DATA & ANALYSIS OF IMMUNOGLOBULIN SUPPLY

AND

PLASMA REQUIREMENTS IN EUROPE

2010-2021

May 2023

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INTRODUCTION

The concept of regional self-sufficiency for the supply of Plasma Derived Medicinal products (PDMPs) and particularly immunoglobulin (IG) has recently become more pressing in Europe, due to the IG shortage that several countries experienced during the COVID-19 pandemic, the escalating dependency of patients on U.S. source plasma and continuously climbing prices for some PDMPs. Furthermore, the risks of another disruption of the U.S. plasma supply caused by the emergence of a new pathogen or by political or economic events have raised the urgency of the issue.

The present document is an attempt to clarify the data about the plasma industry to set the stage and scope of the problem and to provide data and information so that all sides can have some historical usage facts about the market and need for PDMPs. This should help in the context of the discussion about the European Union's revising of the Substance of Human Origin (SoHO) regulations which are ongoing in 2023.

1) Patients' Needs for Immunoglobulin in the European Union and Worldwide

Between 2014 and 2020 (latest full market data available), the European immunoglobulin market grew by 6.7% annually, going from 42.0 tons to 61.8 tons. With 24% of the global IG market, Europe was the second largest region in the world in units after North America, which uses close to half of the world supply, and slightly higher than Asia & Pacific.

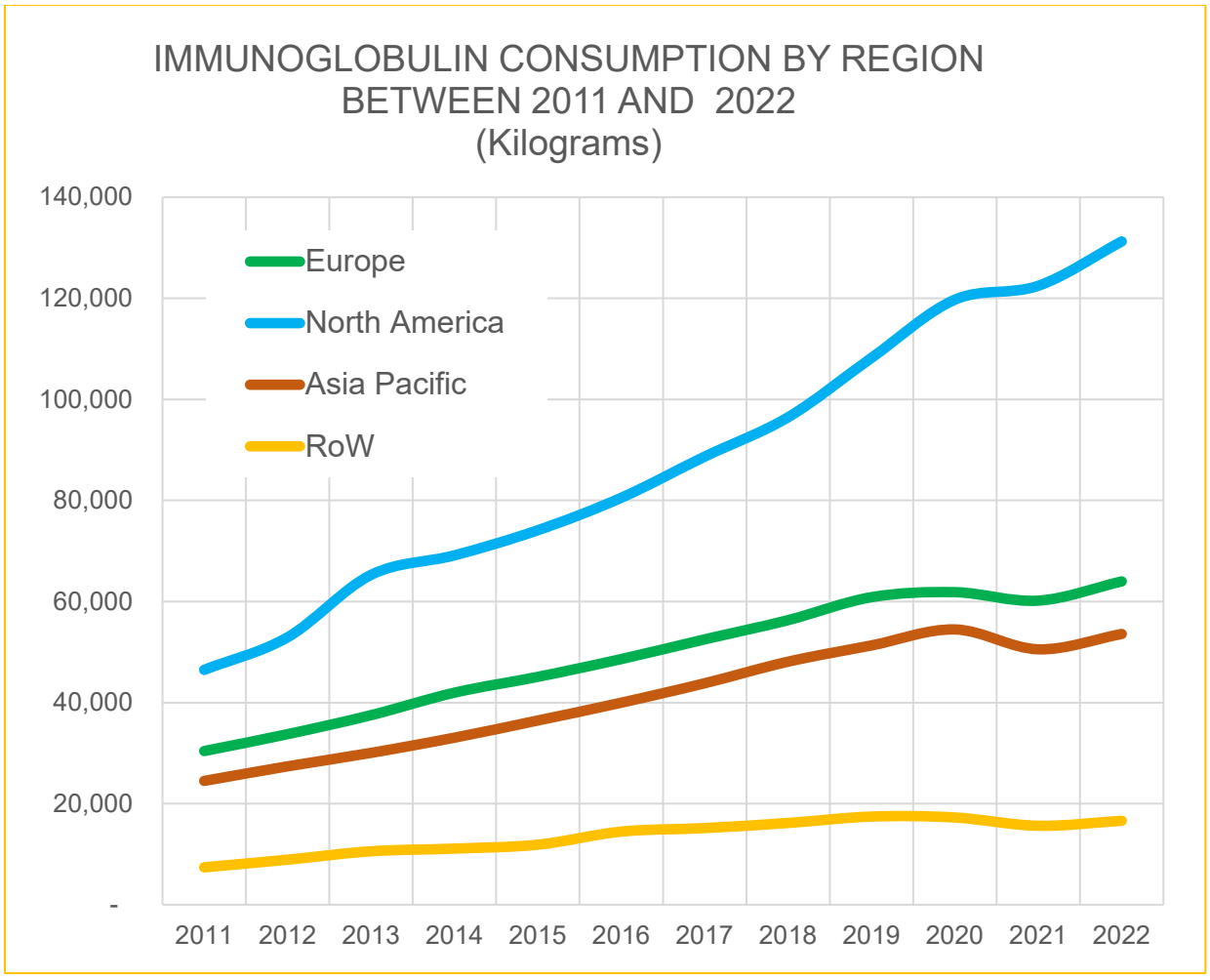
These increasing IG needs are essentially attributed to patients' level of access to IG therapies, improved treatment funding, expanded diagnoses and new patient identifications, in part spurred by patients' organizations and new indications. In addition, there are now more patients in existing indications such as secondary immunodeficiencies caused by the growth of underlying diseases conditions (cancer), as well as the opening of new markets, and population aging. These trends are especially important for the growth of chronic diseases.

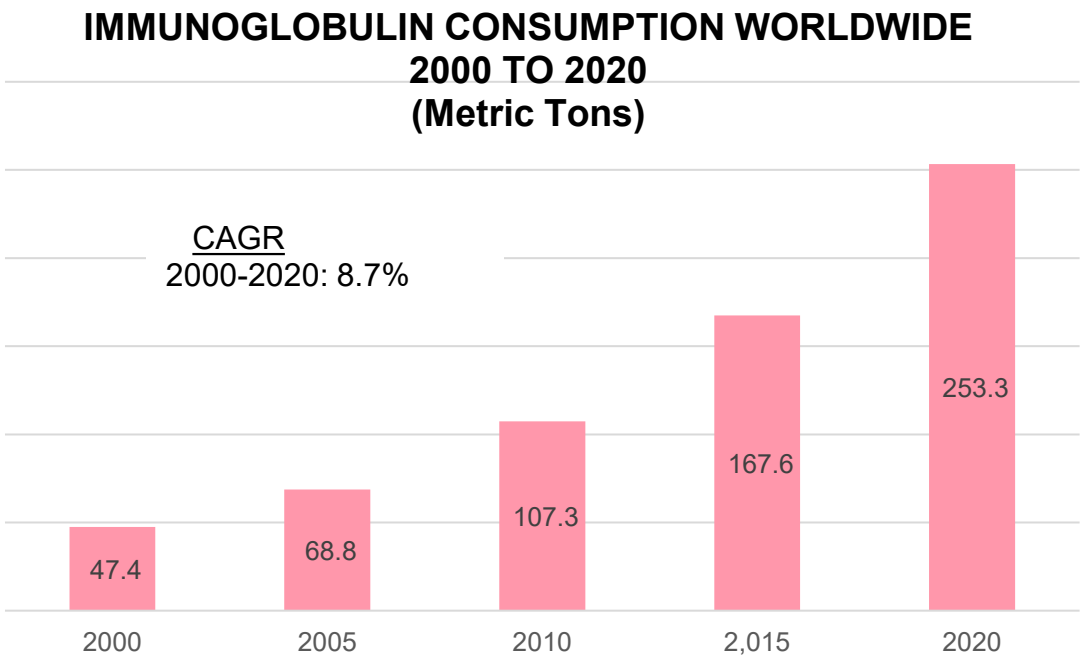
The data below illustrate the increased IG consumption per capita in selected countries between 2014 and in 2020. In this time period, the consumption of IG per capita in the E.U. grew from 57 to 81 kilograms per million population.

The consumption data shown for the year 2020 below largely reflect a pre-COVID situation because the shortage gradually occurred during that year.

IMMUNOGLOBULIN CONSUMPTION PER CAPITA IN SELECTED COUNTRIES
(Kg. per Million Inhabitants)

	2014	2017	2020
Austria	107	119	152
Belgium	108	174	218
France	130	167	174
Germany	93	103	126
Hungary	13	26	42
Italy	73	89	111
Spain	77	93	116
Sweden	126	150	177
E.U. Average	57	71	81
USA	200	248	334





Going forward, the global IG consumption is expected to continue to increase, due to:

Continued and expanded use in Primary Immune Deficiency

Both in high- and low-income countries, but primarily in the former, due expanded diagnosis, easier access to care, improved financial support to cover the therapy costs, especially for the chronic conditions. The patient organizations will continue to disseminate awareness, support public education and advocate for therapy cost recovery for more patients.

Continued and expanded use in Neurology, especially CIDP and auto-immune conditions

Despite the market introduction of competitive therapies, IG treatments will continue to retain the favor of many patients and prescribers, due to its safety track record and efficacy, as well as pricing.

Growing Acceptance of IG Therapy in new and emerging indications, such as Secondary Immune Deficiency (SID)

GBS for emerging pathogens such as Zika, SID from immunosuppressive therapies and for transplants.

2) Plasma Fractionation Process and Supply

This describes the way the commercial plasma sector operates, and how it differs compared to the non-profit sector.

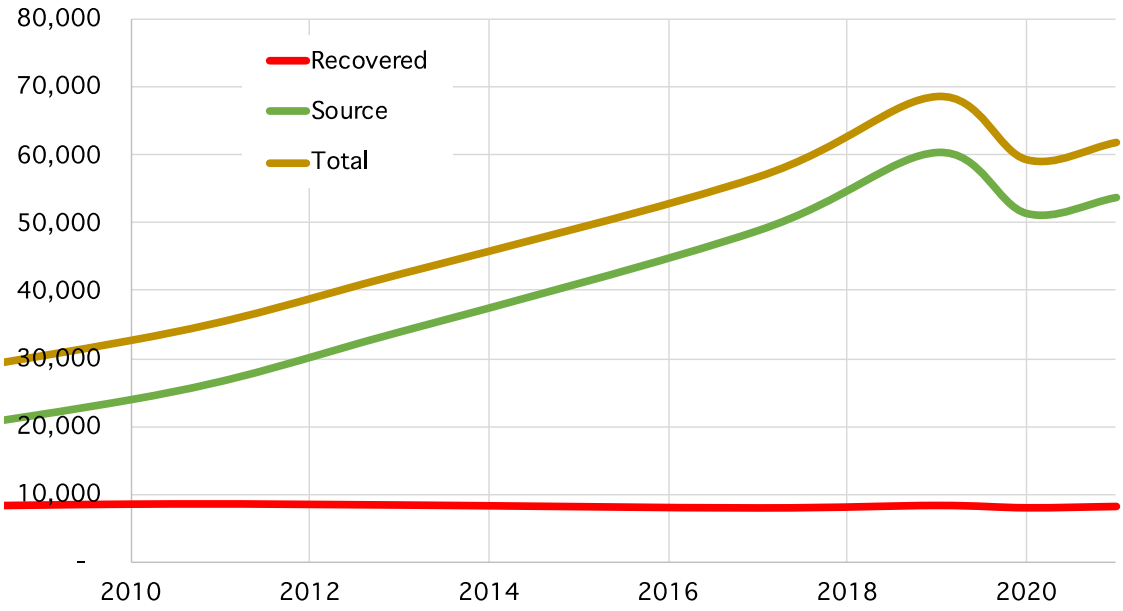
Due to their size, logistics and strategies, the multinational plasma companies collect plasma mostly in the United States, using their network of plasma centers, where donors give plasma and are compensated for it. Most of these companies also buy or collect plasma in Europe; some have plasma centers there, and/or they buy it from other suppliers. They also buy plasma from blood collection organizations which are generally public entities. Once the plasma has been tested and passed the mandatory inventory hold period, the companies send the plasma to their fractionation plants, which may be in a different country. With rare exceptions, the companies are not mandated to fractionate the plasma in the country where it has been collected. Once the "base fractionation," - turning plasma into intermediate bulk paste - has been completed, the companies process these bulk intermediates into finished products. This can be done in the same facility or at another location. The finished PDMPs, including IG do not necessarily return to the place where the plasma was collected. Instead, they are dispatched to those countries where the company markets these products, independently from the origin of the plasma.

In other words, for the large multinational companies, there is not a perfect correlation between the quantity of plasma that they collect in a region (Europe or United States, possibly elsewhere) and the quantity of PDMPs that they sell in that region. There often are business reasons for aligning the two, including costs to collect and IG prices, but it is not a hard and fast rule. The quantities and kinds of product they sell in Europe, for example and to individual country markets, depend more on commercial considerations and not on the volume of plasma coming from this region or a given country, except, in special situations, as described below.

For their part, the blood collection organizations, usually a National Blood Center and a network of regional and local blood centers, are mandated by their government to collect whole blood, and to produce and distribute blood components in sufficient quantities to meet the country's patients' needs. For plasma sent for fractionation, the plasma products produced may either be returned to the country of plasma origin, or the plasma may be sold and not returned. Generally, blood collection organizations have a responsibility to use the plasma donated on a non-remunerated basis for the patients of that country, so they want to have products returned from the plasma sent for fractionation.

3) Global Plasma Supply between 2010 and 2021

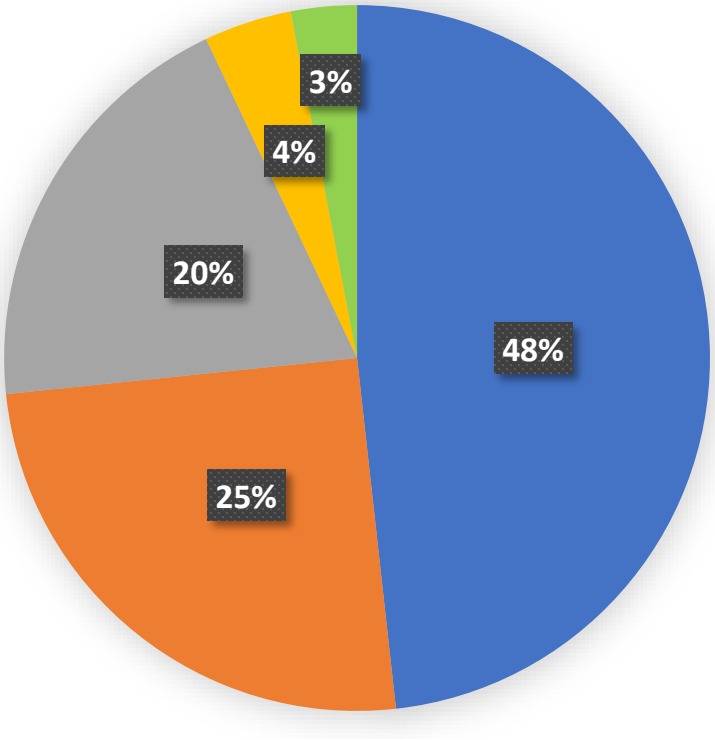
GLOBAL PLASMA FOR FRACTIONATION
2010-2020 (Liters X 000)



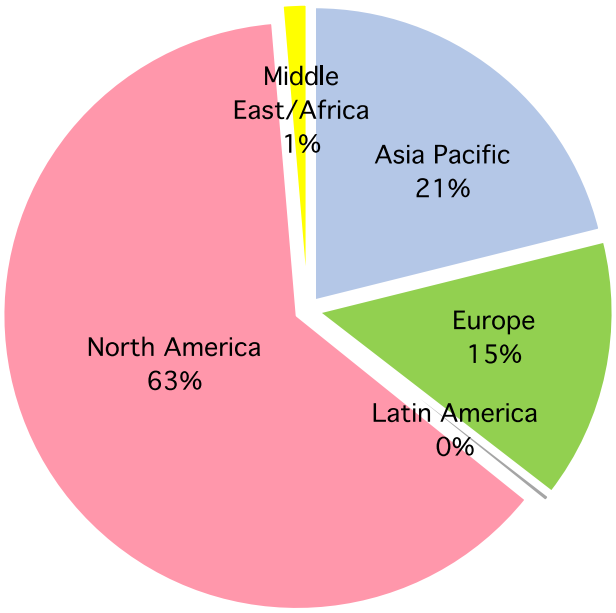
Over the period 2010-2021, global source plasma collections grew by 9.5% annually whereas the volume of recovered plasma declined 0.5% per year.

The chart above shows the dip caused by the COVID-19 pandemic at the beginning of 2020. The pandemic caused the global volume of plasma for fractionation to fall 14% in 2020 from 2019 and it merely regained 3% through 2021. This comparatively low gain was attributed to the continuing impact of the pandemic and of the precautionary measures to limit its dissemination. The first half of 2022 was also disappointing but the second half of that year experienced a strong turnaround leading to globally more plasma collected in 2022 than in 2019. This has enabled collections to return to quasi normal levels in early 2023.

2020 IG Usage by Region (~250 tons)



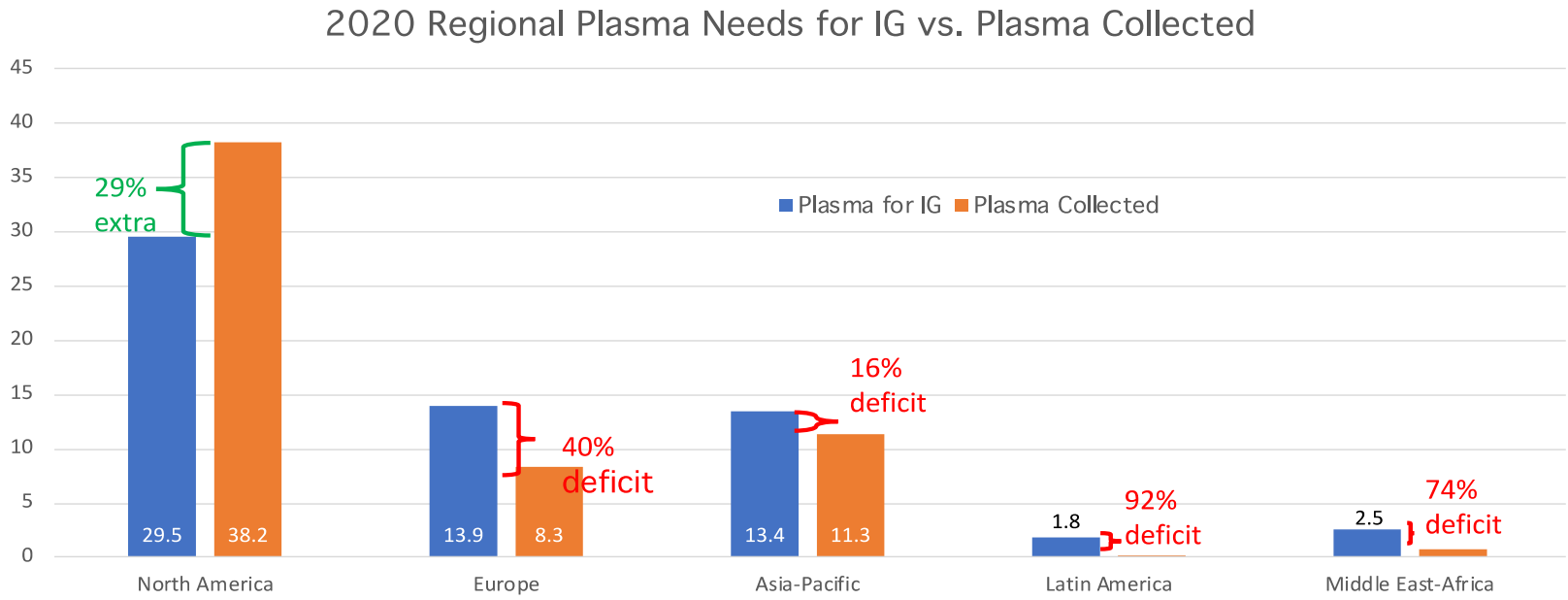
REGIONAL DISTRIBUTION OF THE SUPPLY OF PLASMA FOR FRACTIONATION BY REGION IN 2021
(Liters x 1000)
Total: 61.8 million liters



The two above pie charts show that Europe needs about 25% of the global IG supply but collects a mere 15% of the plasma for fractionation, leading to a deficit of roughly 40% of plasma based on actual IG usage. In contrast, North America uses close to 50% of the IG sold worldwide, but supplies 63% of the plasma for fractionation, having a surplus of IG which is used to supply Europe, Latin America, Middle East and parts of Asia.

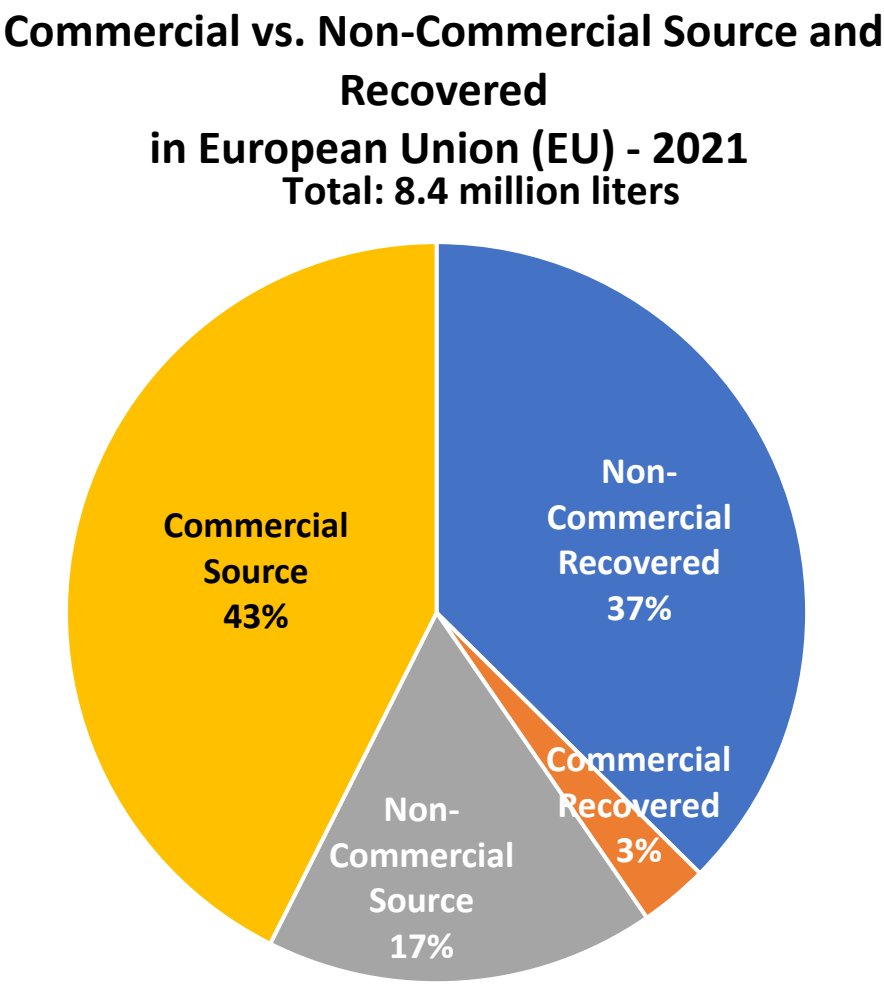
The chart below illustrates the imbalance in plasma procurement, showing that the volume of plasma collected in the U.S. exceeds by 29% the IG quantity needed by patients in this country. This plasma is processed by multinational, commercial or non-commercial fractionators in their sites in multiple countries.

In 2020, the US continued to supply extra plasma for the rest of the world



As mentioned above, the surplus of plasma collected in North America (all United States), is used to cover the deficit in all the other regions of the world.

3) Respective Contributions of the Public and Private Sectors to the Supply of Plasma for Fractionation in the European Union

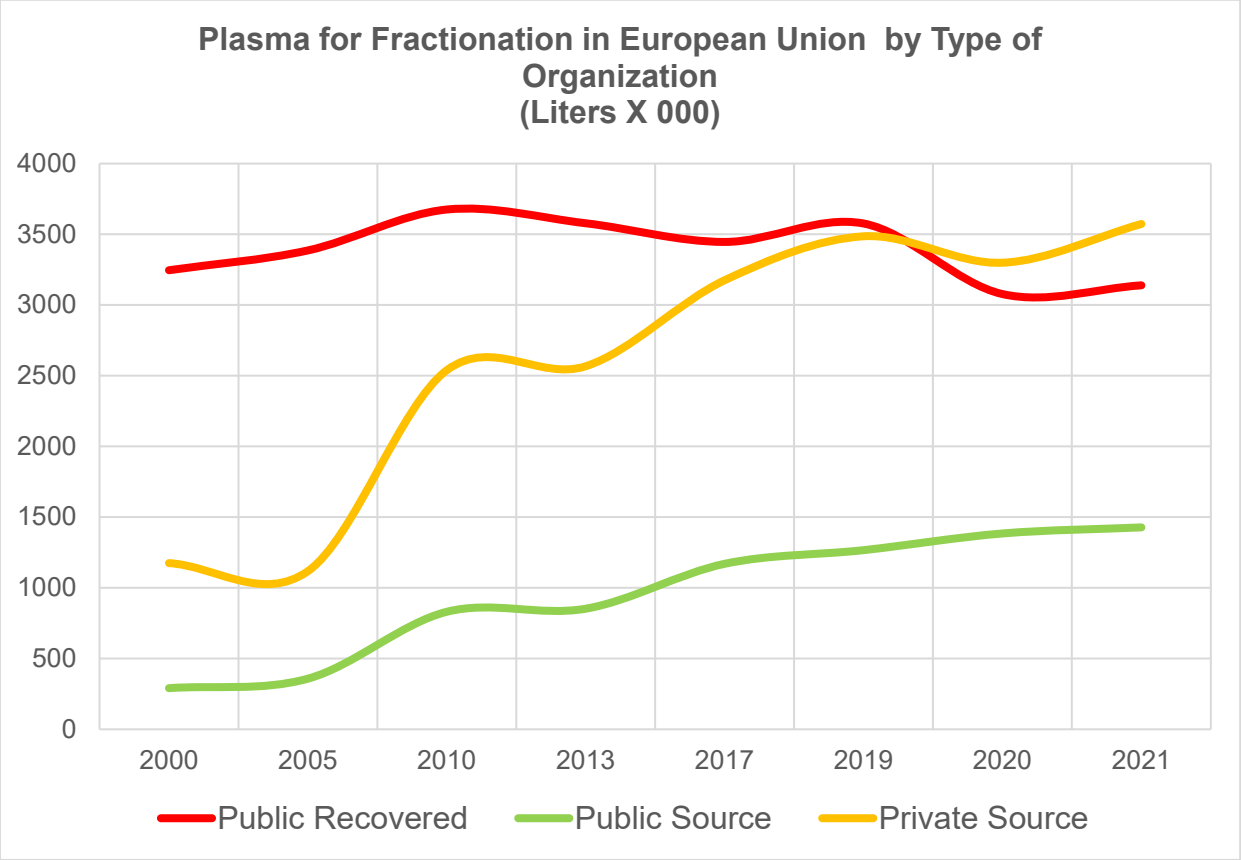


In 2021, most of the plasma for fractionation was supplied by the public sector in the European Union, representing 54% of the total. Of this, it was mostly recovered plasma (37% of the total), with 17% coming from plasmapheresis (source plasma). The commercial source plasma constitutes 42% of the total, and total commercial plasma for fractionation is 46%. This is nearly half the total plasma for the European Union despite only coming from 4 member states: Germany, Austria, Czech Republic and Hungary. The public sector showed some small amount of growth over the past 10 years, but most of the growth has largely come from the private sector, as shown in the chart below.

The volume of recovered plasma, supplied almost exclusively by the public sector, has declined at a rate of 0.3% per year between 2000 and 2021. This is a consequence of the Patients' Blood Management (PBM) that has globally led to a substantial reduction in the

number of whole blood and red blood cells units administered to patients undergoing many surgeries, mainly elective. Over the ten-year period since the PBM has been introduced, hospitals have ordered less and less blood from the blood centers which in turn cut down on their whole blood collections, thus resulting in less recovered available plasma for fractionation.

Today, the consensus is that PBM has largely achieved its goal, and a slight turnaround in blood collections seems to emerge in some high-income countries, This, however, must be considered in the light of the return to a normal activity level in the delivery of healthcare services after the pandemic, during which elective surgeries were postponed. Furthermore, the return to normal after the pandemic has also been reported as causing more accidents and traumas of all kinds, as people are returning to their routine activities.

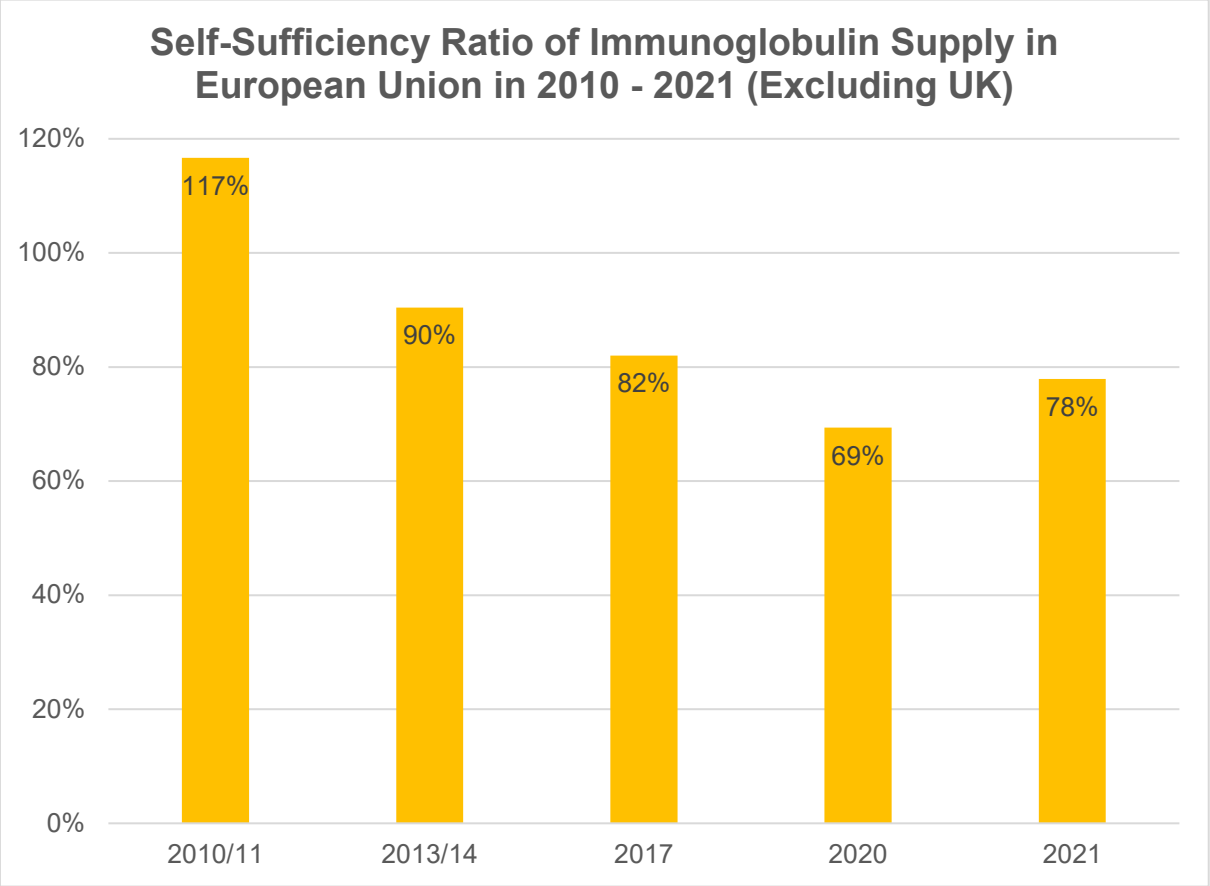


The volume of source plasma collected by the public sector has increased by a strong 15.6% per year between 2000 and 2021, reaching 1.4 million liters in 2021, or 17.5% of the total plasma for fractionation in Europe (less UK). For its part, the private sector collected about 3.6 million liters in 2021, growing by 10.6% annually over the same time period. This volume exceeded the quantity of recovered plasma for fractionation (3.1 million liters) in 2021.

4) Plasma and Immunoglobulin Supplies in European Union

The COVID-19 pandemic has caused plasma collections to decrease in the United States, Europe and elsewhere in 2020. In 2021, plasma collections recorded a modest increase in the U.S. and in Europe, while IG usage fell in both markets due to the lower IG supply and product shortages in Europe.

As a result of these opposite trends, the self-sufficiency rate for the European Union went from 117% (excluding UK) over a decade ago to 69% in 2020 (excluding UK) and rebounded slightly in 2021 to 78%, due mostly to commercial plasma collection providing higher volumes of plasma for fractionation. In addition, the rebound in EU self-sufficiency for IG usage was impacted significantly by lower IG consumption. This was due to patients having shortages of product, product rationing and delayed new patients starting IG therapy. In fact, if the historical growth rate of 9.1% for IG usage in the EU from 2011 to 2019 would have been sustained in 2021 over the 2020 levels, the regional self-sufficiency would have fallen to 66% in 2021. In 2022, we estimate the EU self-sufficiency rose again slightly, due largely to higher commercial plasma collection volumes again.



Europe would need to increase its plasma collections by 4.5 million liters, or 54%, to provide enough plasma for fractionation to meet the IG needs of all its patients in 2021. An estimate for 2022 suggests that it is just slightly less, but still over 50% more than the current collections level.

5) Immunoglobulin (IG) Procurement in Selected European countries and Self-Sufficiency

There are significant variations from country to country in Europe with respect to the way the volumes and kinds of plasma they collect, as shown in the charts below. Four countries collect more plasma that they theoretically need in order to meet their patients' needs: Austria, the Czech Republic, Germany and Hungary. In Poland, the plasma collected just about meets the requirements. Three other countries below (France, Italy, and Spain) must import IG products made from foreign plasma, either from the commercial plasma collections in the 4 European Union countries which allow it, or from United States.

However, as mentioned earlier, the IG availability of IG in any country is not only a function of the quantity of the plasma collected. The particular situation of each country in terms of plasma supply essentially results from historical developments and current regulations and reflects its blood and plasma organization and policy.

In order to reach complete independence from U.S. plasma, and become self-sufficient for the procurement of IG, the European Union collectively should increase its collection of plasma for fractionation to a level that would render all imports of products made with U.S. plasma unnecessary. In doing so, the size of the market would not change, it would only be the origin of the plasma (and the security of the origin of the source material), which would change.

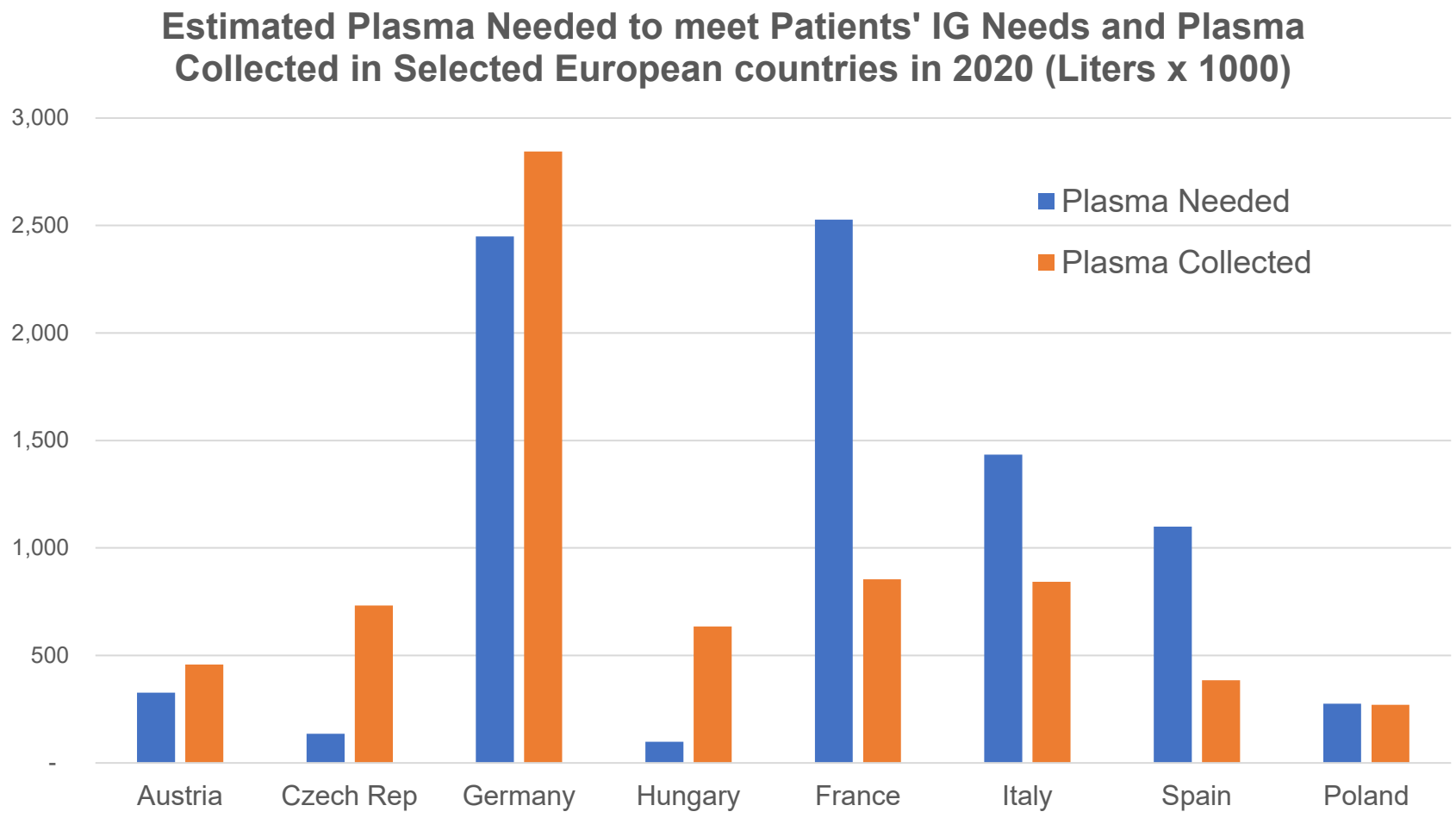
Here is an example to illustrate the above: assuming that the average IG consumption per capita of a country is low, let's say 10 kilograms per million population, the plasma suppliers will have much less difficulties to attain self-sufficiency for supplying plasma for a relatively small number of patients than if the average consumption is 200 kilograms per million inhabitants - meaning many more patients to serve.

In the past, this ambiguity of the self-sufficiency concept has allowed a number of countries to claim to be "self-sufficient" in their procurement of IG to patients simply because many patients were not diagnosed but the country's representatives claimed to be "self-sufficient."

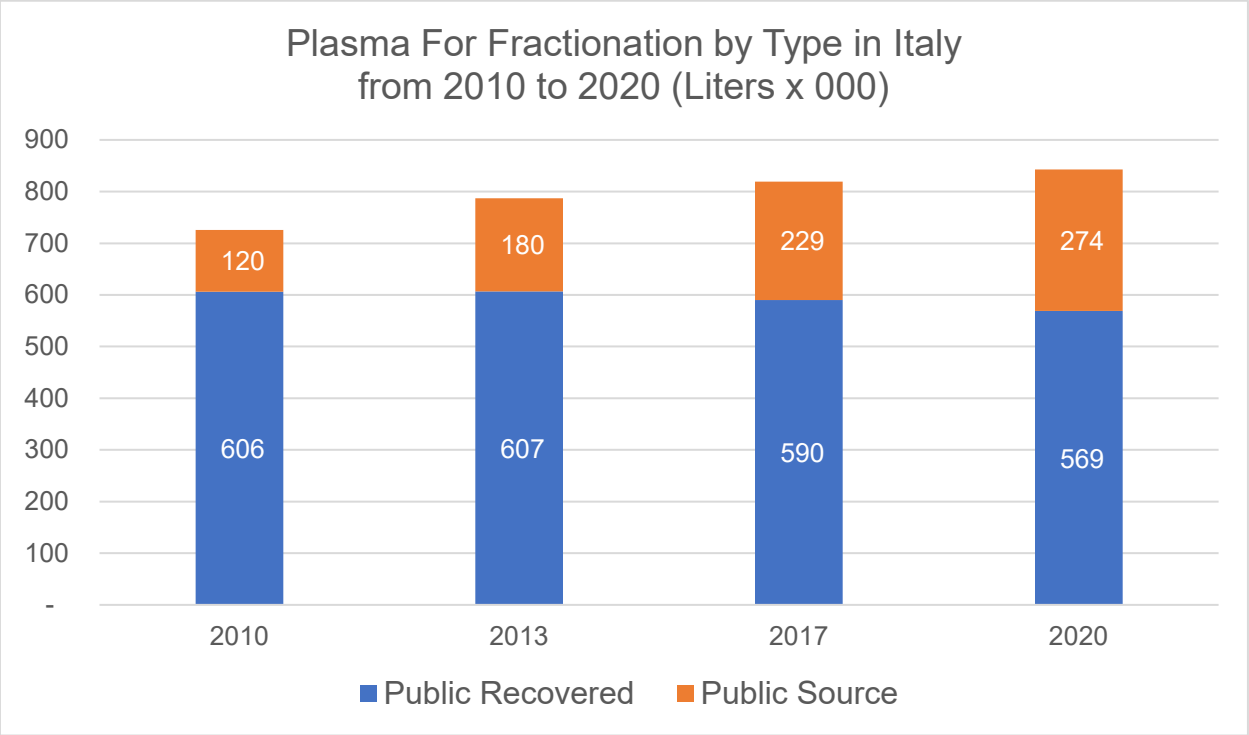
In a study conducted a few years ago by MRB, the volume of plasma required in various European countries at different levels of average IG per capita (65 gr, 120gr., and 150 gr. per 1000 people) was calculated. As expected, the volumes of plasma needed varied considerably among these three levels. From the public health standpoint, the "patients consumption per capita" criterion is a better indicator of the quantity and possibly the quality of the patients' care in a country than plasma self-sufficiency value.

Incidentally, the patients' organizations do not voice any strong preference for the origin of the plasma used to make their IG products, as long as they are efficacious and safe, including carry antibodies to pathogens experienced by the patients in their domestic environment.

In the following pages, the situation prevailing in selected countries is reviewed in support of the data.


Estimated Plasma Needed to meet Patients' IG Needs and Plasma Collected in Selected European countries in 2020 (Liters x 1000)
3,000
2,500
2,000
1,500
1,000
500
-
Plasma Needed
Plasma Collected
Austria
Czech Rep
Germany
Hungary
France
Italy
Spain
Poland

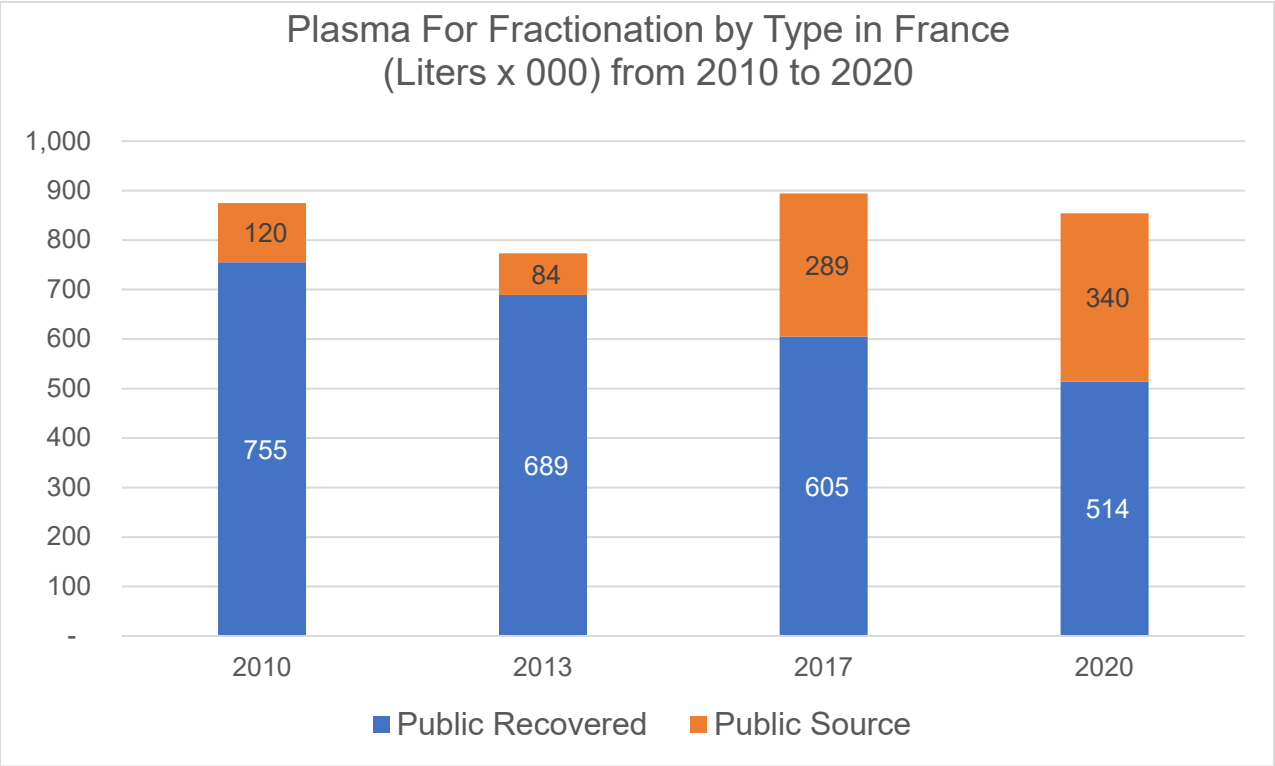
7. Brief Analysis of Selected Countries



Italy (chart above): Self-sufficiency has a long tradition in Italy, and the Ministry of Health, through its National Blood Center, monitors and controls blood and plasma collections, which are under the operational responsibility of the Health Regions. For many years, the plasma collected in the country could not be fractionated outside the country. This regulation was challenged in the early 2000, leading to contract fractionation by foreign fractionators. Italy's IG self-sufficiency ratio was 32% in 2020 (understood as "supplier self-sufficiency ratio, not patients').

As shown in the chart below, between 2010 and 2020, the quantity of plasma for fractionation has grown by 1.5% annually and has not kept pace with the growth of IG consumption. Plasma for fractionation is exclusively produced by the public sector in Italy (there are no private plasma centers) but source and recovered plasma are imported from the U.S. and other European countries to produce IG for the Italian market and make up the IG needs that are not covered by the production generated with domestic source and recovered plasma.

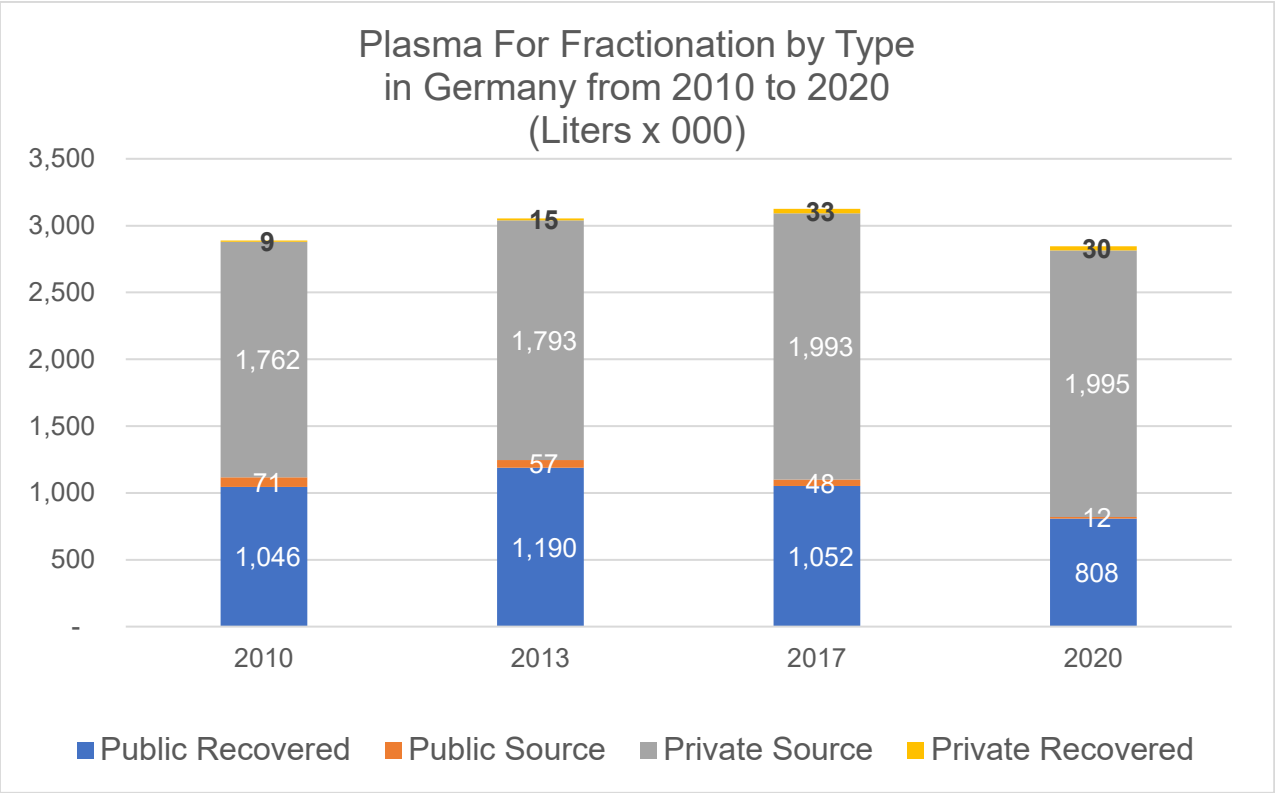
In Italy, there are no commercial plasma centers, and donor monetary compensation in prohibited, even though blood and plasma donors are offered a day off from work in some cases, a valuable benefit to many donors and significant cost to employers.



France: Self-sufficiency remains a long-term objective. Similar to Italy and Spain, the national blood program under the Ministry of Health collects source plasma from non-compensated donors and produces recovered plasma from whole blood donations. Between 2010 and 2020, the volume of plasma for fractionation declined by 0.2% per year, while the IG needs grew, creating a growing gap in terms of IG needs coverage.

A government-owned company fractionates the French plasma, bringing the IG self-sufficiency ratio (understood as "supplier self-sufficiency ratio, not patients') to 27.5% in 2020. The balance has been provided by commercial companies selling IG in France under special marketing authorizations and subjected to special taxes imposed to companies that makes PDMPs suing compensated donors. As in Italy, IG shortages were averted in 2021 when the government accepted to increase the insurance reimbursement rate of IG, as the foreign manufacturers expressed their need to be able to cover their plasma costs in order to maintain a steady supply of IG to the country.

As in Italy, there are no commercial plasma centers in France, and donor monetary compensation in prohibited, even though, as in Italy, blood and plasma donors are offered some free time from work.

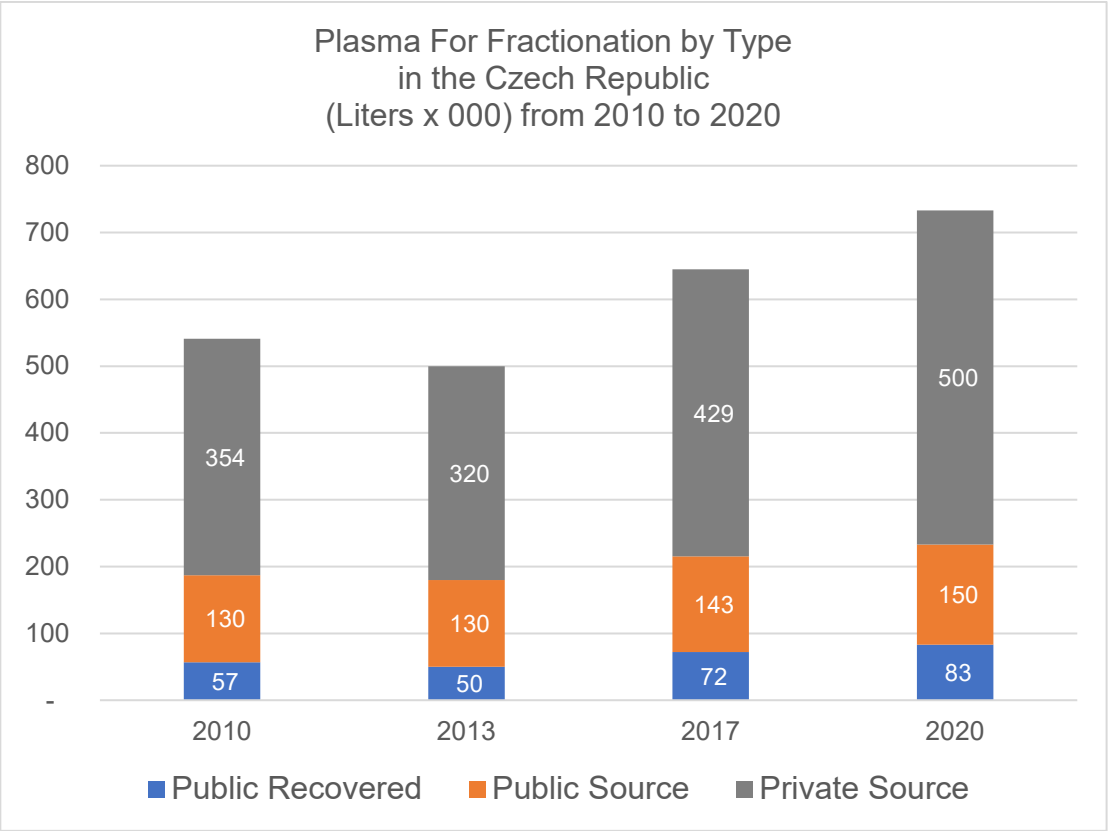


Germany: The official federal government position on the procurement of PDMPs is that the country ought to be self-sufficient. The "Länder" (states) are responsible for their respective blood program, in which the Red Cross competes with university, hospitals and community blood centers, as well as a small number of commercial blood collectors. These entities sell both source and recovered plasma to commercial fractionators. There is no government-owned fractionation plant. In addition, commercial plasma collection centers have been allowed for a long time, and the country boast just over 200 centers.

In 2020, Germany was just about self-sufficient as it supplied enough plasma to meet the patient needs. The country has been self-sufficient (from a "suppliers' perspective") for several years, even though its plasma collections remained flat over the ten year period (2010-2020), declining by 0.1% per year. In 2021, plasma for fractionation rose 4%.

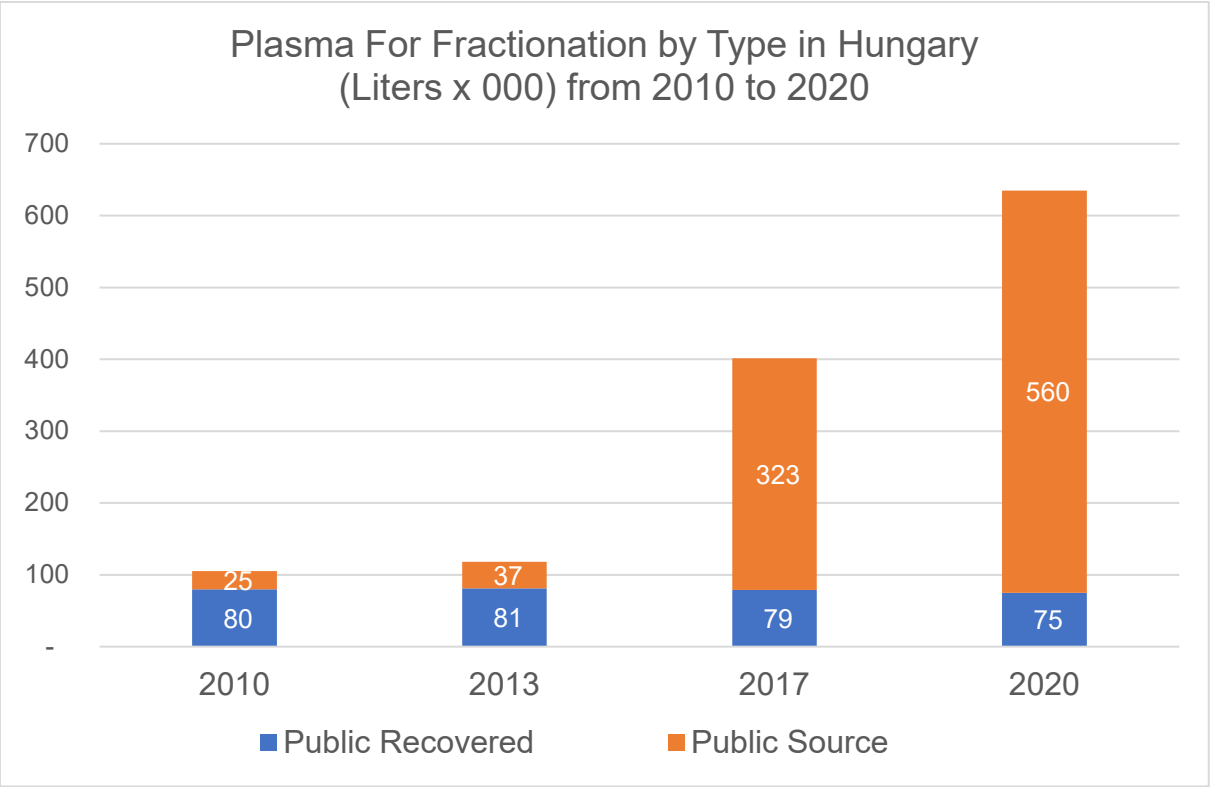
In Germany, blood and plasma donors may receive a compensation for donating blood and plasma, although it is capped by the Federal government (currently around €30 per donation.) In practice, donors may decline the compensation and offer it to charitable organizations if they desire.

A few years ago, Germany adopted new regulations pertaining to the frequency and maximum volume of plasma donations, beyond those suggest by E.U. guidelines. The German regulations offers more flexibility to both donors and plasma centers.



Czech Republic: About fifteen years ago, the Czech government allowed private companies to collect plasma for fractionation. In a relatively short period of time, the volume of plasma available for fractionation exceeded the volume required to meet the needs of patients depending on IG therapies. Between 2010 and 2020, plasma for fractionation volumes increased at an annual rate of 3.1%.

Plasma collected by both the private and public sectors was sold to commercial fractionators which distributed IG in the Czech Republic independently from their plasma collections in the country. A shortage of IG was reported during the COVID-19 pandemic, which led the health authorities to consider mandating the fractionators to commit a certain quantity of IG to be made available to Czech patients before using the excess plasma collected in the Czech Republic to manufacture IG shipped to other countries. Companies began to offer more IG supply to hospitals due to this threat, as it is in their interest to supply IG to their plasma suppliers.



Hungary: In Hungary, commercial plasma collections were in operation long before the Czech Republic, as a private fractionation plant existed, alongside with a public fractionation plant - now closed - in Budapest. The government blood program, which owned and managed this public fractionation plant conducted an intensive program of source plasma collections with non-compensated donors' sector in the 1980s for the main purpose of producing coagulation factors so as to be independent from factor products imported from the U.S. This program was successful for the benefit of hemophilia patients, but short-lived when IG began to drive the Hungarian plasma market.

The recent and dramatic rise of commercial source plasma collections in Hungary does not appear to have caused the same IG supply issue as in the Czech Republic. There are concerns about paid plasma donations "crowding out" non-remunerated blood donations, but an obligation for plasma donors to also donate blood once every year appears to have largely solved this issue.

Between 2010 and 2020, the volume of plasma for fractionation (source and recovered combined) rose by 19.7% annually, far exceeding the needs of Hungarian patients for IG. This excess plasma is used primarily to provide product in European Union countries which do not have commercial plasma operations, such as Italy or France.

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