglobin*™.

Table 86. National and Regional mean price per international unit for the purchase of plasma-derived factor VIII by distribution channel. Absolute and percentage values for associated utilisation and expenditure in 2017

Region	Mean price per IU			Demand				Total expenditure			
	NHS facilities	Pharmacies	Total	NHS facilities		Pharmacies		NHS facilities		Pharmacies	
				UI	%	UI	%	UI	%	UI	%
Abruzzo	0.56	-	0.56	960,000	100%		0%	534,917	100%	-	0%
Aosta Valley	-	-	-	-	-	-	-	-	-	-	-
AP Bolzano	0.55	-	0.55	730,000	100%	-	0%	398,664	100%	-	0%
AP Trento	0.55	-	0.55	49,500	100%	-	0%	27,005	100%	-	0%
Apulia	0.51	-	0.51	7,314,000	100%	-	0%	3,762,937	100%	-	0%
Basilicata	0.56	-	0.56	357,000	100%	-	0%	200,277	100%	-	0%
Calabria	0.55	0.60	0.55	389,000	98%	6,000	2%	212,939	98%	3,619	2%
Campania	0.51	0.56	0.51	4,823,000	99%	37,000	1%	2,454,789	99%	20,788	1%
E.-Romagna	0.54	-	0.54	2,947,000	100%	-	0%	1,602,457	100%	-	0%
Friuli-V. Giulia	0.52	-	0.52	871,000	100%	-	0%	453,955	100%	-	0%
Latium	0.52	0.60	0.52	11,873,500	99%	132,000	1%	6,162,004	99%	79,627	1%
Liguria	0.53	-	0.53	479,000	100%	-	0%	255,752	100%	-	0%
Lombardy	0.75	0.60	0.72	5,392,000	77%	1,639,000	23%	4,065,492	80%	985,799	20%
Marche	0.52	-	0.52	493,000	100%	-	0%	254,370	100%	-	0%
Molise	0.55	-	0.55	178,000	100%	-	0%	98,296	100%	-	0%
Piedmont	0.52	-	0.52	7,761,000	100%	-	0%	4,060,748	100%	-	0%
Sardinia	0.62	0.00	0.58	1,465,000	94%	94,000	6%	901,363	100%	-	0%
Sicily	0.57	-	0.58	5,475,000	100%	-	0%	3,118,492	98%	50,167	2%
Tuscany	0.54	-	0.54	2,034,000	100%	-	0%	1,089,428	100%	-	0%
Umbria	0.52	-	0.52	1,051,000	100%	-	0%	550,956	100%	-	0%
Veneto	0.72	-	0.72	2,957,500	100%	-	0%	2,122,797	100%	-	0%
ITALY	0.56	0.60	0.56	57,599,500	97%	1,908,000	3%	32,327,638	97%	1,140,001	3%

FINAL CONSIDERATIONS

The national demand for albumin was still particularly high and continued to increase in 2017 (583 grams per 1,000 population), a countertendency to the trend observed in the previous year.

An upward demand was observed, in particular, in the AP of Trento (+19%), Calabria (+13%) and Apulia (+13%). The two regions with the highest standardised demand were Campania and Sardinia with standardised volumes of 951 and 940 grams, respectively.

About 12% of the national demand was distributed through public pharmacies, reaching a quantity significantly higher than the previous year. Pharmacies as a distribution channel are particularly used in Calabria, Campania and Latium, where they account for between 20 and 30% of regional demand.

The demand for IG rose sharply in the two-year period 2016-2017 (+9.4%), especially for the SC/IM formulations (+23.3%), and there were notable differences from one region to another. The three regions with the highest standardised demand per 1,000 population were Tuscany, Aosta Valley and Marche, with around 191, 175 and 114 grams respectively.

The demand for plasma-derived labile proteins was stable, in particular for FVIII, AT, and3F-PCCs. An exception was observed for pdFIX the demand of which dropped after the increase recorded in 2016 (-9.1%).

Concerning recombinant medicinal products, the upward trend in the demand observed in the previous years for FVIII and FIX was confirmed.

The total volume of plasma sent by Regions for industrial fractionation increased by 2.8%. The Regional plasma contribution rate for fractionation remained differentiated and the general upward trend was not confirmed in some Regions (range: -7% - +18.6%)

The level of albumin self-sufficiency was stable, despite the increase in demand. For IVIGs, on the other hand, the effective self-sufficiency recorded at national level showed a slight decrease compared to 2016 (-3%) given the rise of the demand and considering that it was too soon to see the effects of the new NAIP tender.

On the other hand, the objective of national self-sufficiency was substantially reached for pdFVIII, pdFIX (in consideration of the peculiarities described in the specific paragraphs) and 3F-PCCs. In general, there was still the need for an improvement in the distribution methods between the Regions and within inter-Regional aggregations, in order to enhance the opportunities offered by the toll fractionation system.

The expenditure sustained by the Regions for PDMPs produced by toll fractionation, excluding the expenditure associated with the production of plasma (collection, processing, biological qualification, storage and transport), was estimated to be about 130 million euros, in accordance with the costs foreseen by the contracts in force in 2017. An additional 3.5 million euros has to be taken into account for the processing of solvent/detergent virus-inactivated plasma, for a total of about 134 million euros (including VAT).

The estimate of the expenditure incurred by the NHS for the procurement on the market of PDMPs and recombinant analogues indicated in the treatment of congenital and acquired haemorrhagic diseases (without considering the expenditure for toll fractionation), amounted to about 707.6 million euros and was around 3% of the total NHS pharmaceutical expenditure recorded in 2017 (51). The aforementioned expenditure is composed of approximately 286.7 million euros (4.73 euros *per capita*) for PDMPs and approximately 420.8 million euros (6.95 euros *per capita*) for recombinant products. However, *per capita* expenditure varied considerably from one Region to another as it was influenced by both the volumes of purchases and the mean purchase price per unit.

The next report on the analysis of the demand for PDMPs for the year 2018 will take into account the evolution of toll fractionation at national level, which will be characterised by the effective availability of other products in the Regions' portfolio, the reduction of costs for processing plasma and the increase in production yields of some PDMPs such as IG. Therefore, the report will help to support the management of the highly complex plasma and PDMP system by the Regional and national government bodies, as well as all the stakeholders involved.

REFERENCES

1. Council of Europe. *European Pharmacopoeia*. 8th ed. Strasbourg: Council of Europe; 2014. Human Plasma for Fractionation; p. 2425.
2. European Commission, Health and Consumers Directorate-General. *Eudralex-EU Guidelines to good manufacturing practice medicinal products for human and veterinary use, manufacture of medicinal products derived from human blood or plasma.* Vol. 4, Annex 14. Brussels: European Commission; 2010.
3. Calizzani G, Profili S, Candura F, Lanzoni M, Vaglio S, Cannata L, Catalano L, Chianese R, Liumbruno GM, Grazzini G. Plasma and plasma-derived medicinal product self-sufficiency: the Italian case. *Blood Transfus* 2013;11(Suppl 4):s118-31.
4. Italia. Legge 21 ottobre 2005, n. 219. Nuova disciplina delle attività trasfusionali e della produzione nazionale degli emoderivati. *Gazzetta Ufficiale – Serie Generale* n. 251, 27 ottobre 2005.
5. Ministero della Salute. Decreto 15 luglio 2004. Istituzione, presso l'Agenzia Italiana del farmaco, di una banca dati centrale finalizzata a monitorare le confezioni dei medicinali all'interno del sistema distributivo. *Gazzetta Ufficiale – Serie Generale* n. 2, 4 gennaio 2005.
6. Italia. Legge 24 novembre 2003, n. 326. Conversione in legge, con modificazioni, del decreto-legge 30 settembre 2003, n. 269, recante disposizioni urgenti per favorire lo sviluppo e per la correzione dell'andamento dei conti pubblici. *Gazzetta Ufficiale* n. 274 del 25 novembre 2003 - Supplemento Ordinario n. 181.
7. Ministero della Salute. Decreto 31 luglio 2007. Istituzione del flusso informativo delle prestazioni farmaceutiche effettuate in distribuzione diretta o per conto. *Gazzetta Ufficiale – Serie Generale* n. 229, 2 ottobre 2007.
8. Ministero della Salute. Decreto 11 febbraio 1997. Modalità di importazione di specialità medicinali registrate all'estero. *Gazzetta Ufficiale – Serie Generale* n. 72, 27 marzo 1997.
9. Accordo, ai sensi degli articoli 2, comma 1, lett. b) e 4 del decreto legislativo 28 agosto 1997, n.281, tra il Governo, le Regioni e le Province Autonome di Trento e di Bolzano concernente "Indicazioni in merito al prezzo unitario di cessione, tra Aziende sanitarie e tra Regioni e Province autonome, delle unità di sangue, dei suoi componenti e dei farmaci plasmaderivati prodotti in convenzione, nonché azioni di incentivazione dell'interscambio tra le aziende sanitarie all'interno della Regione e tra le Regioni" in attuazione degli articoli 12, comma 4 e 14, comma 3 della legge 21 ottobre 2005, n.219.
10. Ministro della Salute. Decreto 11 maggio 2001. Definizione di procedure da applicarsi in caso di temporanea carenza di specialità medicinali nel mercato nazionale. *Gazzetta Ufficiale – Serie Generale*, n. 124, 30 maggio 2001.
11. Agenzia Italiana del Farmaco. Gli strumenti: il metodo di classificazione secondo il sistema ATC/DDD. *Bollettino d'informazione sui Farmaci* 2002;6:59-62.
12. Istituto Nazionale di Statistica. *Popolazione residente al 1° gennaio.* Available at: demo.istat.it; Accessed on 31/08/2016.
13. Legge 23 dicembre 1996, n. 662. Misure di razionalizzazione della finanza pubblica. *Gazzetta Ufficiale – Serie Generale* n. 303, 28 dicembre 1996.
14. Legge 30 luglio 2010, n. 122. Conversione in legge, con modificazioni, del decreto-legge 31 maggio 2010, n. 78, recante misure urgenti in materia di stabilizzazione finanziaria e di competitività economica. *Gazzetta Ufficiale – Serie Generale* n. 176, 30 luglio 2010.
15. Caraceni P, Tufoni M, Bonavita ME. Clinical use of albumin. *Blood Transfus* 2013;11(Suppl 4):s18-25.

16. Caraceni P, Angeli P, Prati D, Bernardi M; Italian Association for the Study of the Liver (AISF), Liumbruno GM, Bennardello F, Piccoli P, Velati C; Italian Society of Transfusion Medicine and Immunohaematology (SIMTI). AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis. *Blood Transfus* 2016;14(1):8-22.
17. Candura F, Calizzani G, Profili S, Chelucci C, Brutti C, Biffoli C, Liumbruno GM, *Analisi della domanda dei principali medicinali plasmaderivati in Italy. Anni 2014-2015.* Roma: Istituto Superiore di Sanità; 2017. (Rapporti ISTISAN 17/20).
18. Lanzoni M, Biffoli C, Candura F, *et al.* Plasma-derived medicinal products in Italy: information sources and flows. *Blood Transfus* 2013; 11(Suppl 4):s13-7.
19. Società Italiana di Medicina Trasfusionale e Immunoematologia. *Raccomandazioni SIMTI sul corretto utilizzo degli emocomponenti e dei plasmaderivati.* Milano: SIMTI; 2008.
20. Burnouf T. Modern plasma fractionation. *Transfus Med Rev* 2007;21:101-17.
21. Liumbruno GM, Franchini M, Lanzoni M, *et al*. Clinical use and the Italian demand for antithrombin. *Blood Transfus* 2013; 11 Suppl 4: s86-93.
22. Mannucci PM, Tuddenham EG. The hemophilias – from royal genes to gene therapy. *N Engl J Med* 2001;344:1773-9.
23. Franchini M, Mannucci PM. Past, present and future of hemophilia: a narrative review. *Orphanet J Rare Dis* 2012;7:24.
24. Chtourou S. Production and clinical profile of human plasma coagulation Factor VIII. In: Bertolini J, Goss N, Curling JM (Ed.). *Production of plasma proteins for therapeutic use.* Hoboken, NJ: John Wiley & Sons; 2013. p. 29-40.
25. National Institute for Biological Standards and Control. *WHO International Standard. 8th International Standard Factor VIII Concentrate.* Geneva: WHO, 2010.
26. Chtourou S, Poulle M. Production and clinical profile of human plasma-derived Von Willebrand Factor. In: Bertolini J, Goss N, Curling JM (Ed.). *Production of plasma proteins for therapeutic use.* Hoboken, NJ: John Wiley & Sons; 2013. p. 41-48.
27. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet* 2012;379:1447-56.
28. White GC, Rosendaal F, Aledort LM, *et al*. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001;85:560.
29. Franchini M, Liumbruno GM, Lanzoni M, Candura F, Vaglio S, Profili S, Facco G, Calizzani G, Grazzini G. Clinical use and the Italian demand for prothrombin complex concentrates. *Blood Transfus* 2013;Suppl 4:s94-100.
30. Römisch J, Pock K. Prothrombin complex. In: Bertolini J, Goss N, Curling JM (Ed.). *Production of plasma proteins for therapeutic use.* Hoboken, NJ: John Wiley & Sons; 2013. p. 65-79.
31. Candura F, Calizzani G, Profili S, Chelucci C, Salvatori ML, Brutti C, Biffoli C, Liumbruno GM. *Sistema trasfusionale italiano 2016: analisi della domanda dei medicinali plasmaderivati. Volume 2/Italian Blood System 2016: demand for plasma-derived medicinal products. Volume 2.* Roma: Istituto Superiore di Sanità; 2019. (Rapporti ISTISAN 19/12).
32. Council of Europe. *European Pharmacopoeia*. 8th ed. Strasbourg: Council of Europe; 2014. Human varicella immunoglobulin for intravenous administration; p. 2425. 1528 (01/2014).
33. Committee for Medicinal Products for Human Use. *Core SPC for human varicella immunoglobulin for intramuscular use.* London: European Medicines Agency: 2005. (CPMP/BPWG/3726/02). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003432.pdf; accessed on: 15/12/2017.

34. Council of Europe. *European Pharmacopoeia*. 8th ed. Strasbourg: Council of Europe; 2014. Human varicella immunoglobulin for intravenous administration; p. 2425. 0723 (01/2014).
35. Committee for Medicinal Products for Human Use. *Core summary for product characteristics for human rabies immunoglobulin for intramuscular use.* London: European Medicines Agency; 2005. (CPMP/BPWG/3728/02). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/core-spc-human-rabies-immunoglobulin-intramuscular-use-cpmp/bpwg/3728/02_en.pdf. accessed on: 15/12/2017.
36. Marx G. Fibrinogen: Science and biotechnology. In: Bertolini J, Goss N, Curling JM (Ed.). P *Production of plasma proteins for therapeutic use*. Hoboken, NJ: John Wiley & Sons; 2013. p. 117-35.
37. Committee for Medicinal Products for Human Use. *Core summary of product characteristics for human fibrinogen products*. London: European Medicines Agency; 2015 (EMA/CHMP/BPWP/691754/2013 Rev 1). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-summary-product-characteristics-smpcfor-human-fibrinogen-products_en.pdf; accessed on: 15/03/2016.
38. Lebing W. Alpha1-proteinase inhibitor: the disease, the protein, and commercial production. In: Bertolini J, Goss N, Curling JM (Ed.). *Production of plasma proteins for therapeutic use*. Hoboken, NJ: John Wiley & Sons; 2013. p. 227-40.
39. Over J, Kramer C, Koenderman A, Wouters D, Zeerleder S. C1-Inhibitor. In: Bertolini J, Goss N, Curling JM (Ed.). *Production of plasma proteins for therapeutic use*. Hoboken, NJ: John Wiley & Sons; 2013. p. 241-58.
40. Menegatti M, Peyvandi F. Factor X deficiency. *Semin Thromb Hemost* 2009; 35(4): 407-415.
41. Bolton-Maggs PHB, Perry DJ, Chalmers EA, *et al*. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004;10:593-628.
42. Inbal A, Oldenburg J, Carcao M, Rosholm A, Tehranchi R, Nugent D. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood* 2012;119(22):5111-5117.
43. Dorey E. First recombinant Factor XIII approved. *Nat Biotech* 2014;210.
44. Radosevich M, Zhou FL, Huart JJ, Burnouf T. Chromatographic purification and properties of a therapeutic human protein C concentrate. *J Chromatogr B* 2003, 790:199–207.
45. Decreto legislativo 20 dicembre 2007, n. 261. Revisione del decreto legislativo 19 agosto 2005, n. 191, recante attuazione della direttiva 2002/98/CE che stabilisce norme di qualità e di sicurezza per la raccolta, il controllo, la lavorazione, la conservazione e la distribuzione del sangue umano e dei suoi componenti. *Gazzetta Ufficiale – Serie Generale* n. 19, 23 gennaio 2008.
46. Ministero della Salute. Decreto 2 dicembre 2016. Programma nazionale plasma e medicinali plasmaderivati, anni 2016-2020. *Gazzetta Ufficiale – Serie Generale* n. 9 del 12 gennaio 2017.
47. Ministero della Salute. Decreto 12 aprile 2012 (1). Schema tipo di convenzione tra le Regioni e le Province autonome e le Aziende produttrici di medicinali emoderivati per la lavorazione del plasma raccolto sul territorio nazionale. *Gazzetta Ufficiale – Serie Generale* n. 147, 26 giugno 2012.
48. Ministero della Salute. Decreto 5 dicembre 2014 recante "Individuazione dei centri e aziende di frazionamento e di produzione di emoderivati autorizzati alla stipula delle convenzioni con le regioni e le province autonome per la lavorazione del plasma raccolto sul territorio nazionale". *Gazzetta Ufficiale – Serie Generale* n.80, 7 aprile 2015.
49. Cicchetti A, Berrino A, Casini M, Codella P, Coretti S, Facco G, Fiore A, Marano G, Marchetti M, Midolo E, Minacori, Refolo P, Romano F, Ruggeri M, Sacchini D, Spagnolo AG, Urbina I, Vaglio S, Grazzini G, Liumbruno GM. Health Technology Assessment of pathogen reduction technologies applied to plasma for clinical use. *Blood Transfus* 2016;14:287-386.

50. Agenzia Italiana del Farmaco. Determina del 05/08/2006. *Gazzetta Ufficiale – Serie Generale* n. 182, 7 agosto 2006.

51. Osservatorio Nazionale sull'impiego dei Medicinali. *L'uso dei farmaci in Italia. Rapporto Nazionale 2017.* Roma: Agenzia Italiana del Farmaco, 2018.

Serie Rapporti ISTISAN
numero di agosto 2020

Stampato in proprio
Servizio Comunicazione Scientifica – Istituto Superiore di Sanità

Roma, settembre 2020